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From Immobilization to Catalyst Use: a Complete Continuous-Flow Approach Towards the Use of Immobilized Organocatalysts

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Abstract: The combination of chiral supported-organocatalysts and flow chemistry promotes the sustainable production of enantioenriched compounds providing a very powerful tool for chemical and pharmaceutical industries. However, the rapid deactivation of these catalysts in heterogeneous asymmetric reactions has been limiting the expansion of the area. In this work we report for the first time the advantages of synthesizing, immobilizing, and using a silica-supported organocatalyst under a complete continuous-flow approach, showing the impact of this method on the morphology, structure and lifetime of the organocatyst. The first generation MacMillan's organocatalyst was prepared from L-phenylalanine and immobilized in silica through a carbamate linkage under batch and continuous-flow conditions. We also evaluated the performance of both batch and continuous-flow organocatalysts in the Diels-Alder reaction for proof of concept.

Introduction

Organocatalysis has emerged as one of the key tools for asymmetric synthesis, promoting high yields and enantioselectivities for chemical transformations.[1-4] Combined with ease of handling, chiral organocatalysts are also inexpensive to prepare and versatile, providing different modes of substrate activation and asymmetric induction, being employed in various types of reactions.[5-8] However, there are still some inherent problems with these reactions, such as the low turnover and the impossibility of recovering the catalyst.[9] To overcome these difficulties, some efforts have been made to support the organocatalysts in a range of solid materials, such as polymers or silica, affording heterogeneous reactions.[10-16] This strategy has allowed their usage in continuous-flow reactors, enabling a rapid continuous production of chiral substances and becoming organocatalysis an even greater tool for chemical and pharmaceutical industries.[17-21]

Despite the exponential growth of the field of asymmetric organocatalysis in the last decades and the advantages of merging it with flow chemistry, this area still remains little explored. In recent years, a small group of homogeneous and heterogeneous asymmetric reactions were successfully conducted under continuous-flow conditions, employing certain organocatalysts and modes of catalyst activation.[22],[23],[24] Nevertheless, one of the main limitations of these processes is the rapid deactivation of organocatalysts, reducing the efficiency of the transformations and impeding large-scale application. Undoubtedly, identifying the causes of the organocatalyst deactivation and solving this problem is an important challenge to be overcome for the continued expansion of the area.[25-28] Once the method used for organocatalyst immobilization can impact its performance, herein we report for the first time the advantages of synthesizing and immobilizing an organocatalyst under continuous-flow conditions and the impact of this method on the lifetime of the organocatalysts. For such, we chose the first generation MacMillan's organocatalyst and evaluated its performance in the enantioselective Diels-Alder reaction for proof of concept.

Results and Discussion

We started our investigation preparing the silica-supported organocatalyst **6a** in batch. The modified first generation MacMillan's organocatalyst **4** was easily synthesized from L-phenylalanine (**1**) after 3 steps and 38% overall yield (Scheme 1). Initially, the amino acid **1** was treated with thionyl chloride and methanol at room temperature for 24 hours to afford ester **2** in 97% yield, followed by reaction with ethanolamine at room temperature for 12 hours to formation of the corresponding amide **3** in 75% yield, introducing the hydroxyl group, essential for anchoring the organocatalyst on support matrix. Then, **3** was submitted to a cyclization with acetone in the presence of *p*-toluenesulfonic acid in isopropanol and reflux for 12 hours, providing the 4-imidazolidinone **4** in 53% yield.[29] The immobilization was performed after activation of hydroxyl group in **4** with 1,1'-carbonyldiimidazole (CDI) in the presence of triethylamine in dichloromethane at room temperature for 12 hours to furnish the intermediate **5** in 90% yield, followed by reaction with the commercial 3-aminopropyl-functionalized silica (particles size 40-63 μm, 1 mmol.g^{-1} NH_2 loading) and triethylamine in dichloromethane at room temperature for 72 hours leading to the desired silica-supported organocatalyst **6a** through a carbamate link with 55% of catalyst incorporation, determined by elemental analysis.

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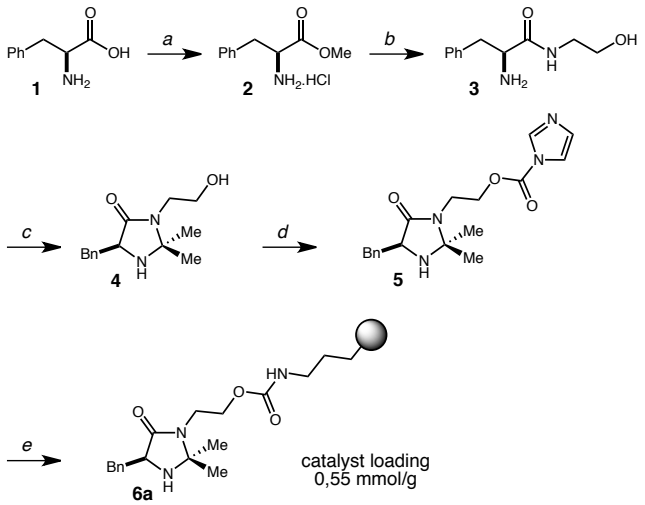


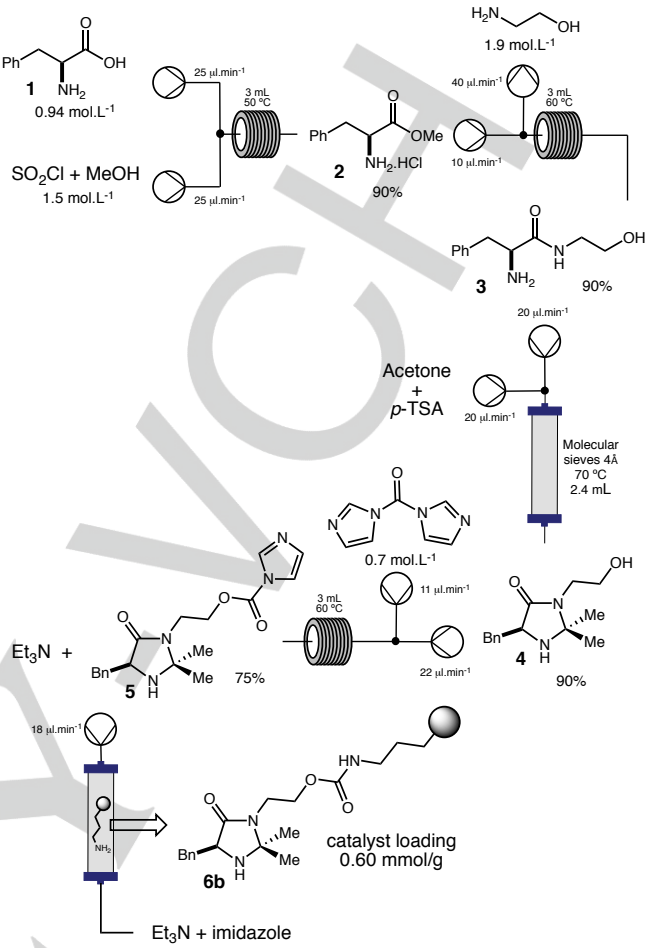
a. $SOCl_2$, MeOH, 0 °C - rt, 24 h, 97%; b. Ethanolamine, rt, 12 h, 75%; c. Acetone, *p*-TSA, *i*-PrOH, reflux, 12 h, 53%; d. CDI, Et_3N, CH_2Cl_2, 0ºC - rt, 12 h, 90%; e. H_2N , Et_3N, CH_2Cl_2, rt, 72 h, 55%.

Scheme 1. Synthesis and immobilization of organocatalyst **6b** in batch.

During the immobilization reaction we observed that gently and constant magnetic stirring and long reaction time were essential With the purpose of evaluating the differences between batch and continuous-flow conditions, the same organocatalyst was first synthesized and immobilized in a continuous-flow reactor (Scheme 2).

