

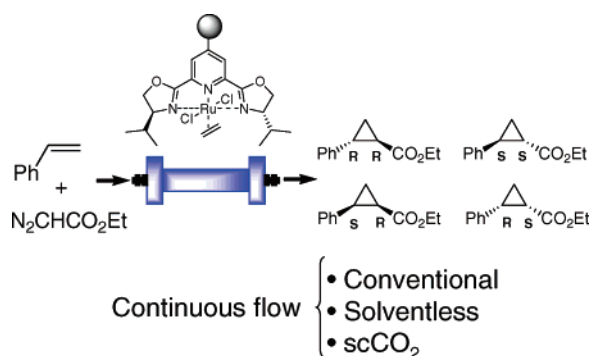
## Pybox Monolithic Miniflow Reactors for Continuous Asymmetric Cyclopropanation Reaction under Conventional and Supercritical Conditions

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Supported catalysts having pybox chiral moieties were prepared as macroporous monolithic miniflow systems. These catalysts are based on styrene-divinylbenzene polymeric backbones having different compositions and pybox chiral moieties. Their corresponding ruthenium complexes were tested for the continuous flow cyclopropanation reaction between styrene and ethyldiazoacetate (EDA) under conventional conditions and in supercritical carbon dioxide (scCO<sub>2</sub>). Ru-Pybox monolithic miniflow reactors not only provided a highly efficient and robust heterogeneous chiral catalyst but also allowed us to develop more environmental reaction conditions without sacrificing the global efficiency of the process.

### Introduction

In the 21st century, we can expect the drive toward cleaner technologies brought about by public, legislative, and corporate pressure to provide new and exciting opportunities for catalysis and catalytic processes.<sup>1</sup> Within this contest, the development of highly stereoselective cleaner carbon-carbon bond-forming reactions continues to be a major challenge.

Enantioselective catalysis is the most interesting method for asymmetric synthesis, given that the chiral information of the

catalyst is multiplied to obtain a large number of new chiral molecules of product.<sup>2</sup> Although homogeneous enantioselective catalysis has given rise to a large number of successful procedures, some of them with industrial application, the immobilization of the valuable chiral catalyst in a phase different from that of the reaction presents several advantages from a practical point of view.<sup>3</sup> In particular, supporting the catalysts greatly facilitates separation processes and, consequently, allows

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(1) (a) Anastas, P. T.; Kirchhoff, M. M.; Williamson, T. C. *Appl. Catal. A* **2001**, 221, 3. (b) *Catalyst Separation, Recovery and Recycling: Chemistry and Process Design*; Cole-Hamilton, D. J., Tooze, R. P., Eds.; Springer: Dordrecht, 2005.

(2) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley, New York, **1994**. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin-Heidelberg, 1999. (c) *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, 2004.

(3) (a) See thematic issue on recoverable catalysts and reagents (Gladysz, J. A., Ed.): *Chem. Rev* **2002**, 102. (b) Brase, S.; Lauterwasser, F.; Ziegert, R. E. *Adv. Synth. Catal.* **2003**, 345, 869. (c) Dooos, B. M. L.; Vankelecom, I. F. J.; Jacobs, P. A. *Adv. Synth. Catal.* **2006**, 348, 1413.

more simple and efficient recovery and reuse of the chiral catalyst or ligand, facilitating the corresponding synthetic procedure and the development of more environmentally benign processes.

Our group has undertaken a systematic study to gain a deep understanding on supported chiral catalysts.<sup>4</sup> This study has been done through the immobilization of a wide range of chiral ligands and complexes onto a variety of supports (organic: polymers or ionic liquids; inorganic: silicas or clays) and using different strategies (polymerization, grafting, or electrostatic immobilization).<sup>5–7</sup> Among these strategies, we have demonstrated that supported chiral catalysts prepared by polymerization as monoliths are highly stable and selective. Moreover, monolithic catalysts enable the development and design of continuous flow processes, which offer a number of potential advantages over existing batch techniques.<sup>8</sup> The reaction conditions (flow rate, stoichiometry, temperature, and pressure) can be independently varied and precisely controlled. This leads to a high level of reproducibility and greatly facilitates the reaction optimization process. Additionally, rapid serial processing may be used to screen new transformations or to generate compound libraries. Finally, flow processes are readily scalable by employing multichannel or parallel reactors (number-up vs scale-up). Although some interesting approaches were recently reported for continuous asymmetric processes using either organic or inorganic supports, the applicability of these approaches is sometimes limited due to the uncontrolled fluid dynamics of the process.<sup>9</sup> Catalysts packed as random catalytic fixed-bed reactors lead to stagnation zones, hot-spot formations, and large residence times distribution, resulting in low process efficiency.<sup>10</sup> Catalysts based on monolithic polymers can solve some of those drawbacks.<sup>8b,11</sup>

