Green Chemistry

Cite this: *Green Chem.*, 2011, **13**, 983

www.rsc.org/greenchem

PAPER

Efficient enhancement of copper-pyridineoxazoline catalysts through immobilization and process design†

C. Aranda,[a] A. Cornejo,[a] J. M. Fraile,[b] E. García-Verdugo,[c] M. J. Gil,[a] S. V. Luis,[c] J. A. Mayoral,[b] V. Martinez-Merino*[a] and Z. Ochoa[a]

Received 4th November 2010, Accepted 27th January 2011
DOI: 10.1039/c0gc00775g

Copper-pyridineoxazoline (Cu-*pyox*) complexes are poor homogeneous catalysts for asymmetric cyclopropanation reactions. *Pyox* ligands have been immobilized by polymerization of monomers possessing a vinyl group directly attached to position 6 with styrene and divinylbenzene. The corresponding heterogeneous catalysts show a significant enhancement in enantioselectivity, up to 7-fold that of the analogous homogeneous Cu-*pyox* catalysts. This effect is due to a synergic effect between the proximity of the polymeric backbone and the presence of a bulky substituent in the chiral oxazoline ring around copper. The obtained values of enantioselectivity are similar to those found with supported C_2-symmetric bis(oxazolines), but with only half the chiral information given the presence of only one oxazoline ring in *pyox*. Besides, the co-polymerization in the presence of the right porogen inside a column allows the preparation of monolithic mini-flow reactors. Continuous flow processes contribute to further improve the catalytic efficiency in both classical solvents (dichloromethane) and neoteric greener ones, such as supercritical CO_2. The use of $scCO_2$ as solvent yields the same selectivities obtained in batch processes in combination with higher productivity avoiding the use of VOC.

Introduction

Catalysis is one of the foundation pillars of green chemistry. The greenness of chemical transformations is closely related to the use of catalysts.[1] Catalysis can improve the efficiency of a reaction by lowering the energy input required, by avoiding the use of stoichiometric reagents, and by obtaining higher product selectivity. Furthermore, catalysts can be designed to mimic enzyme behaviour, leading to highly chemo- and enantioselective chemical transformations. This is of great importance, particularly, for fine chemicals, drugs and agrochemicals, products in general characterised by the presence of a diversity of stereogenic centres.

Among the different methodologies to synthesize enantiomerically enriched compounds, the use of a chiral chemocatalyst represents in principle a highly attractive procedure. In spite of the success, at a laboratory scale, of many enantioselective homogeneous catalysts,[2] only a few of them have found industrial application,[3] due to several issues that hamper their transference from lab to large scale processes. Chiral catalysts are normally expensive and difficult to prepare through multistep synthetic sequences. Besides, a high catalytic loading (1–10 mol%) is usually required. Furthermore, metal can leach from the homogeneous catalyst into the products, being particularly unacceptable for pharmaceutical production. Therefore, easy procedures for the isolation, recovery, and reuse of chiral catalysts are demanded.

The immobilization of chiral catalysts can help to overcome some of above-mentioned issues.[4] Moreover, it is considered advantageous because of the ease of separation, with the possibility of reuse, increasing in this way the productivity of the catalyst.[5] However these advantages do not seem to be enough to consider immobilized catalysts suitable for industry, mainly due to the increase in cost associated with immobilization, together with reduced activity and enantioselectivity reported in many cases.[6] Nevertheless, the covalent bonding of the chiral ligand to an insoluble support remains the most popular immobilization method, as it prevents the possible leaching of the valuable chiral ligand.[7]

The synthetic effort must be then compensated by additional advantages, such as improved activity, chemoselectivity,[8] or enantioselectivity, as a consequence of the "*positive polymeric*

[a]*Department of Applied Chemistry, Universidad Publica de Navarra, E-31006, Pamplona, Spain. E-mail: merino@unavarra.es*
[b]*Instituto de Ciencia de Materiales de Aragón and Instituto Universitario de Catálisis Homogénea, Universidad de Zaragoza-C.S.I.C., E-50009, Zaragoza, Spain*
[c]*Department of Inorganic and Organic Chemistry, Universidad Jaume I, E-12071, Castellon, Spain*

† Electronic supplementary information (ESI) available: Synthesis details and experimental procedures are given. See DOI: 10.1039/c0gc00775g

effect",[9] and operational advantages, allowing process design moving from batch to continuous flow processes, which leads to cleaner, simpler and more efficient catalytic asymmetric processes.[10] In this paper, we describe the synthesis of supported chiral catalysts, which are more efficient in terms of productivity and (*enantio*)selectivity than the related homogenous ones, being one of the few examples in which catalytic efficiency is significantly enhanced by the immobilisation onto a polymeric support.

Experimental

Safety note: *Some of the experiments described in this paper involve the use of relatively high pressures and require equipment with the appropriate pressure rating. It is the responsibility of individual researchers to verify that their particular apparatus meet the necessary safety requirements.*

All chemicals were reagent grade and used as purchased. All reactions were performed under an inert atmosphere of dry nitrogen. THF and toluene were distilled on sodium and dichloromethane was distilled on phosphorous pentoxide. ^{1}H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz in a Varian Gemini 2000 spectrometer at 293 K, using $CDCl_3$ as the solvent. Chemical shifts are given in ppm using the residual signal from $CHCl_3$ as the reference. High resolution mass spectrometry ESI+ spectra were recorded on a Bruker MicroTOF-Q Spectrometer using MeOH as the solvent. IR spectra were collected on a Nicolet Avatar 360 FT-IR spectrometer. The cyclopropanes used for analytical determinations were synthesized an analyzed as previously reported.[11] Asymmetric cyclopropanation (ACP) yields and *cis*/*trans* ratio were measured by GC using a HP-1 column. Enantiomeric excesses were measured by GC using a CyclodexB column

The detailed syntheses and characterisation of the compounds (**1**, **3–7** and **10–12**) as well as corresponding polymers are given in the ESI.†

Cyclopropanation under batch conditions

To a stirred solution of *pyox* (0.06 mmol) in anhydrous DCM, $Cu(TfO)_2$ (22 mg, 0.06 mg) was added. After 30 min stirring the solution was microfiltered. To the resulting solution, styrene (0.69 mL, 6.0 mmol) and a known amount of decane (*ca.* 80 μL) were added. To this stirred solution 2 mL of a 1 M solution of ethyl diazoacetate (EDA) in DCM were added during 2 h and the resulting mixture was stirred overnight.