Under optimized conditions, the esterification of amino acid **1** was carried out at 50 °C in a 3 mL coil (1 hour residence time) with 90% yield, followed by the formation of ethanolamide **3** at 60 °C, also in a 3 mL coil (1 hour residence time) with same yield. The 4-imidazolidinone **4** was then obtained in 90% yield by reacting amide **3** in the presence of acetone and *p*-TSA through a 2.4 mL column containing 4 Å molecular sieves at 70 °C with a residence time of 1 hour. After that, the catalyst **5** was activated with CDI (3 mL coil) at 60 °C with a residence time of 1.5 hour in 75% yield and anchored in silica by pumping this intermediate and Et_3N in acetonitrile in a pumping rate of 18 $\mu L.min^{-1}$ through a 1.2 mL packed-bed reactor containing 3-aminopropyl-functionalized silica at room temperature with a residence time of 1.1 hours yielding the silica-supported organocatalyst **6b** with 60% of catalyst incorporation, determined by elemental analysis.

The synthesis of organocatalyst **5** was accomplished in 60 hours, 4 steps and 34% overall yield in batch, while under continuous-flow, the same steps have taken 4.5 hours and lead to an overall yield of 54%. The immobilization process was also affected by changing from batch to continuous-flow reactors, leading to a 40% reduction on reaction time (132 hours *versus* 52.5 hours), besides an improvement of 1.7 times on overall yield (18% in batch versus 32% under continuous-flow).



Scheme 2. Synthesis and immobilization of organocatalyst **6b** under continuous-flow.

In addition, to differences observed in supported catalyst production time and the process efficiency in general, we could also observe that organocatalysts **6a** and **6b**, respectively immobilized in batch and under continuous-flow conditions, have visually different aspects. While **6a** is a fine powder, **6b** has a larger particle size.

The morphological analysis of the commercial 3-aminopropyl-functionalized silica, organocatalyst **6a** and organocatalyst **6b** revealed that the immobilization under continuous-flow produces a material with a similar morphology to the commercial silica, while the material resulting from the batch process is very different. The SEM images in Figure 1 show that catalyst **6a** presents a more irregular distribution of particles than catalyst **6b**, indicating that silica mechanical degradation occurs in the batch process due to magnetic stirring, altering the matrix properties.

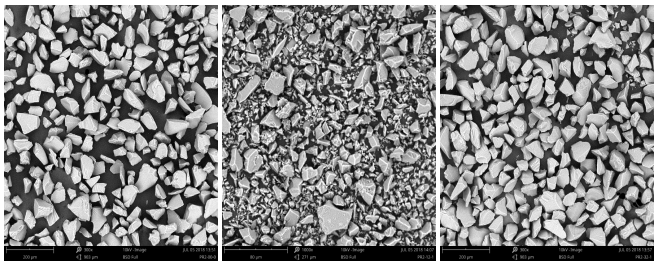


Figure 1. SEM images of commercial silica (left), organocatalyst **6a** (middle) and organocatalyst **6b** (right).

The degradation of support material may be responsible for shortening the lifetime of immobilized organocatalysts. There is a dichotomy in immobilization of the organocatalyst in batch: while vigorous stirring provides effective incorporation of the organocatalyst in matrix at shorter reaction times, degradation of the solid support is observed under this condition. For this reason, gently and constant magnetic stirring for 72 hours was the optimal condition for 55% of catalyst incorporation. In contrast, immobilization under continuous-flow conditions avoids degradation and provides silica-supported organocatalysts with homogeneous particle size at shorter times and 60% of catalyst incorporation, which seems to be the maximum possible incorporation in theses systems.

The organocatalyst **5** was characterized by solution ^{13}C NMR, but for immobilized organocatalysts solid state NMR spectroscopy must be used to this task, and has been used routinely for the characterization of hybrid silica containing organocatalysts.[30-32] Figure 2 shows solid state ^{13}C cross-polarization magic angle spinning (CPMAS) spectra of commercial 3-aminopropyl-functionalized silica and organocatalysts **6a** and **6b**.

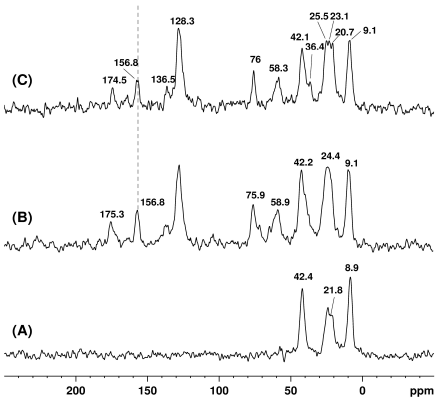
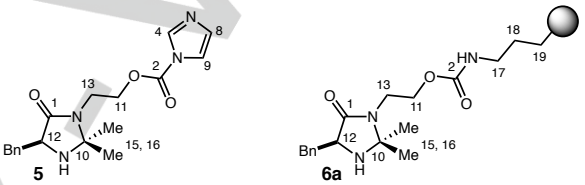


Figure 2. ^{13}C CPMAS solid state NMR spectra: (A) commercial silica; (B) silica-supported organocatalyst **6a**; (C) silica-supported organocatalyst **6b**.

It can be seen that the immobilization occurred, through the formation of the N-(C=O)-O carbamate linkage, whose was confirmed by the presence of the signal at 156.8 ppm in the ^{13}C spectra of batch-prepared **6a** (Figure 2, entry B) and continuous-flow prepared **6b** (Figure 2, entry C). Also benzyl imidazolidinone residue (C=O at 175 ppm, benzyl CH_2 at 36.4 ppm and benzyl C and CH at 136 and 128 ppm resp.) could be clearly seen in both spectra. The whole assignment is listed in Table 1. It is worth point out that although in the ^{13}C CPMAS spectrum of organocatalyst **6a** only one signal could be observed for the two methyl carbons and amine methylene carbon (at 24.4 ppm, Figure 2 entry B), in the spectrum of organocatalyst **6b** the signals due to benzyl methylene carbon and to the methyl groups are clearly resolved (Figure 2, entry C), confirming that the immobilization under continuous-flow produced a higher ordered material compared with batch route.

Table 1. ^{13}C NMR data.



carbon	type	Solution ^{13}C NMR (APT) catalyst **5**	Solid state ^{13}C CPMAS NMR catalyst **6a**; **6b**
1	N-C=O	174.91	174.5; 175.3
2	N-(C=O)-O	148.44	156.8
3	=C benzyl	136.39	136.5
4	N=CH-N	130.73	-
5,5'	=C benzyl	129.58	128.3
6,6'	=C benzyl	128.54	128.3
7	=C benzyl	128.29	128.3
8	C=N	126.94	-
9	C=N	117.10	-
10	**C**$(CH_3)_2$	76.00	75.9; 76.0

^{29}Si CPMAS solid state NMR spectra of those samples are shown in Figure 3. In the spectra of commercial silica and organocatalysts **6a** and **6b** (Figure 3), signals corresponding to T^2[C-SiO$(OH)_2$], T^3 [C-SiO_2(OH)], Q^2 [Si$O_2(OH)_2$], Q^3 [SiO_3(OH)] and Q^4 [SiO_4] can be clearly seen. Although cross polarization is not a quantitative pulse sequence, alterations in the Si moieties can be followed by measuring the $[(Q^2+Q^3)/Q^4]$ and T^2/T^3 ratios (Table 2).

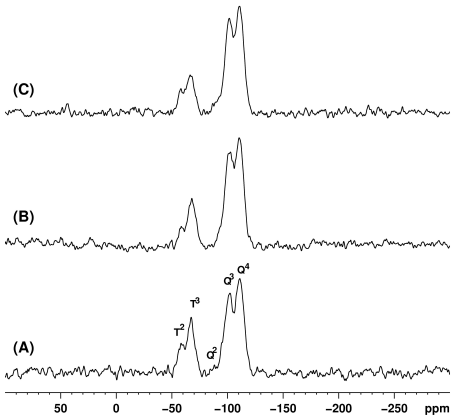


Figure 3. ^{29}Si CPMAS solid state NMR spectra: (A) commercial silica; (B) organocatalyst **6a**; (C) organocatalyst **6b**.

