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Continuous-Flow Stereoselective Organocatalyzed Diels–Alder Reactions in a Chiral Catalytic "Homemade" HPLC Column

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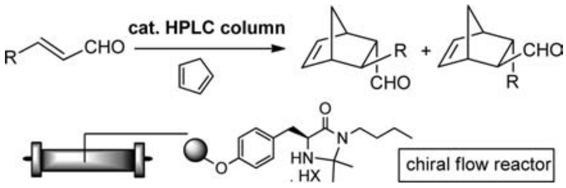
ABSTRACT



Continuous-flow organocatalyzed Diels–Alder reactions have been performed with excellent enantioselectivity for the first time in a chiral "homemade" HPLC column, packed with silica on which a MacMillan catalyst has been supported by a straightforward immobilization procedure. The versatility of the system was also proven by running with the same column continuous-flow stereoselective reactions with three different substrates, showing that the catalytic reactor may efficiently work *in continuo* for more than 150 h; the regeneration of the HPLC column was also demonstrated, allowing to further extend the activity of the reactor to more than 300 operating hours.

Recent progress in flow chemistry techniques using mini- and microflow reactors has opened a new era in chemical synthesis;[1] the use of reactors in combination with supported reagents, scavengers,[2] and catalysts has found widespread application, allowing a rapid continuous production of chemicals with minimum purification. In particular, the heterogenized catalysts can potentially provide easily reusable solid active species; simplification of the reaction workup and recovery and recycling of the precious chiral catalyst represent the more important aspects of the immobilization process of an enantiomerically pure catalyst.[3] If supported chiral catalysts are used in combination with continuous-flow methodologies, the reaction and the product separation are performed simultaneously; additionally, in flow processes, no mechanical stirring is required, thus avoiding the problem of mechanical degradation of the support material that may lead to shortened lifetimes of the immobilized catalysts.

The incorporation of immobilized catalysts in a flow system[4] would broaden the general applicability of flow chemical processes and would facilitate the conversion of laboratory-based flow chemistry experiments to the

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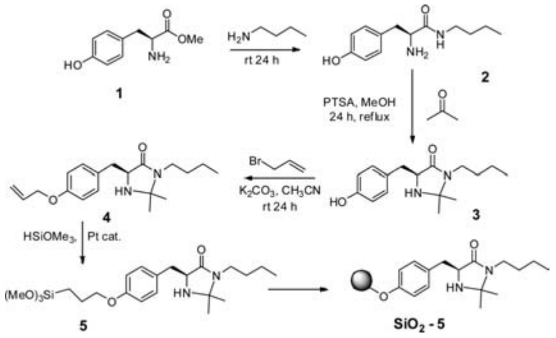
production scale.[5] Therefore, it is not surprising that the use of achiral catalysts under flow conditions recently has been the subject of many studies.[6]

However, much less is known of the use of chiral supported catalysts under flow conditions.[7] The past decade has witnessed an incredibly intense activity focused onto the use of different chiral organometallic catalysts under flow conditions,[8] but only a few examples of chiral organocatalysts were investigated. After the pioneering work by Lectka with polystyrene-immobilized cinchona alkaloid derivatives,[9] in the very past few years, Pericas has reported the use of polymer-supported proline,[10] and prolinol derivatives[11] under flow conditions, showing the great potentialities of the methodology.

In all of these works, packed-bed reactors, filled with a resin-supported catalyst, were used. Nonhomogeneous packing of the reactor, with formation of stagnation zones and hot spots, no control of fluid dynamics, and the problems related to the resin swelling properties are the main drawbacks of those systems. It is also worth mentioning that organocatalyzed reactions in flow are so far limited almost exclusively to proline derivatives and substrate activation via enamine intermediates.[12]

We decided to study the immobilization of chiral imidazolidinones[13] on silica gel, thus expanding the class of chiral organocatalysts used in reactors under continuous-flow conditions and overcoming the problems inherent to a polymeric support. In the intent to make the approach even more appealing and immediately accessible to every synthetic chemist, we decided to use as support commercially available silica, without any modification or special functionalization.[14]