Cyclopropanation under continuous flow conditions

Continuous flow experiments were performed using a reactor set-up as previously reported.[12]

Using DCM as the solvent. A fresh mixture of styrene (1.5 M), EDA (0.5 M) and n-decane (0.14 M) in anhydrous DCM was pumped through the monolithic column at different flow rates using a HPLC pump. Samples were collected and analyzed every 30 or 60 min. Significant results are given when the product stream was stabilized after reaching the steady state (*ca.* 1 h).

Using scCO$_2$ as the solvent. CO_2 was pressurised and delivered by a refrigerated pump running in constant flow mode and the organic substrates (styrene 6.15 M, EDA 2.05 M and decane 0.41 M were delivered at a constant rate by an HPLC pump. Both feed streams were mixed by a dynamic mixer before being passed through the monolithic catalytic bed stabilized at 40 °C. Products were collected after a single stage depressurization of the fluid mixture by an electronic backpressure regulator and analyzed.

Results and discussion

Immobilisation strategy: let the polymer play an active role!

In general, a structural modification of the catalyst is required in order to attach it to a polymeric support. This modification can have a big impact on the efficiency of the corresponding supported catalyst. Usually, the immobilisation is carried out on commercially available polymeric supports, which are not optimised for immobilisation, thus leading to deceiving catalytic performances. Hence, it is generally concluded, not necessarily a correct idea, that "*the best homogeneous catalyst will remain the best upon immobilization*", assuming that the polymeric matrix can have either no effect, in the best case, or a negative one, leading to less efficient catalysts upon the immobilisation. Thus, since the pioneering work of Soai and coworkers, spacers have been used to attach the ligand to the polymer by a point remote from the active site (tail-tie, Fig. 1),[13] hoping that the catalyst will be able to mimic a solution-like behaviour reducing any possible "polymeric (negative) effect". This approach, not always successful, disregards the role played by the polymeric matrix, concentrating only on the simple isolation and ease of reuse provided by the insoluble resin.

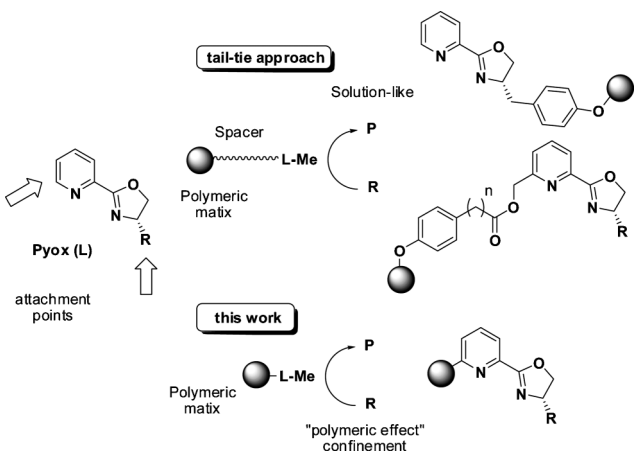


Fig. 1 Immobilization strategies for *pyox* ligands.

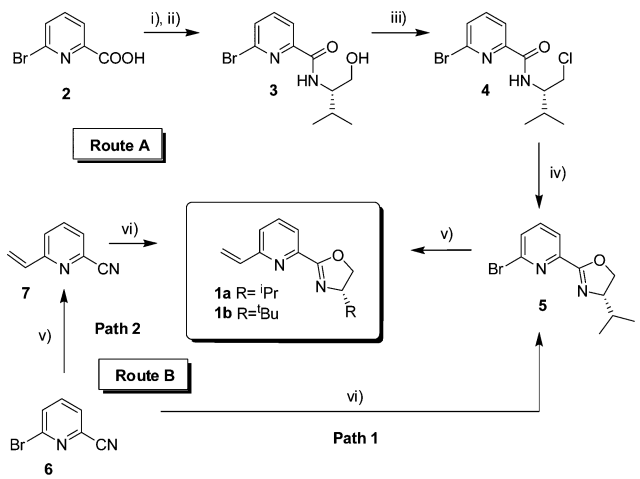
A more difficult, but probably better, approach is the design of both ligand and polymeric matrix specifically to obtain a given supported catalyst. Accordingly, through the optimisation of the ligand and support, the same matrix effect that leads to bad results after immobilization of a good homogeneous catalyst might be able to improve a bad one. Some results based on systematic studies clearly reflect how the presence of the well-designed support can be advantageous to increase the efficiency, especially, in terms of activity and selectivity of the supported species relative to that of the homogeneous ones.[9]

Oxazoline-containing ligands are among the most useful chiral ligands for enantioselective catalysis.[14] Therefore their immobilization by different methods has been deeply studied.[15] The complexes of pyridineoxazoline (*pyox*) with several metals have been used as catalysts for different synthetic transformations leading to moderate to good enantioselectivity.[16–19] However, Cu-*pyox* have shown poor performance in terms of enantioselectivity in asymmetric cyclopropanation (ACP).[20] Therefore, they would be a good example to demonstrate that the polymeric matrix might have a positive effect leading to more efficient catalysts upon immobilisation.

Even considering the wide variety of applications of these ligands, only two previous publications report the immobilization of *pyox* ligands *via* covalent bonding to polymeric supports.[21,22] In both cases, the *pyox* ligand was separated from the polymeric matrix by the introduction of a spacer (Fig. 1). Here, we propose the immobilisation of the ligand to maximise the possible polymeric effect. Hence the introduction of a vinyl group directly in position 6 of the pyridine ring may favour any steric hindrance or electronic effect provided by the polymeric backbone.

Synthesis and immobilisation of vinyl-*pyox* ligand

The synthesis of 6-vinyl-*pyox* ligand (**1a**) can be performed following the Nishiyama protocol. This synthetic pathway involves five reaction steps (route A, Scheme 1).[23] Thus, the compound **5** was obtained with an overall yield of 57% (referred to the aminoalcohol). Finally, bromine was replaced by a vinyl group *via* Stille coupling with 41% yield of **1a**. Each step requires the isolation and purification of the intermediates in a rather tedious and wasteful synthetic procedure with moderate global yield (23%).