Table 2. ^{29}Si CPMAS NMR data.

entry[a]	T (C-Si) ppm	%	Q^2 $[Si(OSi)_2(OH)_2]$ ppm	%	Q^3 $[Si(OSi)_3(OH)]$ ppm	%	Q^4 $[Si(OSi)_4]$ ppm	%	$[(Q^2+Q^3)/Q^4]$	T^2/T^3
1	-58.3;-67.6	26.9	-94.7	4.6	-102.1	29.2	-110.9	39.2	0.86	0.34
2	-58.5;-67.8	22.6	-92.5	2.4	-100.6	34.8	-110.5	40.2	0.92	0.25
3	-56.7;-66.4	20.4	-92.1	3.6	-100.9	33.8	-109.8	42.1	0.89	0.49

a. (1) commercial silica, (2) organocatalyst **6a**, (3) organocatalyst **6b**.

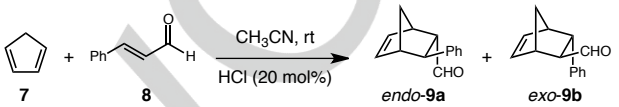
As can be observed in Table 2 and Figure 3, while $[(Q^2+Q^3)/Q^4]$ ratios are similar for commercial silica and organocatalysts **6a** and **6b**, T^2/T^3 ratios are quite different. Apparently, the functionalized surface of the silica has structural differences between **6a** and **6b**, where C-$SiO(OH)_2$ is more present than C-$SiO_2(OH)$ in organocatalysts immobilized under continuous-flow conditions. These evidences suggest that the type of immobilization in silica causes not only morphological but also structural differences in organocatalysts.

Subsequently, the performances of organocatalysts **6a** and **6b** were evaluated by running the enantioselective Diels-Alder reactions between cyclopentadiene (**7**) and *E*-cinnamaldehyde (**8**) both in batch and continuous-flow. Selected results for the batch experiments are summarized in Table 3.

The first reaction was carried out in acetonitrile employing 20 mol% of silica-supported organocatalyst **6a** in the presence of hydrochloric acid at room temperature and after 24 hours afforded a mixture of *endo* and *exo* cycloadducts **9a** and **9b** in high enantioselectivities but only 15% yield (Table 3, entry 1). The increase in reaction time to 48 and 72 hours provided better yields but slightly lower enantioselectivities (Table 3, entries 2 and 3). Afterwards, the catalyst **6a** used in the reaction by 72 hours was recycled and the products were surprisingly obtained in higher yields, but with a significant decrease in enantioselectivities (Table 3, entry 4).

The organocatalyst **6b** was also employed to activate the Diels-Alder reaction under the same conditions above and after 48 hours afforded a mixture of *endo* and *exo* cycloadducts in slightly higher yields and enantioselectivities than organocatalyst **6a** (Table 3, entry 5). Unexpectedly, the reactions with organocatalyst **6b** lead to lower yields and better enantioselectivities with longer reaction time and in the first recycle of organocatalyst (Table 3, entries 6 and 7).

Table 3. Diels-Alder reaction in batch.



7 **8** *endo*-**9a** *exo*-**9b**

entry	catalyst	loading	time	yield	*endo*:*exo*	*ee* (*endo*, *exo*)[b]	P[c]
1	**6a**	20 mol%	24 h	15%	54:46	80%, 86%	0.31
2	**6a**	20 mol%	48 h	52%	54:46	75%, 78%	0.54
3	**6a**	20 mol%	72 h	65%	54:46	78%, 82%	0.45
4	**6a**-recycle[a]	20 mol%	48 h	76%	52:48	64%, 78%	0.79
5	**6b**	20 mol%	48 h	56%	53:47	78%, 80%	0.58
6	**6b**	20 mol%	72 h	43%	54:46	83%, 81%	0.30
7	**6b**-recycle[a]	20 mol%	48 h	26%	53:47	82%, 83%	0.27

[a]First reuse after 72 h. [b]Determined by GC analysis using a chiral β-Dex 325 column (30 mm x 0.25 μm ID). [c]Productivity: mmol(product).h^{-1}.$mmol^{-1}$(catalyst).

Considering the best results in which the products **9a** and **9b** were obtained in both good yields and enantioselectivities, the productivities of organocatalysts **6a** and **6b** in batch were similar: 0.45 and 0.58 mmol(product).h^{-1}.$mmol^{-1}$(catalyst), respectively (Table 3, entries 3 and 5). The process of organocatalyst immobilization did not have a significant impact in these Diels-Alder reactions.

The responses of organocatalysts **6a** and **6b** in the activation of Diels-Alder in batch were just a little different. Organocatalyst **6a** showed an improvement in its efficiency with increasing time, while **6b** decreased it. Although the organocatalyst **6a** led to the products **9a** and **9b** with higher yields, the organocatalyst **6b** presented better enantioselectivities.

Following, the performances of organocatalysts **6a** and **6b** were evaluated by running the enantioselective Diels-Alder reactions between cyclopentadiene (**7**) and *E*-cinnamaldehyde (**8**) under continuous-flow conditions.

We started the investigation of these flow reactions using a looping system. In this process, the reaction was conducted in a continuous-flow reactor using a 0.7 mL packed-bed containing the silica-supported organocatalyst **6a**, under a flow rate of 3.8 μL.min^{-1} and residence time of 3 hours.

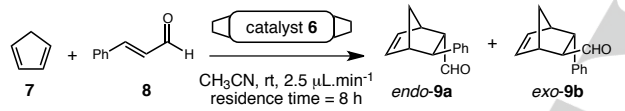
Before the solutions of the reagents were pumped, the silica-supported organocatalyst was treated with 0.4 M HCl solution in acetonitrile at room temperature for activation of the organocatalyst. Then cyclopentadiene (**7**) and aldehyde **8** in acetonitrile were pumped through the packed-bed reactor

containing the supported organocatalyst **6a** and the collected reaction mixture was recirculated through the loop system. After 48 hours, the cycloadducts **9a** and **9b** were obtained in 50% yield and 77% *ee* and 78% *ee*, with productivity of 0.50 mmol(product).h^{-1}.$mmol^{-1}$(catalyst). This result was very similar to the results found in batch (Table 3, entries 2 and 5).

Faced to that, the reactions were conducted in a continuous-flow reactor using a 1.2 mL packed-bed containing the silica-supported organocatalysts **6a** and **6b**, flow rate of 2.5 μL.min^{-1} and residence time of 8 hours, without recirculation of the reaction mixture. Since the immobilized organocatalysts **6a** and **6b** have different particle sizes, the 1.2 mL packed-bed reactor was totally filled with 0.25 mmol of **6a** (450 mg) and 0.35 mmol of **6b** (580 mg). The selected results are summarized in Table 4.

The silica-supported organocatalyst was also treated with 0.4 M HCl solution in acetonitrile for activation of the organocatalyst before the solutions of the reagents were pumped. After optimizations, it was observed the necessity for a conditioning time of 10 and 9 hours to achieve a steady-time regime of chemical and enantioselective activities of both organocatalysts **6a** and **6b**, respectively. The same was observed in batch conditions, since the reaction had very low yield in 24 hours, being necessary longer times to reach more efficiency.

Table 4. Diels-Alder reaction under continuous-flow.



7 **8** *endo*-**9a** *exo*-**9b**

entry	catalyst	t (h)	yield (%)	*dr endo:exo*	*ee endo:exo*[a]	P[b]
1	**6a**	11	60	54:46	86%, 89%	0.90
2	**6a**	13	64	54:46	85%, 89%	0.96
3	**6a**	14	67	54:46	87%, 89%	1.01
4	**6a**	18	70	54:46	86%, 89%	1.05
5	**6a**	20	70	54:46	84%, 87%	1.05
6	**6b**	10	73	54:46	90%, 87%	0.78
7	**6b**	15	89	54:46	89%, 91%	0.95
8	**6b**	36	97	54:46	86%, 79%	1.04
9	**6b**	42	92	53:47	80%, 70%	0.99
10	**6b**	57	95	53:47	78%, 69%	1.02
11	**6b**	64	89	53:47	71%, 59%	0.95
12	**6b**	81	97	52:48	62%, 48%	1.04

[a]Determined by GC analysis using a chiral β-Dex 325 column (30 mm x 0.25 μm ID).
[b]Productivity: mmol(product).h^{-1}.$mmol^{-1}$(catalyst).