Here we report on the application and advantages of monolithic reactors based on pybox chiral ligands for a flow-

through asymmetric catalytic cyclopropanation reaction. The reactions were performed under conventional conditions, using CH<sub>2</sub>Cl<sub>2</sub> as the solvent and, alternatively, using more environmentally benign procedures in the absence of solvent or using scCO<sub>2</sub> as the reaction medium.

## Results and Discussion

Initial results from our group have shown that supported pybox chiral ligand can be synthesized by either polymerization of 4-vinyl-substituted pybox or by the grafting onto silica supports.<sup>7</sup> We have also demonstrated that corresponding pybox-Ru supported complexes on macroporous monolithic polymers are efficient catalysts for the cyclopropanation reaction.<sup>7</sup> The polymeric monoliths, when the reaction is performed in batch, can be removed as a single piece and the catalyst can be easily reused. However, the recyclability of the Ru-pybox supported catalyst is strongly dependent on the total exclusion of oxygen and moisture in the filtration process. On the other hand, we have also shown that supported air-sensitive chiral catalysts prepared as column minireactors inside of stainless steel columns preserve the initial activity and selectivity for a long term, when they are used either in batch or as flow-through minireactors.<sup>5</sup> Besides, monolithic minireactors based on porous materials are ideal for developing continuous flow-through processes due to their low pressure drop and the large contact area of the reagent or catalysts with the fluid.<sup>8</sup> Thus, monolithic miniflow reactors provide a simple system that greatly facilitates their reuse and recycling under controlled conditions and provide the chemical engineering requirements for a continuous flow process.

Pybox monolithic minireactors were prepared by thermally induced radical solution polymerization of a monomeric mixture containing the corresponding vinylic derivative (**1** and **2**), styrene (**3**), and divinylbenzene (**4**), using toluene/1-dodecanol as the precipitating porogenic mixture and AIBN as the radical initiator into a stainless steel column (15 cm × 1/4 in.) (see Scheme 1). Several monolithic minireactors were designed to evaluate the influence of the different polymerization parameters on the appropriate mechanical and morphological properties. In all cases, the amount and composition of the porogenic mixture was kept constant (ca. 60% of the total mixture, 10% toluene, 50% 1-dodecanol), and the effect of the variation in the composition of the monomeric mixture was analyzed (see Table 1). As can be seen in the table, significant backpressures were obtained in all cases. This can be ascribed to the formation of monolithic polymers with low pore size distribution.<sup>5d</sup>

The corresponding monolithic Ru-py-ox complex were prepared, under an inert atmosphere, by treatment of the monolithic flow-minireactor (**M-fm-R**) with an excess of a solution of dichlororuthenium(II) (*p*-cymene) in dichloromethane. The solution was passed through the column at a low flow rate (0.1 mL/min) during 24 h using a recirculation system similar to that previously reported.<sup>5c,d</sup> After this period the column was washed with CH<sub>2</sub>Cl<sub>2</sub> to eliminate all ruthenium not complexed to the active sites.<sup>12</sup>

The resulting Ru-pybox monolithic minireactors were assayed as catalysts for the cyclopropanation reaction (Figure 1) between styrene (VB) and ethyl diazoacetate (EDA). First, the cyclopropanation reaction was carried out under flow conditions using CH<sub>2</sub>Cl<sub>2</sub> as the reaction solvent and the miniflow reactors as

(4) Altava, B.; Burguete, M. I.; Garcia-Verdugo, E.; Luis, S. V.; Vicent, M. J. *React. Funct. Polym.* **2001**, *48*, 25.