Scheme 1 Reaction conditions. Route A: (i) $COCl_2$, DMF, DCM; (ii) (*S*)-valinol, DCM, Et_3N; (iii) $SOCl_2$, DCM; (iv) NaH, Et_4NI, 18C6, THF; (v) tributylvinyltin, $Pd(PPh_3)Cl_2$, toluene. Route B: *Path 1*: (vi) (*S*)-valinol, $Zn(TfO)_2$, toluene, reflux; *Path 2*: (vi) aminoalcohol, $Zn(TfO)_2$, toluene, reflux.

Alternatively, the oxazoline ring can be prepared in a single step starting from the nitrile **6** and (*S*)-valinol in the presence of a metal salt as a catalyst.[24–26] The main drawbacks of this synthetic methodology is the large excess of chiral aminoalcohol needed in order to complete the reaction, and that chromatography is required as a final purification step. However, in a novel one-pot method to synthesize *pybox* ligands starting from 2,6-pyridinedicarbonitrile,[27] a stoichiometric amount of aminoalcohol was used with $Zn(TfO)_2$ as catalyst. Besides, only aqueous workup of the reaction mixture was required. Using this methodology, the compound **5** was obtained by reaction of **6** with (*S*)-valinol with 75% yield. Once again, bromine can be replaced with a vinyl group *via* Stille coupling (Route B-Path 1, Scheme 1).

Table 1 Routes used in the synthesis of **1a**

Route	Solvent	Steps	Yield (%)	E factor
A	DCM	5	23	1982
B (path 1)	Toluene	2	31	358
B (path 2)	Toluene	2	65	137

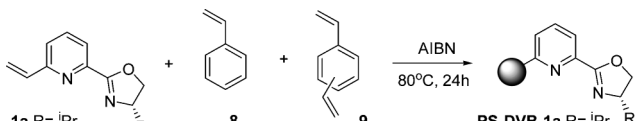
Considering that the lowest yield was obtained in the Stille coupling step of both synthetic routes (A and B-path 1, Scheme 1), the synthesis of 6-vinyl-2-pyridinecarbonitrile (**7**) was alternatively evaluated (route B-path 2). Thus compound **7** was prepared from **6** with good yield (78%). Subsequent reaction of the nitrile **7** with the (*S*)-valinol and $Zn(TfO)_2$ as catalyst gave the ligand 2-[(*S*)-4,5-dihydro-4-isopropyl-1,3-oxazol-2-yl]-6-vinylpyridine **1a** (vinyl-*pyox*) with 83% yield.

It is noteworthy that the synthetic methodology based in the route B-path 2 significantly reduced the number of steps as well as isolation and purification of intermediates, leading to a significant decrease in the E factor (Table 1). Besides, the global yield for the synthesis of vinyl-*pyox* **1a** was improved from 23% yield (route A) to 65% yield (route B-path 2).

Once this synthetic methodology was optimised, the vinyl-*pyox* ligand **1b** derived from (*S*)-*tert*-leucinol was also prepared following route B-path 2 with 52% global yield.

The preparation of the corresponding supported ligands was carried out by bulk polymerisation of **1** with styrene (**8**) as co-monomer and divinylbenzene (DVB, **9**) as cross-linking agent in toluene at 80 °C for 24 h (Table 2). The content of immobilized ligand was determined by nitrogen analysis, which can be assimilated to that of the corresponding polymerization mixture.

Table 2 Copolymerization conditions of vinyl-*pyox* ligands[a]



Polymer	**1** (%)[b]	**8** (%)[b]	**9** (%)[b]	% N	mmol *pyox*/g	Yield (%)[c]
PS-DVB-1a	6.9	42.1	50.9	1.58	0.55	99
PS-DVB-1b	7.0	42.0	51.0	1.79	0.64	99

[a] Toluene was used as porogen. Co-polymerization was initiated by AIBN and carried out at 80 °C using a monomers/porogen mass ratio of 2 : 3. [b] Expressed in % molar amount. [c] Compared with the content of ligand in the initial mixture.

Batch ACP of styrene with EDA

Polymers **PS-DVB-1a** and **PS-DVB-1b** were complexed with $Cu(OTf)_2$, thoroughly washed and tested as catalysts for ACP in batch processes. The results obtained are gathered in Fig. 2.

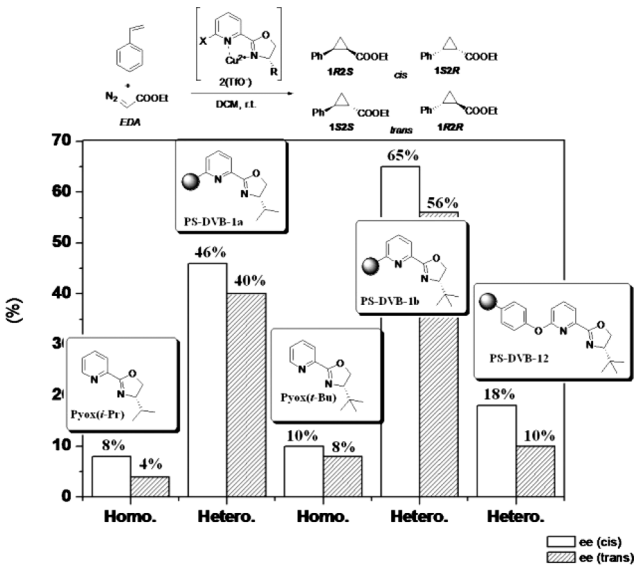


Fig. 2 Enantioselectivity of homogeneous *vs.* heterogeneous *pyox*-Cu(II) catalysts in the ACP between styrene and EDA. Reaction conditions: styrene/EDA = 3, 6% catalyst, dichloromethane solvent, rt, slow addition of EDA (data for *pyox*(^{i}Pr) from ref. 20).

In addition to the corresponding cyclopropanes, both homogeneous and heterogeneous Cu complexes yield diethyl fumarate and maleate, resulting from EDA homo diazo coupling. The polymeric catalysts gave lower yields, *ca.* 20%, than the homogeneous ones, *ca.* 60%. It is worth noting that Cu(II) has to be reduced to Cu(I) in the first step, before the carbene intermediate formation. A lower reduction rate, as a consequence of diffusion limitations, may account for this lower yield. Regarding diasteroselectivity, a slight decrease from *ca.* 65–69% *trans* in homogeneous phase to *ca.* 56% *trans* with the supported catalyst was also found. However, a remarkable enhancement in enantioselectivity was observed.