After this conditioning time, the reaction using organocatalyst **6a** was able to produce the products **9a** and **9b** in yields from 60% to 70% with enantioselectivities from 84% to 89% for around 10 hours (Table 4, entries 1 to 5). However, after this time, a drastic drop in yields and enantioselectivities was observed. Then the column was treated again with 0.4 M HCl solution in acetonitrile, but low yields and enantioselectivities continued to be observed, indicating that there was an irreversible loss of catalyst activity, possibly influenced by chemical degradation of the support material.

In contrast, under the same conditions, the reaction employing organocatalyst **6b** was able to produce **9a** and **9b** in yields from 73% to 97% for 72 hours with enantioselectivities ranging from 80% to 90% for 26 hours and 48% to 80% for further 45 hours (Table 4, entries 6 to 12).

The productivities of organocatalysts **6a** and **6b** were very similar during the reactions under continuous-flow and the total productivity of both catalysts was 1.01 mmol(product).h^{-1}.$mmol^{-1}$(catalyst).

Although **6a** and **6b** have similar productivities, the organocatalyst **6b**, immobilized under continuous-flow conditions, has a lifetime 7 times greater than the organocatalyst **6a**, immobilized in batch. Analysing the results of table 2, it is clear that the conditions of immobilization process have a large influence in the time of deactivation of supported organocatalyst, showing that immobilization under continuous-flow conditions is the best choice for these silica-supported organocatalysts.

Besides, when we compare the results of enantioselective Diels-Alder reactions carried out under continuous-flow and batch, we observe higher enantioselectivities and productivities using the flow process. The productivities of flow experiments were 2 times higher then the ones of the batch experiments. We also observed that the flow reaction conditions leaded to simpler reaction mixtures, containing essentially the products and the starting materials, simplifying the purification steps.

Figure 4 shows solid state ^{13}C CPMAS spectra of recycled catalyst **6a** from the Diels-Alder batch reaction, recycled catalyst **6a** from the Diels-Alder continuous-flow reaction, recycled catalyst **6b** from the Diels-Alder batch reaction and recycled catalyst **6b** from the Diels-Alder continuous-flow reaction.

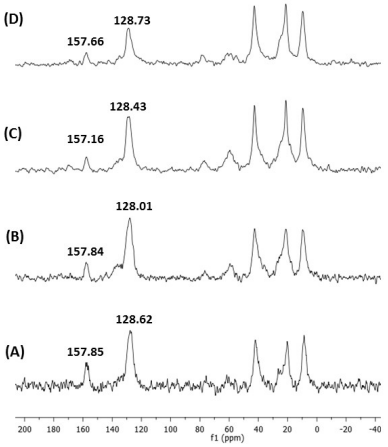


Figure 4. ^{13}C CPMAS solid state NMR spectra: (A) recycled **6a** from the batch reaction; (B) recycled **6a** from the continuous-flow reaction; (C) recycled **6b** from the continuous-flow reaction; (D) recycled catalyst **6b** from the batch reaction.

These spectra are comparable worse resolved than the spectra shown in Figure 3, with the signals broadened. Although the carbamate linkage can be clearly seen, the signal corresponding to the carbonyl group of imidazolidinone portion (around 175 ppm) has disappeared, evidencing some sort of organocatalyst degradation.

The recycled organocatalysts were also analyzed by ^{29}Si CPMAS solid state NMR (Figure 5). All recycled catalysts spectra showed an increase of the signals corresponding to Si-OH (-102 ppm) and $Si(OH)_2$ (-92 ppm), when compared with catalysts **6a** and **6b** spectra.

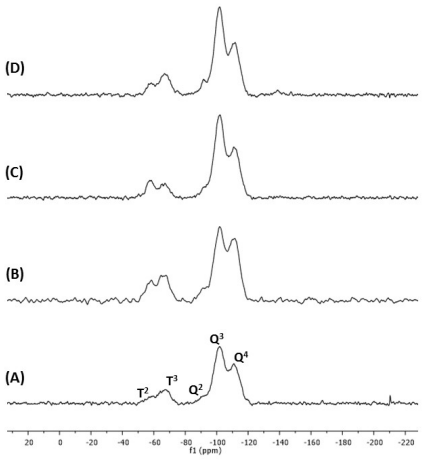


Figure 5. ^{29}Si CPMAS solid state NMR spectra: (A) recycled **6a** from the batch reaction; (B) recycled **6a** from the continuous-flow reaction; (C) recycled **6b** from the continuous-flow reaction; (D) recycled catalyst **6b** from the batch reaction.

The areas of these peaks were measured and $[(Q_2+Q_3)/Q_4]$ and T^2/T^3 ratios were calculated (Table 5). $[(Q_2+Q_3)/Q_4]$ ratio showed to increase from 0.89-0.92 (immobilized organocatalysts) to 1.34-1.87 (recycled organocatalysts), thus evidencing that part of ordered Si-O structure was lost. Besides, a larger increase from 0.49 (Table 2, entry 3 and Figure 3, entry C) to 1.15 (Table 5, entry 3 and Figure 5, entry C) in T^2/T^3 ratio of the recycled organocatalyst **6b** after 80 hours of use in Diels-Alder reaction under continuous-flow was observed. This means that after a long period of exposure to Diels-Alder reaction, in addition to the degradation of the catalyst structure observed in ^{13}C CPMAS, there is also an increase of C-$SiO(OH)_2$ and a decrease of C-$SiO_2(OH)$ contributing to deactivation of immobilized organocatalysts.

Table 5. ^{29}Si CPMAS NMR data.

entry[a]	T (C-Si)		Q^2 $[Si(OSi)_2(OH)_2]$		Q^3 $[Si(OSi)_3(OH)]$		Q^4 $[Si(OSi)_4]$		$[(Q^2+Q^3)/Q^4]$	T^2/T^3
	ppm	%	ppm	%	ppm	%	ppm	%		
1	-57.8;-67.0	14.7	-92.1	4.3	-102.2	48.6	-110.9	31.9	1.65	0.40
2	-58.1;-67.3	16.2	-91.2	3.3	-101.9	47.6	-110.9	31.8	1.34	0.36
3	-58.4;-67.1	15,7	-92.4	4.1	-102.1	50.0	-110.9	29.4	1.83	1.15
4	-58.4;-66.7	16.6	-92.3	5.8	-101.9	48.5	-111.6	28.9	1.87	0.34

a. (1) recycled **6a** from the batch reaction; (2) recycled **6a** from the continuous-flow reaction; (3) recycled **6b** from the continuous-flow reaction; (4) recycled catalyst **6b** from the batch reaction.

Conclusions

In conclusion, we observed improvements in overall yields and a large decrease in time during the synthesis and immobilization of organocatalyst under continuous-flow conditions when compared to the batch process. It has also leaded to a longer lifetime silica-supported organocatalyst, with morphological and structural differences. Finally, the Diels-Alder reactions conducted in continuous-flow reactors using the silica-supported organocatalyst showed higher yields, higher enantioselectivities and a simpler reaction mixture when compared to the batch process.

In the last decade, 4-imidazolidinones have been widely used in enantioselective reactions activated by enamine or iminium intermediates to promote various types of reactions such as conjugate Friedel-Crafts, aldehyde and ketone Diels-Alder, Mukaiyama-Michael reaction, conjugate hydride reduction, amination, oxygenation, sulphenylation, etc..[33] However, these applications have not yet been explored in flow chemistry and the expansion of this scope must be one of the challenges in this field.