(5) (a) Altava, B.; Burguete, M. I.; Garcia-Verdugo, E.; Luis, S. V.; Salvador, R. V.; Vicent, M. J. *Tetrahedron* **1999**, *55*, 12897. (b) Altava, B.; Burguete, M. I.; Fraile, J. M.; Garcia, J. I.; Luis, S. V.; Mayoral, J. A.; Vicent, M. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1503. (c) Burguete, M.; Garcia-Verdugo, E.; Vicent, M. J.; Luis, S. V.; Pennemann, H. N.; Keyserling, N. G.; Martens, J. *Org. Lett.* **2002**, *4*, 3947. (d) Altava, B.; Burguete, M. I.; Garcia-Verdugo, E.; Luis, S. V.; Vicent, M. J. *Green Chem.* **2006**, *8*, 717. (e) Karbass, N.; Sans, V.; Garcia-Verdugo, E.; Burguete, M. I.; Luis, S. V. *Chem. Commun.* **2006**, 3095.

(6) (a) Burguete, M. I.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Luis, S. V.; Mayoral, J. A. *Org. Lett.* **2000**, *2*, 3905. (b) Burguete, M. I.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Herreras, C. I.; Luis, S. V.; Mayoral, J. A. *J. Org. Chem.* **2001**, *66*, 8893.

(7) (a) Cornejo, A.; Fraile, J. M.; Garcia, J. I.; Gil, M. J.; Legarreta, G.; Luis, S. V.; Martínez-Merino, V.; JMAYoral, A. *Org. Lett.* **2002**, *4*, 3927. (b) Cornejo, A.; Fraile, J. M.; Garcia, J. I.; Gil, M. J.; Luis, S. V.; Martínez-Merino, V.; Mayoral, J. A. *J. Org. Chem.* **2005**, *70*, 5536.

(8) (a) Hodge, P. *Curr. Opin. Chem. Biol.* **2003**, *7*, 362. (b) Jas, U.; Kirschning, A. *Chem. Eur. J.* **2003**, *9*, 5708. (c) Kirschning, A.; Jas U.; Kunz G. *Chemistry in flow—new continuous flow reactors in organic synthesis*. In *Innovation and Perspectives in Solid Phase Synthesis and Combinatorial Libraries*; Epton, R., Ed.; MPG Books Ltd.: Cornwall, U.K., 2004. (c) Hodge, P. *Ind. Eng. Chem. Res.* **2005**, *44*, 8542. (d) Kirschning, A.; Solodenko, W.; Mennecke, K. *Chem. Eur. J.* **2006**, *12*, 5972.

(9) (a) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147. (b) Sandy, A. J.; Petra, D. G. I.; Reek, J. N. H.; Kramer, P. C. J.; Van Leewen, P. W. N. M. *Chem. Eur. J.* **2001**, *7*, 1202. (b) Jonsonn, C.; Lundgren, S.; Haswell, S. J.; Morberg, C. *Tetrahedron* **2004**, 10515. (c) Mandoli, A.; Orlandi, S.; Pini, D.; Salvadori, P. *Tetrahedron: Asymmetry* **2004**, *15*, 3233.

(10) Cybulski, A.; Moulijn, J. A. *Structured Catalysts and Reactors*; Marcel Dekker: New York, 1998.

(11) (a) Svec, F.; Frechet, J. M. J. *Science* **1996**, *273*, 205. (b) Svec, F.; Frechet, J. M. J. *Ind. Eng. Chem. Res.* **1999**, *38*, 34.

(12) The functionalization degree for Ru-pybox catalysts was found by ICP-MS to range from 70% to 65% of the functional sites.

SCHEME 1. Synthesis of Monolith Miniflow Reactors: (i) AIBN, toluene/1-dodecanol, 70 °C, (ii) Washing with THF