Scheme 1. Synthesis of the Silica-Supported Chiral Catalyst



A properly modified MacMillan-type catalyst was easily prepared in three steps and a single purification; starting from (*S*)-tyrosine methyl ester **1**, imidazolidinone **3** was easily obtained in 77% yield by *N*-butyl amide **2** formation, followed by treatment with acetone (Scheme 1). Reaction with allyl bromide allowed introducing the carbon–carbon double bond, instrumental to catalyst immobilization.[15] Platinum-catalyzed hydrosilylation of **4** with trimethoxysilane led to the enantiopure trialkoxysilane **5** in 99% yield, which was attached to silica particles by a standard grafting process to afford the supported MacMillan-type catalyst **SiO_2-5**.[16]

In the present preliminary study, two different types of commercially available silica were used as supports (particle sizes of 8 and 10 μm). Materials, of different morphological properties, were purchased from different companies. For Apex Prepsil Silica Media 8 μm (Grace Davison - Discovery Sciences; asymmetry, 0.9; pore diameter, 120 Å; mean particle size, 8.4 μm; surface area, 162 m^2/g), a loading of 0.39 mmol/g was determined, whereas for Luna Silica 10 μm (pore diameter, 101 Å; mean particle size, 8.57 μm; surface area, 380 m^2/g), the loading was found to be 0.53 mmol/g.[16]

The Diels–Alder cycloaddition between cyclopentadiene and *trans*-cinnamaldehyde, carried out in the presence of various salts of the supported imidazolidinones at different temperatures, was used to evaluate the performance of the catalysts.[17] At first, the behavior of the catalytic HPLC column filled with the tetrafluoroborate salt of the 8 μm silica-supported imidazolidinone **SiO_2-5** was studied.[18]

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(16) See the Supporting Information for synthesis, analysis, and characterization of the supported chiral catalyst.

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(18) For details on the preparation of the catalytic column, see the Supporting Information.

A solution of the reagents was pumped with a syringe pump into the HPLC column (flow rate = 5 μL/min) (Scheme 2). It was observed that a conditioning time was necessary to reach a steady-state regime of high chemical and stereochemical activity; 18 h was necessary to stabilize the chemical output of the process. After 20 h, the catalytic column was continuously producing the cycloadduct in 91% yield and about 70−75% ee for both the *endo* and the *exo* isomers (Table 1, entries 1 and 2).

To further increase the stereochemical efficiency, a longer retention time was set up by decreasing the flow rate, and the reaction was carried on for a further 50 h: the product was collected in yields higher than 91% and an enantioselectivity higher than 85% (Table 1, entry 4).[19] However, after a total of 75 working hours, we observed a small decrease in the chemical yield, while the same level of enantioselection was retained (85% ee, entry 5). Simply by slowing the flow rate, the best performing conditions were re-established and the column operated for a further 70 h (> 83% ee and > 95% yield).[20] After a total of 150 h, a little erosion of ee was observed (78% ee vs 83% ee), probably due to some catalyst degradation caused by a very prolonged use of the column, possibly leading to the formation of structurally modified (and less efficient) catalytic species.

Scheme 2. Organocatalyzed Diels−Alder Reaction under Continuous-Flow Conditions

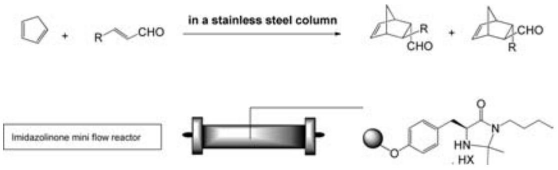

Table 1. Catalytic HPLC Column Filled with Silica-Supported HBF_4 Salt of a Chiral Imidazolidinone

entry	*t* (h)	flow rate (μL/min)	res. time (h)	yield (%)	dr *endo*/*exo*	ee *endo* (*exo*)
1	10−20	5	10	55	46/54	40 (60)
2	20−30	5	10	91	47/53	71 (73)
3	**30−50**	3	**16.5**	**97**	**42/58**	**85** (81)
4	50−75	3 (0 °C)	16.5	91	43/57	87 (85)
5	75−77	3	16.5	81	44/56	85 (83)
6	**77−147**	2	**25**	**95**	**44/56**	**83** (80)
7	147−150	2	25	97	45/55	78 (75)