Considering these aspects, the application of continuous-flow in processes of synthesis, immobilization and use of organocatalysts overcome the reported limitations and has a huge potential to increase exploration in this area.

Experimental Section

General Methods

Dry solvents were purchased and stored properly. All reactions were monitored by thin layer chromatography (TLC) using silica gel F_{254} pre-coated aluminium backed plates (250 μm thickness) and visualized using UV light or phosphomolibdic acid. Purifications were done by flash chromatography with silica gel (230-400 mesh). ^{1}H and ^{13}C NMR data were recorded at 25 ºC using Varian 400 MHz and 500 MHz spectrometer. Chemical shifts values (δ) are reported in part per million (ppm). Peak multiplicity is summarized as br (broad), s (singlet), d (doublet), t (triplet), m (multiplet). The *endo/exo* ratios was established on the purified product using the CHO signals at 9.59 ppm (*endo*) (**9a**) and 9.91 ppm (*exo*) (**9b**).^{13}C and ^{29}Si solid state NMR data were obtained using a Bruker Avance III400 WB (9.4T) and a Bruker DRX300 NB (7.05T) superconducting magnets, operating at Larmor frequencies of 100.5 MHz (for ^{13}C) and 59.3 MHz (for ^{29}Si), using a Bruker CPMAS probeheads and 4mm ZrO_2 rotors with Kel-F stoppers. Samples were powered on a mortar and packed into a rotors and spinning at 10 KHz and 5 KHz resp. ^{13}C spectra were acquired using cross polarization with ^{1}H amplitude 50-100 ramped, a contact pulse of 2.5 ms duration and recycle time of 3 s, whereas for ^{29}Si spectra the contact time was 4 ms and recycle time of 4 s. TPPM-15 ^{1}H decoupling was employed for both ^{13}C and ^{29}Si spectra. The spectra were referenced externally by using adamantane (CH_2 at 38.6 ppm) and caulinite (Q^3 at -91.5 ppm) for ^{13}C and ^{29}Si chemical shifts. Enatiomeric excess determinations for **9a** and **9b** were performerd by Chiral GC analysis on a Shimadzu GC-2010 chromatograph equipped with a FID, an AOC-20i auto sampler and a chiral β-Dex 325 (30 mm × 0.25 μm ID) column using hydrogen as carrier gas in 46 mL/min. Injector temperature was set at 200 ºC and detector temperature was set at 220 ºC. GC-FID temperature program: after 1 min at 115 ºC the temperature was increased in 15 ºC.min^{-1} to 140 ºC, then after 1 more min increased in 5 ºC.min^{-1} to 150 ºC and kept for 1 min until

increase again at 1 ºC.min^{-1} to 160 ºC to be kept at that temperature for 5 min. All reactions under continuous flow were performed using an Asia system, which consists of a syringe pump, liquid phase PTFE coil, a solid phase glass column reactor (Omnifit column; 900 PSI) and a heater. All equipment was purchased from Syrris. Scanning electron microscopy (SEM) was obtained by a Phenom Prox Desktop operating at 10 kV. Fourier-transform infrared spectroscopy (FTIR) analysis were acquired on a Shimadzu FTIR Spectrometer (IRPrestigie-21).

Synthesis and immobilization of organocatalyst in batch

Preparation of *(S)*-methyl 2-amino-3-phenylpropanoate hydrochloride (2):

A suspension of L-Phenylalanine (**1**) (10 g, 61 mmol) in methanol (70 mL) was cooled in an ice/water bath. Thionyl chloride (5.30 mL, 73 mmol) was added dropwise creating a clear solution that was kept stirring at room temperature for 24 h. Volatiles were removed *in vacuo* giving our L-phenylalanine methyl ester hydrochloride (**2**) as a white solid. (12.8 g, 98%).^{1}H NMR (400 MHz, CD_3OD): δ = 7.23 – 7.39 (m, 1H), 4.32 (t, *J* = 6.5 Hz, 1H, $CHNH_3$), 3.76 (s, 3H, OCH_3), 3.24 (d, *J* = 6.7 Hz, 2H $PhCH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.97, 133.98, 129.13, 128.73, 127.50, 53.88, 52.28, 35.91. IR = 2852, 2615, 1707 cm^{-1}. $[\alpha]_D^{25}$ = +36.4º (c = 2.0, EtOH).

Preparation of *(S)*-2-amino-N-(2-hydroxyethyl)-3-phenylpropanamide (3):

(S)-methyl 2-amino-3-phenylpropanoate hydrochloride (**2**) (10 g, 0,056 mmol) was dissolved in ethanolamine (23 mL, 371 mmol) with vigorous magnetic stirring, forming a deep yellow solution that was stirred at room temperature overnight. The reaction was then diluted in 100 mL of CH_2Cl_2 and washed with a 20% solution of K_2CO_3. The aqueous phase was extracted three times with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, and evaporated under vacuum, affording the pure amide **4** as a pale yellow solid (10.2 g, 85%). HRMS-ESI (*m/z*): found for $C_{11}H_{16}N_2O_2$ $[M+H]^+$: 209.1284 , $[M+Na]^+$: 231.1103. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.62 (s, 1H), 7.18 – 7.34 (m, -, Ar-H), 3.67 (t, *J* = 5.0 Hz, 2H, $C\underline{H}_2OH$), 3.61 (dd, *J* = 9.1, 4.3 Hz, 1H, $CHNH_2$), 3.40 (dd, *J* = 10.5, 5.5 Hz, 2H, $NHC\underline{H}_2$), 3.23 (dd, *J* = 13.7, 4.2 Hz, 1H, $PhCH_2$), 2.73 (dd, *J* = 13.7, 9.1 Hz, 1H, $PhCH_2$).^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.42, 137.71, 129.27, 128.69, 126.85, 77.35, 77.09, 76.84, 61.75, 56.52, 42.11, 41.13. IR = 3352, 2939, 1640 cm^{-1}. $[\alpha]_D^{25}$ = +15.4º (c = 1.0, MeOH).

***(S)*-5-benzyl-3-(2-hydroxyethyl)-2,2-dimethylimidazolidin-4-one hydrochloride (4):**

(S)-2-amino-N-(2-hydroxyethyl)-3-phenylpropanamide (**3**) (3.4 g, 16.4 mmol) was dissolved under magnetic stirring in a mixture of propanone (16 mL, 215 mmol) and isopropanol (22 mL) containing p-TSA (0.085 g, 0.49 mmol). The reaction was refluxed overnight under argon atmosphere with a Dean-Stark trap, and then evaporated *in vacuo* to form a deep yellow oil. This oil was dissolved in MeOH (10 mL) and the mixture was cooled in an ice-bath for the dropwise addition of acetyl chloride (3 mL, 42 mmol). Under vigorous stirring, cold ethyl ether was added until turbidity of reaction media. The stirring was continued for 1 h at room temperature and the product **4** obtained as a white solid after vacuum filtered and washed with Et_2O. (2.8 g, 85%). HRMS-ESI (*m/z*): found for $C_{14}H_{20}N_2O_2$ $[M+H]^+$: 249.1597 , $[M+Na]^+$: 271.1416. ^{1}H NMR (500 MHz, CD_3OD) δ = 7.29 – 7.47 (m, 5H, Ar-H), 4.66 (dd, *J* = 10.5, 2.7 Hz, 1H, CH), 3.74 (m, 2H, NCH_2CH_2), 3.48 – 3.59 (m, 2H, NCH_2CH_2), 3.43 (dd, *J* = 13.2, 7.0 Hz, 1H, HCH), 3.02 – 3.14 (m, 1H, HCH), 1.78 (s, 3H, CH_3), 1.63 (s, 3H, CH_3). ^{13}C NMR (101 MHz, CD_3Cl_3) δ = 175.46, 136.73, 129.46, 128.58, 126.90, 76.58, 61.25, 58.78, 43.49, 36.98, 27.70, 26.36. IR = 2852, 2283, 1670 cm^{-1}. $[\alpha]_D^{25}$ = -76.6º (c = 1.0, MeOH).