In contrast with the almost no-enantioselection obtained with both Cu-*pyox*(^{i}Pr) and Cu-*pyox*(^{t}Bu) catalysts in solution,[20] the analogous supported catalysts led to significant enantioselectivity values (Fig. 2), 46% ee (*cis*) and 40% ee (*trans*) for **PS-DVB-1a** and 65% ee (*cis*) and 56% ee (*trans*) for **PS-DVB-1b**.

These results seem to indicate the positive role played by the proximity of the polymeric backbone to the catalytic site. The steric hindrance provided by the rigid highly cross-linked polymeric backbone around the position 6 of the pyridine, in connection with the chiral information in the oxazoline ring with the bulky substituent, may increase the steric hindrance in several of the possible transition states, responsible for the enhancement in enantioselectivity. At the same time, this may minimize the steric interaction between the phenyl group of styrene and the ester group of the carbene, responsible for the diastereoselectivity.

Furthermore, a certain "*chirality economy*" regarding the use of starting chiral aminoalcohol was also observed. Indeed, the supported Cu-*pyox* system, for similar polymeric composition and ligand loadings, achieved slightly better chiral induction than that obtained for related immobilized bis(oxazolines) with only half of stereogenic centres involved in the asymmetric induction (Fig. 3).[28]

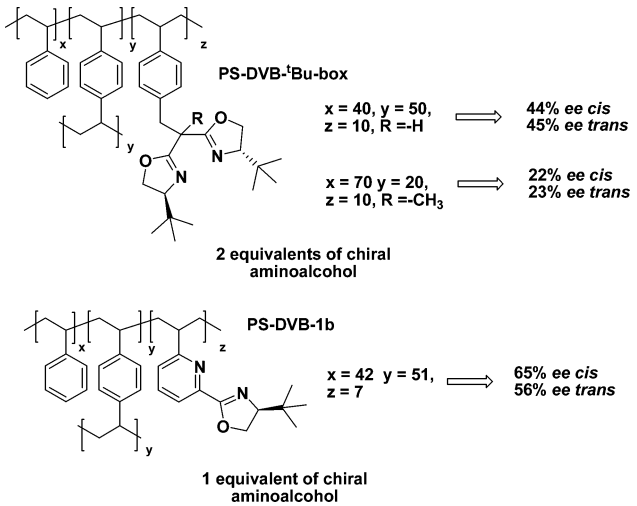
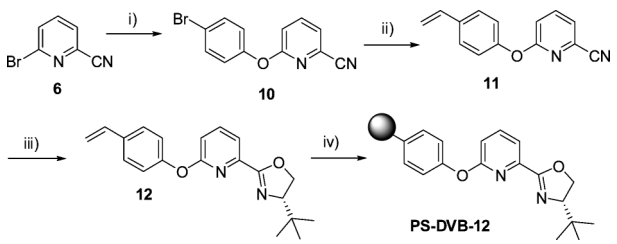


Fig. 3 "Chirality economy" of *pyox vs. box* in ACP.

In order to demonstrate this positive "*polymeric effect*", a ligand with a phenoxy spacer (**12**) was also synthesized starting from 6-(4-bromophenoxy)-2-pyridinecarbonitrile (**10**). This would be the immobilization choice if the common statement "the support is a necessary evil, and the catalyst must be placed far away from it in order to obtain a solution-like behaviour" were assumed. In this case, if the catalysts will behave as in solution, a reduction in enantioselectivity should be observed.

The compound **10** was obtained *via* nucleophilic replacement of bromine of **6** by 4-bromophenoxyde anion with 83% yield (Scheme 2). Stille coupling with tributylvinyltin led to **11** in 88% yield. The subsequent oxazoline **12** was obtained by reaction of **11** with (*S*)-*tert*-leucinol in 87% yield after purification. Polymerisation of this monomer **12** with styrene **8** and DVB **9**, under conditions similar to those previously employed (Table 2) yielded polymer **PS-DVB-12**.



Scheme 2 Reaction conditions: (i) 4-bromophenol, K_2CO_3, DMF, 100 °C, (ii) tributylvinyltin, $Pd(PPh_3)Cl_2$, toluene; (iii) (*S*)-*tert*-leucinol, $Zn(TfO)_2$, toluene; (iv) **8** and **9**, AIBN, toluene, 80 °C.

The catalytic behavior of the corresponding supported copper(II) complex of **PS-DVB-12** was evaluated for ACP benchmark reaction. It is noteworthy that the introduction of the spacer, which pushes the polymeric matrix further away from the catalytic center, led to a reduction of the enantioselectivity compared with that obtained for the same catalyst closely

Table 3 Recycling of immobilized Cu-*pyox* complexes in batch ACP[a]

Supported *pyox*	Run	Yield (%)	*cis* : *trans*	% ee *cis*[b]	% ee *trans*[b]
1a	Hom	55	31 : 69	8	4
PS-DVB-1a	1	17	44 : 56	46	40
	2	30	44 : 56	47	40
	3	30	44 : 56	48	37
	4	28	48 : 52	42	32
	5	22	50 : 50	39	29
1b	Hom	64	36 : 64	10	8
PS-DVB-1b	1	18	43 : 57	65	56
	2	41	44 : 56	64	57
	3	42	45 : 55	59	51
	4	43	47 : 53	57	51
	5	19	47 : 53	50	43
PS-DVB-12	1	13	38 : 62	18	10
	2	40	39 : 61	20	12

[a] Reaction conditions: styrene/EDA = 3, 6% catalyst, dichloromethane solvent, rt, slow addition (2 h) of EDA. Yield of cyclopropanes and selectivities determined by GC. [b] Major enantiomers: *cis* 1*R*,2*S*; *trans* 1*R*,2*R*.

attached to the polymeric backbone (Fig. 2). Thus, the positive "polymeric effect" for the case of Cu-*pyox* catalyst directly attached to position 6 of pyridine was confirmed.

Other important characteristic of the polymer supported catalysts is that they can be easily separated and reused in consecutive cycles. Therefore, the recyclability of the polymeric Cu-*pyox* complexes was tested for ACP. The achieved results are summarized in Table 3.

After the first cycle, the yield of cyclopropanes was increased to reach values around 30% with **PS-DVB-1a** and 42% with **PS-DVB-1b**. Both diastero- and enantioselectivity kept stable for at least 3 successive runs. The productivity of the catalysts was obviously increased by recycling and reuse. Thus, a 90% increase in productivity, maintaining the enantioselectivities, was obtained with **PS-DVB-1a**, while a 125% increase was obtained with **PS-DVB-1b**.