The catalytic performance of the trifluoroacetate salt of the supported MacMillan catalyst under flow conditions was then studied. Looking at the data of Table 2, a few observations may be made: the column reached the optimal level of chemical activity and enantioselectivity in a shorter period of time in comparison to the reactor discussed before (data in Table 1). Indeed, after the conditioning time (10 h), the cyloadducts were obtained in 94% yield and 85% ee (entry 1, Table 2). The TFA-treated catalytic column afforded the products with high chemical yield for the first 90 h, then showing a decrease in activity. However, it is remarkable that the catalytic reactor with the TFA salt of MacMillan imidazolidinone was able to produce the final cycloadduct in 85% ee at rt with a 5 μL/min flow rate, thus providing a higher productivity.

Table 2. Catalytic HPLC Column Filled with Silica-Supported TFA Salt of a Chiral Imidazolidinone[a]

entry	*t* (h)	yield (%)	dr *endo*/*exo*	ee *endo* (*exo*)
1	10−20	94	48/52	85 (85)
2	**20−96**	**84**	**47/53**	**85 (83)**
3	96−120	78	48/52	73 (71)
4	120−147	78	49/51	77 (73)
5	147−168	60	49/51	75 (74)

[a] Conditions: rt, flow: 5 μL/min, residence time: 10 h.

The regeneration of the catalytic reactor was then preliminarily investigated (Table 3).[21] A previously used HPLC column filled with tetrafluoroborate salt (180 working hours) was first washed with aqueous acetonitrile, and then fluxed with 0.33 mL of an aqueous acetonitrile solution of HBF_4.[18] The so-regenerated catalytic column was employed again in the cycloaddition of cyclopentadiene with cinnamic aldehyde (Table 3). Longer times were necessary to reach satisfactory conditions at the steady-state regime (entries 1 and 2); it must be noted that the regeneration process requires the addition of tetrafluoroboric acid to an already used material (silica particles of the column) that is probably contaminated by the reactants, still adsorbed on the silica surface and possibly entrapped in the pores of the particles (the phenomenon has been already discussed in ref 14). However, after 30 h, the products were collected in yields comparable to those obtained in Table 1 (entries 3 and 4 in Table 3 vs entries 3−5 in Table 1). Noteworthy, if one considers the performance of the HPLC column before and after regeneration, this simple, homemade catalytic reactor demonstrated to work for more than 300 h under continuous-flow conditions to generate a chiral product, with four stereocenters, in good yield, and an enantioselectivity constantly higher than 83% for the first 150 h and higher than 75% for the second period of use.

Some interesting considerations may be made also by comparing the behavior of the silica-supported catalyst in batch or under continuous-flow conditions. The same model cycloaddition reaction between cyclopentadiene and cinnamaldehyde was performed with silica-supported catalyst **SiO_2-5** in batch, in the presence of HBF_4 or TFA, with silica particles of 8 and 10 μm; with both materials, modest results were obtained. For example, by running the reaction at rt, in the presence of a 30% mol amount of the

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(19) By cooling the reaction temperature at 0 °C, no significant improvement of the stereoselectivity was observed.

(20) Imidazolidinone **5** grafted to 10 μm silica particles led to less satisfactory results. See tables in the Supporting Information.

(21) For a regeneration procedure of a resin-supported chiral catalyst, see ref 11.

Table 3. Regenerated Catalytic Column Filled with Silica-Supported HBF_4 Salt of a Chiral Imidazolidinone[a]

entry	t (*h*)	yield (%)	dr *endo*/*exo*	ee *endo* (*exo*)
1	0−24	40	48/52	60 (57).
2	20−30	55	49/51	71 (75)
3	30−55	87	48/52	80 (73)
4	55−168	85	47/53	75 (71)
5	168−192	78	47/53	70 (66)

[a] Conditions: rt, flow: 2 μL/min.