Preparation of *(S)*-2-(4-benzyl-2,2-dimethyl-5-oxoimidazolidin-1-yl)ethyl 1H-imidazole-1-carboxylate (5):

A stirred portion of imidazolidinone **4** (0.43 g, 1.5 mmol) in CH_2Cl_2 (3 mL) was dissolved after dropwise addition of triethylamine (0.21 mL, 1.5 mmol). The resulting mixture was then slowly added to a 25 mL round bottomed flask containing a solution of 1,1'-carbonyldiimidazole (0.40 mg 2.46 mmol) in CH_2Cl_2 (3 mL) and triethylamine (0.21 mL, 1.5 mmol). The reaction was stirred for 24 h at room temperature and then concentrated in vacuum. Saturated $NaHCO_3$ was added to the crude mixture and extracted with AcOEt (3x 20 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuum giving a light brown oil (0.46 g, 90%). HRMS-ESI (*m/z*): found for $C_{18}H_{22}N_4O_3$ $[M+H]^+$: 343.1765 , $[M+Na]^+$: 365.1584. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.07 (s, 1H, Ar-H), 7.38 (t, *J* = 1.4 Hz, 1H, Ar-H), 7.15 – 7.25 (m, 5H, Ar-H), 7.07 (dd, *J* = 1.6, 0.8 Hz, 1H), 4.43 – 4.55 (m, 2H, NCH_2CH_2), 3.78 – 3.83 (m, 1H, CH), 3.71 (dt, *J* = 14.6, 5.5 Hz, 1H, HCH), 3.30 (ddd, *J* = 14.6, 7.0, 5.5 Hz, 1H, HCH), 3.08 (qd, *J* = 14.2, 5.4 Hz, 2H, NCH_2CH_2), 1.28 (s, 3H, CH_3), 1.14 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.91, 148.44, 136.39, 130.73, 129.58, 128.54, 128.29, 126.91, 117.10, 76.00, 65.24, 58.64, 38.96, 36.68, 27.90, 26.41. IR = 2974, 1759, 1693 cm^{-1}. $[\alpha]_D^{25}$ = -34.6º (c = 1.0, MeOH).

Preparation of silica-supported organocatalyst 6a:

The aminopropyl functionalized silica (1.12 g 1.12 mmol) was added to a solution of *(S)*-2-(4-benzyl-2,2-dimethyl-5-oxoimidazolidin-1-yl)ethyl-1*H*-imidazole-1-carboxylate (**5**) (460 mg 1.35 mmol) in CH_2Cl_2. Thereafter triethylamine (0.21 ml 1.5 mmol) was added and the reaction mixture kept stirring at 150 rpm for 72 h at room temperature to furnish the catalyst **6a** as a white solid. The product is obtained by filtration of the crude mixture, washed with CH_2Cl_2 (2x 10 mL) and dried under high vacuum. (Catalyst loading 0.564 mmol/g, by CHN analysis) ^{13}C NMR (101 MHz) δ = 174.5, 156.8, 136.5, 128.3, 128.3, 128.3, 75.9, 58.9, 58.9, 42.2, 42.2, 42.2, 24.4, 24.4, 24.4, 9.1. CHN analysis**:** C: 10.37%, H: 1.52%, N: 2.37%.

Synthesis and immobilization of organocatalyst under continuous-flow

Preparation of *(S)*-methyl 2-amino-3-phenylpropanoate hydrochloride (2):

In different tubes, a solution of L-phenylalanine (**1**) (0.94 mol.L^{-1}) and thionyl chloride (1.5 mol.L^{-1}) were prepared in methanol. Both solutions were pumped employing a Syrris Asia system at 25 μL/min, mixed by a T mixer and reacted into PTFE reactor coil (3 mL) heated around 50 ºC during 1 h. The solution obtained was concentrated *in vacuo* giving our product **2** as a white solid. (0.24 g, 80%).^{1}H NMR (400 MHz, CD_3OD) δ = 7.23 – 7.39 (m, 1H), 4.32 (t, *J* = 6.5 Hz, 1H, $CHNH_3$), 3.76 (s, 3H, OCH_3), 3.24 (d, *J* = 6.7 Hz, 2H $PhCH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.97, 133.98, 129.13, 128.73, 127.50, 53.88, 52.28, 35.91. IR = 2852, 2615, 1707 cm^{-1}. $[\alpha]_D^{25}$ = +36.4º (c = 2.0, EtOH)

Preparation of *(S)*-2-amino-N-(2-hydroxyethyl)-3-phenylpropanamide (3):

In different tubes, a solution of *(S)*-methyl 2-amino-3-phenylpropanoate (**2**) (0.33 mol.L^{-1}) in isopropyl alcohol and a solution of ethanolamine (1.9 mol.L^{-1}) was prepared in the same solvent. Both solution were pumped at

10 μl/min and 40 μl/min, respectively, mixed in a T-mixer and reacted into a 3 mL PTFE reactor coil heated around 60 ºC during 1 h. The solution obtained was concentrated *in vacuo,* followed by dilution with 20 mL of CH_2Cl_2 and extraction with a 20% solution of K_2CO_3.The aqueous phase was extracted three times with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and evaporated under vacuum, affording the pure amide **3** as a pale yellow solid (0.12 g, 92%). HRMS-ESI (*m/z*): found for $C_{11}H_{16}N_2O_2$ $[M+H]^+$: 209.1284 , $[M+Na]^+$: 231.1103. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.62 (s, 1H), 7.18 – 7.34 (m, 5H, Ar-H), 3,67 (t, *J* = 5.0 Hz, 2H, C$\underline{H}_2$OH), 3.61 (dd, *J* = 9.1, 4.3 Hz, 1H, C$\underline{H}$NH$_2$), 3.40 (dd, *J* = 10.5, 5.5 Hz, 2H, NHC$\underline{H}_2$), 3.23 (dd, *J* = 13.7, 4.2 Hz, 1H, PhC$\underline{H}_2$), 2.73 (dd, *J* = 13.7, 9.1 Hz, 1H, PhC$\underline{H}_2$) ^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.42, 137.71, 129.27, 128.69, 126.85, 77.35, 77.09, 76.84, 61.75, 56.52, 42.11, 41.13. = 3352, 2939, 1640 cm^{-1} $[\alpha]_D^{25}$ = +15.4º (c = 1.0, MeOH).

(*S*)-5-benzyl-3-(2-hydroxyethyl)-2,2 dimethylimidazolidin-4-one hydrochloride (4):

A solution of *(S)*-2-amino-N-(2-hydroxyethyl)-3-phenylpropanamide (**3**) in isopropranol (0.5 mol.L^{-1}) and in a different tube, a solution of *p*-TSA were prepared in acetone (1.9x10^{-3} mol.L^{-1}). Both solutions were pumped at 20 μl.min^{-1}, mixed in a T-mixed and reacted into an Omnifit glass column (2,4 mL) filled with dry molecular sieves at 80 ºC during 1h. The system is also adapted with a backpressure device on its end. The mixture obtained was concentrated under vacuum to give a light brown oil. The oil was diluted with MeOH (1.5 mL) and kept at 0 ºC for the addition of acetyl chloride (0.28 mL). The warm solution was diluted with Et_2O (15 mL) slowly under vigorous stirring, to give a suspension of white crystals. After being stirred for 1h, the suspension was filtered by vacuum, washed with Et_2O and dried at room temperature to give **4** as a white powder (0.33 g, 77 %). HRMS-ESI (*m/z*): found for $C_{14}H_{20}N_2O_2$ $[M+H]^+$: 249.1597 , $[M+Na]^+$: 271.1416. ^{1}H NMR (500 MHz, CD_3OD) δ = 7.29 – 7.47 (m, 5H, Ar-H), 4.66 (dd, *J* = 10.5, 2.7 Hz, 1H, CH), 3.74 (m, 2H, NCH_2CH_2), 3.48 – 3.59 (m, 2H, NCH_2CH_2), 3.43 (dd, *J* = 13.2, 7.0 Hz, 1H, HCH), 3.02 – 3.14 (m, 1H, HCH), 1.78 (s, 3H, CH_3), 1.63 (s, 3H, CH_3). ^{13}C NMR (101 MHz, CD_3Cl_3) δ = 175.46, 136.73, 129.46, 128.58, 126.90, 76.58, 61.25, 58.78, 43.49, 36.98, 27.70, 26.36. IR = 2852, 2283, 1670 cm^{-1} $[\alpha]_D^{25}$ = -76.6º (c = 1.0, MeOH).