From batch to continuous ACP

The supported copper catalysts derived from **PS-DVB-1a** and **PS-DVD-1b** present some limitations related to diffusion problems leading to lower yields than homogeneous system. Besides, a drop on the catalytic efficiency was observed after the third cycle. The use of monolithic materials prepared by polymerisation can help to overcome these drawbacks avoiding diffusion problems and improving the stability.[29]

Furthermore, these materials can be obtained as mini flow catalytic reactors to easily develop continuous flow processes.[30] These processes offer a number of potential advantages over batch techniques, such as the possibility of optimizing the reaction variables (stoichiometry, flow rate, temperature) independently, making optimization easier.[10,31] In fact, monolithic polymers can solve problems, such as stagnation zones, hot-spots, and large residence time distribution, produced in fix-bed reactors prepared by random packing of the solid catalyst, resulting in low process efficiency.[10]

Different mini-flow reactors were prepared by a mixture of vinyl-functionalized *pyox* ligands (**1a** and **1b**), styrene and DVB, as the cross-linking agent, with a mixture of toluene and 1-dodecanol, as the porogenic agent (Table 4).[12] The mini-flow reactors were attached to a HPLC pump and after complexation with $Cu(OTf)_2$ a solution of EDA and styrene in DCM was pumped through the reactor.[32] The first measurements were taken once the observed yields were stable. During this initial period the solution of reagents, passing through the reactor, acts as an additional "cleaning" agent for any non-specifically bonded copper triflate.

Table 4 Preparation of mini-flow monolithic reactors by polymerization conditions of vinylic pyox ligand with styrene (**8**) and DVB (**9**)

Mini-flow reactor (*pyox*)	vinyl-*pyox*[a]	**8**[a] (%)	**9**[a] (%)	dod/tol[b]	mmol *pyox* per g
Mf-R1 (*i-Pr*)	7.0 (**1a**)	41.8	51.2	4.5	0.38
Mf-R2 (*t-Bu*)	6.7 (**1b**)	63.0	30.3	5.1	0.42
Mf-R3 (*t-Bu*)	6.3 (**1b**)	45.1	48.6	4.8	0.44

[a] Expressed in % molar amount. [b] Dodecanol/toluene ratio (w/w). Co-polymerization was initiated by AIBN and carried at 70 °C using a polymeric mass/porogen mass of 2 : 3.

The results for the continuous flow ACP using Cu-*pyox*(^{i}Pr) catalytic mini-flow reactor (**Mf-R1**) are summarized in Table 5. Two different reactor assemblies were evaluated. A continuous single pass flow set-up was firstly used. Alternatively a semi-continuous process, where the reaction mixture was recirculated through the mini-flow reactor several times, was also assayed.

Some interesting features can be drafted when the results for the flow processes are compared with those obtained for batch analogous homogeneous or heterogeneous Cu-*pyox* catalyst:

(i) Yields in the range of those obtained for the homogeneous catalysts (*ca.* 50% yield, Table 5) can be obtained under flow conditions by simply adjusting the flow rate and the polymer composition. In the flow process, the reactants are forced to go through the channels defined by monolithic polymeric matrix avoiding,[33] to a great extent, diffusion limitations found for the polymeric runs under batch conditions, increasing in this way the conversion of EDA to cyclopropanes (*ca*. 20% for polymeric batch catalyst *vs ca* 50% for flow processes).

(ii) Continuous flow processes led to higher chemoselectivities towards the formation of cyclopropanes (*ca.* 67–70%) than those achieved for the batch runs.

(iii) Enantioselectivities obtained under flow conditions were similar than those corresponding to related heterogeneous catalyst under batch conditions.

(iv) Processes based on the use of mini-flow reactors were, in terms of productivity, quite superior to the batch processes. In general, the small volume of the mini-flow reactor (*ca*. 660 μL) and the prolonged use without the need for separation of the catalyst lead to quite significant process intensification producing larger amount of cyclopropanes (CP) for a low volume reactor (836 g L^{-1} *vs*. 21 or 6.5 g L^{-1} for the batch processes). When the mini-flow reactor was assayed in a recirculation mode, even though the conversion of EDA was slightly improved, the productivity was clearly reduced (836 g L^{-1} *vs*. 50 g L^{-1}) as a larger reactor volume was used. A similar increase of catalytic efficiency has been recently reported for other catalytic monolithic microreactors.[34]

Table 5 ACP reaction catalyzed by Cu-*pyox*(^{i}Pr) in DCM as solvent[a]

	Homogeneous batch	Heterogeneous batch	Continuous single pass[f]	Semi-continuous recirculation[g]
Support	—	**PS-DVB-1a**	**Mf-R1**	**Mf-R1**
Yield (%)[a]	55	17	49	56
Chemoselectivity[b]	55	17	67	70
% ee (*cis*)[c]	8	46	39	38
% ee (*trans*)[c]	4	40	44	40
TOF[d]	0.86[e]	0.20[e]	2.31	2.31
Productivity (g L^{-1})	21	6	836	50

[a] Yield of cyclopropanes (CP) and selectivities determined by GC. [b] Chemoselectivity = % yield CP/% conversion of EDA. [c] Major enantiomers: *cis* 1*R*,2*S*; *trans* 1*R*,2*R*. [d] TOF (CP-mmol *pyox*-mmol^{-1}) h^{-1} = [EDA (mmol mL^{-1}) × flow (mL min^{-1}) × 60 (min) × (% yield/100)]/[*pyox* loading (mmol g^{-1}) × catalyst mass (g)]. [e] Operation time 12 h, reactor volume = 3 mL. [f] Flow rate 20 µL min^{-1}, reactor volume = 0.66 mL [g] After the first 540 min of flow operation (single pass), 10 mL of reagents solution was re-circulated through the column for 1860 additional min at 20 µL min^{-1}, reactor volume = 10 mL batch reactor + 0.66 mL monolithic reactor.