Table 4. General Applicability of a Catalytic HPLC Column (TFA Salt)[a]

entry	*t* (h)	yield (%)	dr *endo*/*exo*	ee *endo* (*exo*)
1[c]	0−24	44	49/51	81 (85)
2[c]	24−48	41	48/52	80 (75)
3[b]	48−60			
4[d]	60−74	63	51/49	83 (75)
5[d]	74−100	55	51/49	81 (74)
6[b]	100−112			
7[e]	112−144	47	53/47	64 (66)

[a] Conditions: rt, flow: 5 μL/min, residence time: 10 h. [b] The column was washed with 95/5 CH_3CN/H_2O solution. [c] Reaction with 4-bromocinnamic aldehyde. [d] Reaction with 2-nitrocinnamic aldehyde. [e] Reaction with cinnamic aldehyde.

tetrafluoroborate salt of the supported catalyst (silica particles 10 μm), the product was obtained in 52% yield after 24 h and 78% yield after 40 h (87% ee). In the recycling studies, already after one cycle, the recovered catalyst showed a marked decrease in the chemical activity, and a slightly lower stereoselectivity (less than 15% yield, 73% ee).

These data allow for some considerations about the productivity: by using 2 g of silica-supported catalyst (0.7 mmol of catalyst) in batch after 40 h, about 1.9 mmol of product was obtained (78% yield). However, in the conditions of Table 2 (5 μL/min), it was possible to produce *in continuo* in the same time 2.8 mmol of cycloadduct. In addition, in 120 h, with the supported catalyst in batch (3 cycles), 2.9 mmol of products is formed, whereas, in the continuous-flow process, 5.3 mmol of the cycloadduct is produced, in the same time, under the conditions of Table 1. If properly regenerated as demonstrated before, the column could be used for an additional 120 h. Finally, it must be noted that the continuous-flow methodology does not require any workup, separation, and recovery operations, allowing for the easy isolation in a time-saving procedure of the reaction products.

Versatility and general applicability of the silica-immobilized chiral imidazolidinone were then investigated. A HPLC column was filled with the trifluoroacetate salt of **SiO_2-5** anchored to silica 10 μm and employed to promote the cyclopentadiene reaction with three different aldehydes, operating *in continuo*. By pumping a 95/5 CH_3CN/H_2O solution of 4-bromocinnamic aldehyde and cyclopentadiene, after 24 h, the catalytic column was continuously producing the cycloadduct in 43% yield and 81−85% ee for the two diastereoisomers.

After 48 h of operation, the column was washed and further used in a second cycloaddition with a different aldehyde. The reaction of 2-nitrocinnamic aldehyde afforded the cycloadduct in 63% yield and 83% enantioselectivity (Table 4). After 100 h of operation, the column was washed and further used in a third cycloaddition with cinnamic aldehyde.

Finally, another catalytic reactor was assembled and employed to perform under flow conditions the Diels−Alder reaction of cyclopentadiene and crotonic aldehyde; after 24 h, the catalytic column was continuously producing the cycloadducts in quantitative yield and 80% ee. The same quantitative yield and about 77% ee for the two diastereoisomers were retained for an additional 72 h.

In conclusion, a straightforward grafting methodology allowed the easy preparation of a "homemade" silica-based HPLC column, functionalized with a supported enantiomerically pure imidazolidinone. For the first time, a silica-supported MacMillan catalyst was employed to perform stereoselective cycloaddition under continuous-flow conditions, showing that the catalytic reactor may work for at least 150 h, to produce the final adducts at room temperature with an ee higher than 83% and >95% yield. The regeneration of the HPLC catalytic column was also demonstrated, allowing to further extend the activity of the reactor to more than 300 operating hours. Finally, the versatility of the system was also proven by performing *in continuo* with the same column reactions with three different substrates. Although a "handmade" column cannot have all the features of a commercial, certified, industrially prepared HPLC column, however, in our hands, different columns (handled by different operators) always gave similar, reproducible results. Even if many issues still need to be addressed (including the improvement of the reaction rates, the turnover number and the productivity, the influence of the catalyst loading on the reaction efficiency, nonhomogeneous packing and reproducibility in the preparation of the catalytic reactor), the preliminary results obtained with this simple HPLC chiral column are very promising and encourage new studies in the field.

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Supporting Information Available. Preparation, analysis, and characterization of silica-supported chiral catalyst; SEM images of the functionalized and not functionalized materials; description of catalytic experiments; and NMR and HPLC traces of the cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.