Preparation of (*S*)-2-(4-benzyl-2,2-dimethyl-5-oxoimidazolidin-1-yl)ethyl 1H-imidazole-1 carboxylate (5)

A solution of *(S)*-5-benzyl-3-(2-hydroxyethyl)-2,2-dimethylimidazolidin-4-one hydrochloride (**4**) (0.25 mol.L^{-1}) with thiethylamine (0.25 mol.L^{-1}) were dissolved in CH_3Cl and another solution of 1,1'-carbonyldiimidazole (0.70 mol.L^{-1}) were prepared in the same solvent. Each solution were pumped at 11 μl.min^{-1} and 22 μl.min^{-1}, respectively, into a PTFE coil (3 mL) adapted with a backpressure device and heated around 60 °C during 1.5 h. The mixture obtained was concentrated in vacuum, diluted with $NaHCO_3$ and extracted with AcOEt (3x20 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuum to yield the pure product **5** as a light brown oil. (0.96 g, 75%). HRMS-ESI (*m/z*): found for $C_{18}H_{22}N_4O_3$ $[M+H]^+$: 343.1765 , $[M+Na]^+$: 365.1584. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.07 (s, 1H, Ar-H), 7.38 (t, *J* = 1.4 Hz, 1H, Ar-H), 7.15 – 7.25 (m, 5H, Ar-H), 7.07 (dd, *J* = 1.6, 0.8 Hz, 1H), 4.43 – 4.55 (m, 2H, NCH_2CH_2), 3.78 – 3.83 (m, 1H, CH), 3.71 (dt, *J* = 14.6, 5.5 Hz, 1H, HCH), 3.30 (ddd, *J* = 14.6, 7.0, 5.5 Hz, 1H, HCH), 3.08 (qd, *J* = 14.2, 5.4 Hz, 2H, NCH_2CH_2), 1.28 (s, 3H, CH_3), 1.14 (s, 3H, CH_3) ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.91, 148.44, 136.39, 130.73, 129.58, 128.54, 128.29, 126.91, 117.10, 76.00, 65.24, 58.64, 38.96, 36.68, 27.90, 26.41. IR = 2974, 1759, 1693 cm^{-1}. ^{1} $[\alpha]_D^{25}$ = -34.6º (c = 1.0, MeOH).

Preparation of silica-supported organocatalyst 6b:

A 1.2 mL stainless steel column was filled with 590 mg of the commercially available 3-aminopropyl-functionalized silica gel particles (loading 1mmol/g NH_2), and packed with CH_3CN for 30 min (200 μl.min^{-1}). Thereafter, a 3.8 mL solution of *(S)*-5-benzyl-3-(2-hydroxyethyl)-2,2-dimethylimidazolidin-4-one hydrochloride **5** (2.27x10^{-1}mol.L^{-1}) with triethylamine (0.24 mol.L^{-1}) in CH_3CN was pumped through the reactor at 18 μl.min^{-1}. The reaction was performed in a looping fashion during 48 h at room temperature. At the end of the process, the column was washed with CH_3CN for more 30 min and then opened to yield the supported organocatalyst **6b** as a white solid. The organocatalyst was filtered, washed with CH_2Cl_2 (2x10 mL) and dried under high vacuum. (Catalyst loading 0.597 mmol/g, by CHN analysis) ^{13}C NMR (101 MHz) δ = 175.3, 156.8, 136.5, 128.3, 128.3, 128.3, 76.0, 58.3, 58.3, 42.1, 42.1, 36.4, 25.5, 23.1, 20.7, 9.1. CHN analysis: C: 11.05%, H: 1.62%, N: 2.51%.

Enantioselective Diels-Alder reactions in batch

(1*S*,2*S*,3*S*,4*R*)-3-Phenylbicyclo [2.2.1]hex-5-ene-2-carboxaldehyde (9a) and (1*R*,2*S*,3*S*,4*S*)-3-Phenylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde (9b).

The supported catalyst **6a** (330 mg, loading 0.564 mmol/g) or **6b** (330 mg, loading 0.597 mmol/g) hydrochloric acid (0,4 M 0.4 mL) and *(E)*-cinnamaldehyde (**8**) (110 ml 0.9 mmol) in 3 mL of CH_3CN were mixed and stirred for 5 min before the addition of cyclopentadiene (**7**) (740 ml 8.8 mmol). After stirring the reaction at room temperature for 48 h or 72 h, the supported catalyst was isolated by filtration. The filtrate is evaporated under high vacuum followed by purification through flash chromatography (10 % AcOEt/Hexane) to afford the title compound as a light yellow oil. Retention time: t_R (*exo*-minor) = 15.8 min, t_R (*exo*-major) = 16.1 min, t_R (*endo*-minor) = 16.5 min, t_R (*endo*-major) = 16.9 min. Data for *endo*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 2.1 Hz, 1H, CHO), 7.33 – 7.12 (m, 5H, Ar-H), 6.41 (dd, *J* = 5.4, 3.3 Hz, 1H, HC=CH), 6.17 (dd, *J* = 5.6, 2.7 Hz, 1H, HC=CH), 3.32 (brs, 1H, CHCH=CHCH), 3.12 (brs, 1H, CHCH=CHCH), 3.08 (d, *J* = 4.7 Hz, 1H, CHPh), 2.98 (dd, *J* = 4.4, 2.6 Hz, 1H, CHCHO), 1.80 (d, *J* = 8.7 Hz, 1H, CHH), 1.55 (dd, *J* = 8.8, 1.5 Hz, 1H, CHH). Data for *exo:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (d, *J* = 2.1 Hz, 1H, CHO), 7.33 – 7.12 (m, 5H, Ar-H), 6.33 (dd, *J* = 5.2, 3.3 Hz, 1H, HC=CH), 6.07(dd, *J* = 5.2, 2.6 Hz, 1H, HC=CH), 3.72 (t, *J* = 3.9 Hz 1H, CHCH=CHCH), 3.22 (m, 2H, CHCH=CHCH, CHPh), 2,59 (dd, *J* = 3.5, 1.8 Hz, 1H, CHCHO), 1.63 – 1.60 (dd, 2H, *J* = 7.0, 5.4 Hz, 1H, CHH).

Enantioselective Diels-Alder reactions under continuous-flow

Looping Reaction for (1*S*,2*S*,3*S*,4*R*)-3-Phenylbicyclo [2.2.1]hex-5-ene-2-carboxaldehyde (9a) and (1*R*,2*S*,3*S*,4*S*)-3-Phenylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde (9b).

A 0,7 mL stainless steel column was filled with 200 mg of the supported catalyst **6a** (loading 0.564 mmol/g) packed with CH_3CN and then flow treated with HCl (0,4 M in 5 mL of CH_3CN). The Diels-Alder reaction was then carried out at room temperature for 48 h by pumping a CH_3CN solution of *(E)*-Cinnamaldehyde (**8**) (0.24 mol.L^{-1}) and Cyclopentadiene (**7**) (3.52 mol.L^{-1}) at 3.8 μl.min^{-1} directly to the vial containing the starting materials.

(1*S*,2*S*,3*S*,4*R*)-3-Phenylbicyclo [2.2.1]hex-5-ene-2-carboxaldehyde (9a) and (1*R*,2*S*,3*S*,4*S*)-3-Phenylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde (9b).