Regarding stability, the most critical parameters such as yield, *cis*/*trans* diastereoselectivity and *cis* and *trans* enantioselectivities remained almost stable up to 14 h of constant operation. After that time a slight decrease in activity was generally observed. Fig. 4 gathers a representative example (Cu-*pyox*(^{t}Bu) mini-flow reactor **Mf-R2**) of the results obtained for these systems by extended use, under flow conditions. As enantioselectivity remains constant during the time on stream, it can be concluded that the oxazoline moiety remains intact during operation. The observed loss of catalytic activity may be attributed to leaching of copper. Indeed, when the mini-flow reactors were reloaded with copper triflate,[35] a recovery of their activity took place maintaining the same level of selectivity. Theoretical calculations [M06/6-31G(d,p)] point to that the metal leaching could be a consequence of some decomplexation induced by the formation of soluble ethyl maleate-Cu species.

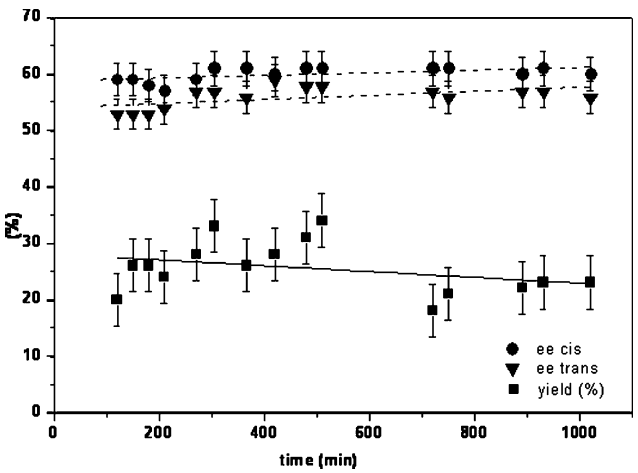


Fig. 4 Long term use of the Cu-*pyox*(^{t}Bu) mini-flow reactor **Mf-R2** in continuous flow ACP in DCM as solvent (20 µL min^{-1}).

The presence of a bulkier group in the oxazoline ring of *pyox* ligand (*tert*-butyl **Mf-R2** *vs.* isopropyl **Mf-R1**) led to clearly improved enantioselectivities, as observed for the batch processes with polymer supported Cu-*pyox* complexes (Table 6). However, lower activity was also obtained with the Cu-*pyox*(^{t}Bu) reactor **Mf-R2** for similar ligand loading and flow rate. This lower activity may be attributed to lower cross-linking degree in **Mf-R2**.

Table 6 ACP reaction in a continuous flow process using DCM as solvent[a]

Mini-flow reactor (*pyox*)	Yield (%)	Chemoselectivity[b] (%)	*cis*/*trans*	% ee *cis*[c]	% ee *trans*[c]	TOF[d]
Mf-R1 (^{i}Pr)	49[e]	67	49 : 51	39	44	2.64[e]
Mf-R2 (^{t}Bu)	24[f]	59	44 : 56	60	57	2.45

[a] Yield of cyclopropanes (CP) and selectivities determined by GC. [b] Chemoselectivity = % yield CP/% conversion of EDA. [c] Major enantiomers: *cis* 1*R*,2*S*; *trans* 1*R*,2*R*. [d] TOF (CP-mmol *pyox*-mmol^{-1}) h^{-1} = [EDA (mmol mL^{-1}) × flow (mL min^{-1}) × 60 (min) × (%yield/100)]/[*pyox* loading (mmol g^{-1}) × catalyst mass (g)]. [e] 20 µL min^{-1}. [f] 23 µL min^{-1}.

Once the efficiency of the Cu-*pyox* monolithic mini-flow reactors had been proved for the continuous flow process using DCM, the benchmark ACP reaction between styrene and EDA was performed using $scCO_2$ as solvent.[36] The reaction was carried out at 40 °C and 8 MPa. Thus, a mixture of styrene/EDA (molar ratio = 3) was mixed with a stream of CO_2 accounting the organic stream for a 10% of the total flow used. Two freshly prepared reactors (Cu-*pyox*(^{i}Pr) **Mf-R1** and Cu-*pyox*(^{t}Bu) **Mf-R3**) were used for cyclopropanation experiments using $scCO_2$ as solvent. The results in terms of yield, selectivities and productivity are gathered in Table 7.

The stability of the Cu-*pyox*(^{i}Pr) **Mf-R1** and Cu-*pyox*(^{t}Bu) **Mf-R3** reactors during a prolonged operation time was tested (see ESI†). In the case of **Mf-R1**, the column was stable for a 470 min run in $scCO_2$, whereas in the case of **Mf-R3** deactivation of the reactor occurred at 930 min.

The cross-linking degree (Table 4) and catalytic activities (CP yields, Table 7) were similar for both reactors. Furthermore their chemoselectivity was moderately high, 56–62%, and similar to those obtained with homogeneous catalysts or in continuous flow using DCM. Regarding selectivities, both diastereo- and enantioselectivity are constant along the operating time (see Table 7). Enantioselectivities are similar to, or slightly lower than those obtained in DCM under flow conditions. The low dielectric constant of $scCO_2$ and the higher operation temperature may account for this slight reduction of ee. It is worth noting that previous experiments on ACP in $scCO_2$ catalyzed by monoliths based in pybox-ruthenium complexes showed that no

Table 7 ACP results in continuous flow reactors using $scCO_2$ as solvent[a]

Mini-flow reactor	*t*/min	Org. fl./μL min^{-1}	Yield (%)[a]	Chemoselectivity (%)[b]	*cis*/*trans*	% ee *cis*[c]	% ee *trans*[c]
Mf-R1 (^{i}Pr)	120[d]	50	45	59	48 : 52	40	39
	165	50	41	57	48 : 52	38	37
	270	20	42	58	47 : 53	38	38
	470	50	28	56	47 : 53	37	37
Mf-R3 (^{t}Bu)	252[d]	20	47	61	46 : 54	57	55
	697	15	47	62	45 : 55	54	52
	927	10	42	61	45 : 55	52	49

[a] Yield and selectivities determined by GC [b] Chemoselectivity = % yield of cyclopropanes/% conversion of EDA. [c] Major enantiomers: *cis* 1*R*,2*S*; *trans* 1*R*,2*R*. [d] First measure after stabilization of the reactor.

significant variation of the reaction parameters such as yield or chemoselectivity was observed with the increase of the pressure, although a slight decrease in regio- and enantioselectivity was found for higher pressures.[12b]

At first sight, it could seem that mini-flow reactors are less stable using $scCO_2$ than DCM. However the amount of EDA, the main agent responsible for deactivation by promoting metal leaching, that circulates through the column is remarkably higher in runs performed using $scCO_2$, 30.8 mmol for **Mf-R1** and 22.6 mmol for **Mf-R3**, in comparison with 13.6 mmol for **Mf-R1** and 11.2 mmol for **Mf-R2** in DCM solution. If we also consider the total production per volume in a given time, the value obtained for **Mf-R1** in $scCO_2$ was noticeably higher than that achieved in DCM (1402 g L^{-1} *vs.* the 836 g L^{-1}). It is noteworthy that this higher volumetric productivity was obtained in shorter time, 165 min for $scCO_2$ compared with 540 min for DCM, and a total 3074 g L^{-1} during the total operation time of **Mf-R1** (470 min). Hence, in $scCO_2$ up to 1.5 mmol cyclopropanes per hour can be obtained, whereas lower values around 0.13–0.21 mmol h^{-1}, were achieved in DCM. All these values show the fact that the use of CO_2 as solvent not only provides the replacement of a volatile and harmful solvent, such as DCM, by a safer and non-toxic one, but also significantly improves the processes in terms of productivity. The lower density of the mixture of reactants in CO_2 might facilitate diffusion to reach the active sites of the supported catalyst allowing the use of faster flow rates to achieve same degree of conversion of EDA to the corresponding cyclopropanes.

Conclusions

It has been demonstrated that the efficiency of supported catalytic systems can be improved in terms of selectivity, particularly enantioselectivity, and productivity by the proper design of the immobilization methodology. In the described system, the polymeric support constitutes most of the catalyst mass. Therefore, by designing an adequate immobilization strategy to take advantage of the presence of the polymeric backbone, a positive "polymeric effect" can be promoted. Hence, it is possible to transform a non-enantioselective homogenous system for ACP such as Cu-*pyox* into a selective one. An enantioselectivity improvement of up to 7-fold for the Cu-*pyox* catalyst was found by letting the polymer, in the corresponding supported system, play an active role.

Furthermore, the efficiency of the catalytic system was additionally improved by process design. Cu-*pyox* can be prepared as mini-flow catalytic reactors allowing the development of continuous flow processes moving away from traditional batch processes. Flow processes based on the use of monolithic *pyox* enable the catalyst stabilization, the easier and more effective catalyst recycle enhancing catalyst turnover. Thus, the productivity for the continuous flow processes can be significantly higher than those found for the homogeneous traditional processes. Finally, the greenness of the process was improved by the substitution of a VOC solvent (DCM) for a more sustainable one such as $scCO_2$. The use of $scCO_2$ provided the additional advantage of the higher productivity than in DCM, while keeping the same selectivities obtained in batch processes.

Acknowledgements

Support by the Spanish 'Ministerio de Ciencia e Innovación' (CTQ2008-05138 and CTQ2005-08016, and Consolider Ingenio 2010 CSD2006-0003) is greatly acknowledged.

Notes and references

1 (*a*) P. T. Anastas, M. M. Kirchhoff and T. C. Williamson, *Appl. Catal., A*, 2001, **221**, 3; (*b*) R. A. Sheldon, I. Arends and U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2007; (*c*) G. Rothenberg, *Catalysis, Concepts and Green Chemistry*, Wiley-VCH Verlag GmbH, Weinheim, 2008; (*d*) R. H. Crabtree, *Handbook of Green Chemistry, Green Catalysis*, Wiley-VCH Verlag GmbH, Weinheim, 2009.
2 *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, 1999.
3 H.-U. Blaser and E. Schmidt, *Asymmetric Catalysis on Industrial Scale*, ed. H.-U. Blaser and E. Schmidt, Wiley-VCH, Weinheim, 2004, pp. 1–19.
4 (*a*) *Chiral Catalysts Immobilization and Recycling*, ed. D. E. De Vos, I. F. J. Vankelecom and P. A. Jacobs, Wiley-VCH, Weinheim, 2000; (*b*) M. Heitbaum, F. Glorius and I. Escher, *Angew. Chem., Int. Ed.*, 2006, **45**, 4732.
5 N. Kann, *Molecules*, 2010, **15**, 6306.
6 J. Lu and P. H. Toy, *Chem. Rev.*, 2009, **109**, 815.
7 Reviews and specials issues: (*a*) P. H. Toy and M. Shi, (ed.), Polymer-Supported Reagents and Catalysts: Increasingly Important Tools for Organic Synthesis, *Tetrahedron*, 2005, **61**, 12013; (*b*) J. A. Gladysz, (ed.), *Chem. Rev.*, 2002, **102**, 3215; (*c*) T. Kehat, K. Goren and M. Portnoy, *New J. Chem.*, 2007, **31**, 1218.
8 (*a*) H. Werner, C. I. Herrerías, M. Glos, A. Gissibl, J. M. Fraile, I. Pérez, J. A. Mayoral and O. Reiser, *Adv. Synth. Catal.*, 2006, **348**, 125; (*b*) J. M. Fraile, I. Pérez, J. A. Mayoral and O. Reiser, *Adv. Synth. Catal.*, 2006, **348**, 1680.

9 (*a*) N. Madhavan, C. W. Jones and M. Weck, *Acc. Chem. Res.*, 2008, **41**, 1153–1165; (*b*) B. Altava, M. I. Burguete, E. García-Verdugo, S. V. Luis, M. J. Vicent and J. A. Mayoral, *React. Funct. Polym.*, 2001, **48**, 25.

10 *Chemical Reactions and Processes under Flow Conditions*, ed. S. V. Luis and E. García-Verdugo, RSC-Green Series, 2009.

11 M. I. Burguete, J. M. Fraile, J. I. García, E. García-Verdugo, S. V. Luis and J. A. Mayoral, *Org. Lett.*, 2000, **2**, 3905.

12 (*a*) M. I. Burguete, A. Cornejo, E. García-Verdugo, J. I. García, M. J. Gil, S. V. Luis, V. Martinez-Merino, J. A. Mayoral and M. Sokolova, *Green Chem.*, 2007, **9**, 1091–1096; (*b*) M. I. Burguete, A. Cornejo, E. García-Verdugo, M. J. Gil, S. V. Luis, J. A. Mayoral, V. Martinez-Merino and M. Sokolova, *J. Org. Chem.*, 2007, **72**, 4344.