A 1,2 mL stainless steel column was filled with 450 mg of organocatalyst **6a** (loading 0.564 mmol/g) or 580 mg of organocatalyst **6b** (loading 0.597 mmol/g), packed with CH_3CN and then flow treated with HCl (0,4 M in 5 mL of CH_3CN). The Diels-Alder reaction was carried out at room temperature by pumping a CH_3CN solution of *(E)*-cinnamaldehyde (**8**) (0.24 mol.L^{-1}) and cyclopentadiene (**7**) (3.52 mol.L^{-1}) at 2.5 µl.min^{-1}. After 24h of operation, the flow was stopped, and our vial recharged with freshly distilled cyclopentadiene (**7**) and cinnamaldehyde (**8**). Retention time: t_R (*exo*-minor) = 15.8 min, t_R (*exo*-major) = 16.1 min, t_R (*endo*-minor) = 16.5 min, t_R (*endo*-major) = 16.9 min. Data for *endo*: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.59 (d, *J* = 2.1 Hz, 1H, CHO), 7.33 – 7.12 (m, 5H, Ar-H), 6.41 (dd, *J* = 5.4, 3.3 Hz, 1H, HC=CH), 6.17 (dd, *J* = 5.6, 2.7 Hz, 1H, HC=CH), 3.32 (brs, 1H, CHCH=CHCH), 3.12 (brs, 1H, CHCH=CHCH), 3.08 (d, *J* = 4.7 Hz, 1H, CHPh), 2.98 (dd, *J* = 4.4, 2.6 Hz, 1H, CHCHO), 1.80 (d, *J* = 8.7 Hz, 1H, CHH), 1.55 (dd, *J* = 8.8, 1.5 Hz, 1H, CHH). Data for *exo:* ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.91 (d, *J* = 2.1 Hz, 1H, CHO), 7.33 – 7.12 (m, 5H, Ar-H), 6.33 (dd, *J* = 5.2, 3.3 Hz, 1H, HC=CH), 6.07(dd, *J* = 5.2, 2.6 Hz, 1H, HC=CH), 3.72 (t, *J* = 3.9 Hz 1H, CHCH=CHCH), 3.22 (m, 2H, CHCH=CHCH, CHPh), 2.59 (dd, *J* = 3.5, 1.8 Hz, 1H, CHCHO), 1.63 – 1.60 (dd, 2H, *J* = 7.0, 5.4 Hz, 1H, CHH).

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Keywords: heterogeneous catalysis • enantioselective organocatalysis • continuous-flow • supported organocatalyst • MacMillan's organocatalysts

[1] P. I. Dalko, L. Moisan, *Angew. Chem., Int. Ed.* **2004**, *43*, 5138-5175.
[2] J. Alemán, S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774-793.
[3] B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jorgensen, *Angew. Chem., Int. Ed.* **2015**, *54*, 13860-13874.
[4] Y. Qin, L. Zhu, S. Luo, *Chemical Reviews* **2017**, *117*, 9433-9520.
[5] D. W. C. MacMillan, *Nature* **2008**, *455*, 304-308.
[6] C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167-178.
[7] V. Marcos, J. Aleman, *Chem. Soc. Rev.* **2016**, *45*, 6812-6832.
[8] M. Silvi, P. Melchiorre, *Nature* **2018**, *554*, 41-49.
[9] S. Y. Park, J.-W. Lee, C. E. Song, *Nat. Comm.* **2015**, *6*, 7512-7512.
[10] E. Alza, S. Sayalero, P. Kasaplar, D. Almaşi, M. A. Pericàs, *Chem. - Eur. J.* **2011**, *17*, 11585-11595.
[11] S. Guizzetti, M. Benaglia, J. S. Siegel, *Chem. Commun. (Cambridge, U. K.)* **2012**, *48*, 3188-3190.
[12] L. Osorio-Planes, C. Rodriguez-Escrich, M. A. Pericas, *Org. Lett.* **2012**, *14*, 1816-1819.
[13] A. M. Goldys, M. G. Núñez, D. J. Dixon, *Org. Lett.* **2014**, *16*, 6294-6297.
[14] A. M. P. Salvo, F. Giacalone, R. Noto, M. Gruttadauria, *ChemPlusChem* **2014**, *79*, 857-862.
[15] J. Xu, J. Pang, D. Feng, X. Ma, *Mol. Cat.* **2017**, *443*, 139-147.
[16] G. Szőllősi, V. Kozma, *ChemCatChem* **2018**, *10*, 4362-4368.
[17] L. Malet-Sanz, F. Susanne, *J. Med. Chem.* **2012**, *55*, 4062-4098.
[18] R. Porta, F. Coccia, R. Annunziata, A. Puglisi, *ChemCatChem* **2015**, *7*, 1490-1499.
[19] R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2-25.
[20] D. Ragno, G. Di Carmine, A. Brandolese, O. Bortolini, P. P. Giovannini, A. Massi, *ACS Catalysis* **2017**, *7*, 6365-6375.
[21] J. Lai, S. Sayalero, A. Ferrali, L. Osorio-Planes, F. Bravo, C. Rodriguez-Escrich, M. A. Pericas, *Adv. Synth. Catal.* **2018**, *360*, 2914-2924.
[22] I. Atodiresei, C. Vila, M. Rueping, *ACS Catalysis* **2015**, *5*, 1972-1985.
[23] F. G. Finelli, L. S. M. Miranda, R. O. M. A. de Souza, *Chem. Commun. (Cambridge, U. K.)* **2015**, *51*, 3708-3722.
[24] C. Rodríguez-Escrich, M. A. Pericàs, *Eur. J. Org. Chem.* **2015**, *2015*, 1173-1188.
[25] E. Alza, M. A. Pericàs, *Adv. Synth. Catal.* **2009**, *351*, 3051-3056.
[26] V. Chiroli, M. Benaglia, F. Cozzi, A. Puglisi, R. Annunziata, G. Celentano, *Org. Lett.* **2013**, *15*, 3590-3593.
[27] A. Puglisi, M. Benaglia, R. Annunziata, V. Chiroli, R. Porta, A. Gervasini, *J. Org. Chem.* **2013**, *78*, 11326-11334.
[28] R. Porta, M. Benaglia, V. Chiroli, F. Coccia, A. Puglisi, *Isr. J. Chem.* **2014**, *54*, 381-394.
[29] T. E. Kristensen, K. Vestli, M. G. Jakobsen, F. K. Hansen, T. Hansen, *J. Org. Chem.* **2010**, *75*, 1620-1629.
[30] S. D. T. Barros, A. V. Coelho, E. R. Lachter, R. A. S. San Gil, K. Dahmouche, M. I. P. Silva, A. L. F. Souza, *Renewable Energy* **2013**, *50*, 585-589.
[31] E. C. C. Gomes, A. F. de Sousa, P. H. M. Vasconcelos, D. Q. Melo, I. C. N. Diógenes, E. H. S. de Sousa, R. F. do Nascimento, R. A. S. San Gil, E. Longhinotti, *Chem. Eng. J.* **2013**, *214*, 27-33.
[32] A. L. De Lima, A. Mbengue, R. A. S. San Gil, C. M. Ronconi, C. J. A. Mota, *Catal. Today* **2014**, *226*, 210-226.
[33] Y. Qin, L. Zhu, S. Luo, *Chem. Rev.* **2017**, *117*, 9433-9520.

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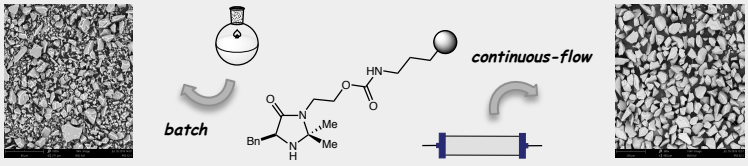

A major issue of silica-supported organocatalysts is the degradation of the solid material and the erosion of the matrix properties during its immobilization and usage in batch. In this work, we report for the first time, the advantages of a complete continuous-flow approach towards the synthesis, immobilization and use of MacMillan's silica-supported organocatalyst.

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