13 (*a*) K. Soai, M. Watanabe and A. Yamamoto, *J. Org. Chem.*, 1990, **55**, 4832; (*b*) K. Soai and M. Watanabe, *Tetrahedron: Asymmetry*, 1991, **2**, 97; (*c*) M. Watanabe and K. Soai, *J. Chem. Soc., Perkin Trans. 1*, 1994, 837; (*d*) M. A. Pericas, D. Castellnou, I. Rodriguez, A. Riera and L. Sola, *Adv. Synth. Catal.*, 2003, **345**, 1305; (*e*) A. Bastero, D. Font and M. A. Pericas, *J. Org. Chem.*, 2007, **72**, 2460.

14 G. Desimoni, G. Faita and K. A. Jørgensen, *Chem. Rev.*, 2006, **106**, 3561.

15 (*a*) E. Framery, B. Andrioletti and M. Lemaire, *Tetrahedron: Asymmetry*, 2010, **21**, 1110; (*b*) J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, E. Pires and L. Salvatella, *Catal. Today*, 2009, **140**, 44; (*c*) J. M. Fraile, J. I. García and J. A. Mayoral, *Coord. Chem. Rev.*, 2008, **252**, 624; (*d*) M. I. Burguete, J. M. Fraile, E. García-Verdugo, S. V. Luis, V. Martınez-Merino and J. A. Mayoral, *Ind. Eng. Chem. Res.*, 2005, **44**, 8580.

16 Allylic alkylation: (*a*) G. Chelucci, S. Deriu, G. A. Pinna, A. Saba and R. Valenti, *Tetrahedron: Asymmetry*, 1999, **10**, 3803; (*b*) G. Chelucci, S. Medici and A. Saba, *Tetrahedron: Asymmetry*, 1999, **10**, 543; (*c*) U. Bremberg, M. Larhed, C. Moberg and A. Hallberg, *J. Org. Chem.*, 1999, **64**, 1082.

17 Michael additions: J. Christoffers, A. Mann and J. Pickardt, *Tetrahedron*, 1999, **55**, 5377.

18 Henry reaction: M. J. Oila, J. E. Tois and A. M. P. Koskinen, *Lett. Org. Chem.*, 2008, **5**, 11.

19 Hydrosilylation: G. Balavoine, J. C. Clinet and I. Lellouche, *Tetrahedron Lett.*, 1989, **30**, 5141.

20 A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, C. I. Herrerias, G. Legarreta, V. Martinez-Merino and J. A. Mayoral, *J. Mol. Catal. A: Chem.*, 2003, **196**, 101.

21 K. Hallman, E. Macedo, K. Nordstrom and C. Moberg, *Tetrahedron: Asymmetry*, 1999, **10**, 4037.

22 M. J. Oila, J. E. Tois and A. M. P. Koskinen, *Tetrahedron*, 2005, **61**, 10748.

23 H. Nishiyama, S. Yamaguchi, M. Kondo and K. Itoh, *J. Org. Chem.*, 1992, **57**, 4306.

24 (*a*) C. Bolm, K. Weickhardt, M. Zehnder and T. Ranff, *Chem. Ber.*, 1991, **124**, 1173; (*b*) G. Chelucci, S. Medici and A. Saba, *Tetrahedron: Asymmetry*, 1999, **10**, 543; (*c*) U. Bremberg, F. Rahm and C. Moberg, *Tetrahedron: Asymmetry*, 1998, **9**, 3437.

25 R. Breslow and M. Schmir, *J. Am. Chem. Soc.*, 1971, **93**, 4960.

26 V. K. Aggarwal, L. Bell, M. P. Coogan and P. Jubault, P., *J. Chem. Soc., Perkin Trans. 1*, 1998, 2037.

27 A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, V. Martinez-Merino, J. A. Mayoral, E. Pires and I. Villalba, *Synlett*, 2005, 2321.

28 M. I. Burguete, J. M. Fraile, J. I. García, E. García-Verdugo, C. I. Herrerıas, S. V. Luis and J. A. Mayoral, *J. Org. Chem.*, 2001, **66**, 8893.

29 (*a*) B. Altava, M. I. Burguete, J. M. Fraile, J. I. García, S. V. Luis, J. A. Mayoral and M. J. Vicent, *Angew. Chem., Int. Ed.*, 2000, **39**, 1503; (*b*) B. Altava, M. I. Burguete, E. García-Verdugo, S. V. Luis and M. J. Vicent, *Green Chem.*, 2006, **8**, 717.

30 (*a*) P. Lozano, E. García-Verdugo, N. Karbass, K. y. Montague, T. De Diego, M. I. Burguete and S. V. Luis, *Green Chem.*, 2010, **12**, 1803–1810; (*b*) A. Gömanna, J. A. Deverell, K. F. Munting, R. C. Jones, T. Rodemann, A. J. Canty, J. A. Smith and R. M. Guijt, *Tetrahedron*, 2009, **65**, 1450; (*c*) M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin and C. D. Smith, *Org. Biomol. Chem.*, 2008, **6**, 1587; (*d*) M. I. Burguete, H. Erythropel, E. García-Verdugo, S. V. Luis and V. Sans, *Green Chem.*, 2008, **10**, 401; (*e*) N. Karbass, V. Sans, E. García-Verdugo, M. I. Burguete and S. V. Luis, *Chem. Commun.*, 2006, 3095.

31 C. G. Frost and L. Mutton, *Green Chem.*, 2010, **12**, 1687.

32 Concentration of each component in DCM solution. EDA (0.50 M), styrene (1.5 M), n-decane (≈0.15 M) as internal standard.

33 *Monolithic materials: preparation, properties and applications*, ed. F. Svec, T. B. Tennikova and Z. Deyl, Elsevier, Amsterdam, 2003.

34 A. El Kadib, R. Chimenton, A. Sachse, F. Fajula, A. Galarneau and B. Coq, *Angew. Chem., Int. Ed.*, 2009, **48**, 4969.

35 Similar high chiral ligand stability allowing long term activity to be kept by metal complex regeneration have been previously reported for monolithic Ti-TADDOLates (see ref. 29).

36 CO_2 has been considered as a "green" alternative solvent due to its properties (non-toxic, non-flammable and tunable solvent system). However, in order to consider that process as more environmental friendly than the same process run in organic solvent, the whole process should be evaluated ("cradle-to-grave" evaluation) including an assessment of the energy consumption. Such study is out of the scope of this paper but it should be kept in mind for possible implementation of this process in CO_2.