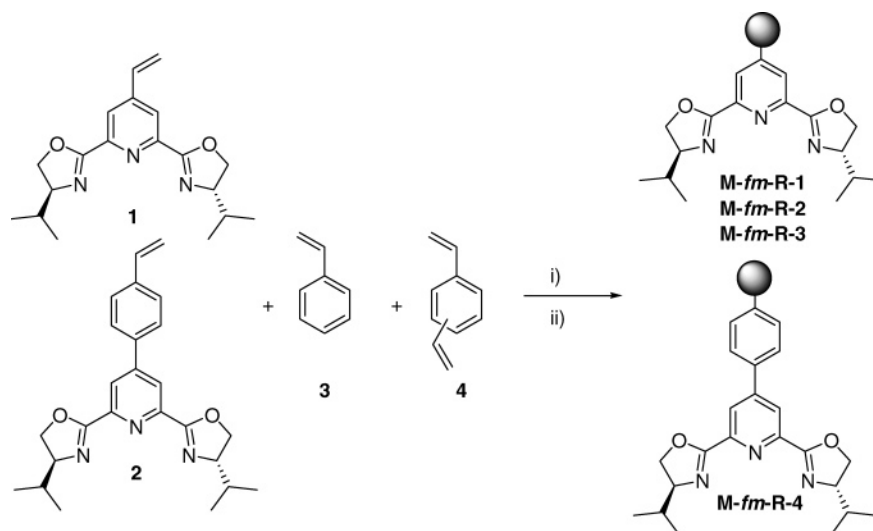


TABLE 1. Properties of Monolithic Flow Minireactors Prepared from Pybox Using Different Monomeric Compositions

entry	catalyst	monomeric composition (mol %) <sup>a</sup>			back pressure (psig) <sup>b</sup>	pybox (mequiv/g)
		pybox	3	4		
1	<b>M-fm-R-1</b>	7 (1)	42	51	919	0.54
2	<b>M-fm-R-2</b>	7 (1)	72	20	1075	0.47
3	<b>M-fm-R-3</b>	7 (2)	73	20	1176	0.47
4	<b>M-fm-R-4</b>	18 (1)	29	53	750	1.07

<sup>a</sup> The porogenic mixture was toluene/1-dodecanol (10:50 w/w) with a 60:40 (w/w) porogens/monomers ratio. The polymerization was performed at 70 °C by using 1% AIBN. <sup>b</sup> Measured at a pressure gauge of 0.2 mL/min THF. <sup>c</sup> Determined by elemental analysis.

catalysts. A solution of EDA and VB (0.25 mol/L EDA and 1.5 mol/L VB) in CH<sub>2</sub>Cl<sub>2</sub> was continuously pumped at different flow rates through the monolithic minireactor to investigate the effect of the residence time of the reagents within the catalyst bed. Aliquots were taken at regular time intervals at the outlet of the reactor and analyzed for the content of cyclopropanes (CP, **7** and **8**), fumarates and maleates (**9** and **10**) and unreacted EDA.

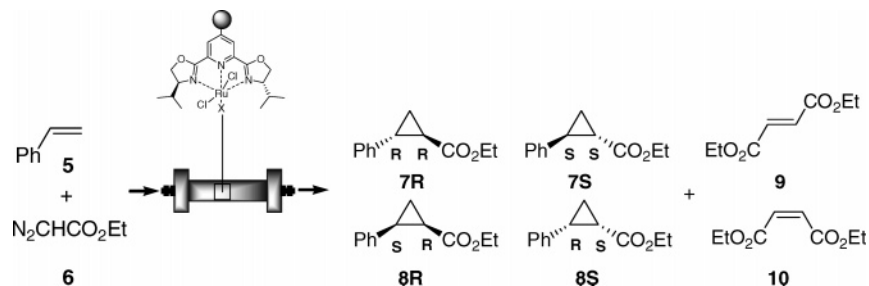
In general, an increase in the flow rate (from 20 to 150 μL/min) led to a corresponding decrease in cyclopropanes yield for all catalysts studied. This is consistent with a reduction in residence time in the flow reactor. Figure 2 shows the achieved results for the catalyst **M-fm-R-1-Ru**. In this way, almost complete conversion of EDA was achieved for the lower flow rate assayed (20 μL/min, 35 min of residence time). The moderate cyclopropanes yield, around 50%, can be explained by the EDA dimerization to produce ethyl fumarate and maleate, reducing the chemoselectivity of the process (ca. 70 ± 5% for the different residence time assayed). This side reaction was also observed when the reaction was performed in homogeneous batch with a fumarate/maleate ratio of 3/1. Besides, both regio- and enantioselectivities gave good values of 80/20 *trans/cis*; 48 ± 5% ee for the *cis* isomer and 75 ± 5 ee for the *trans* isomer, being similar to those found for the homogeneous catalyzed reactions performed in batch (5% catalyst; see entry 1, Table 2).

The deactivation of the catalysts is caused by poisoning through the adsorption of byproducts or by the adsorption of

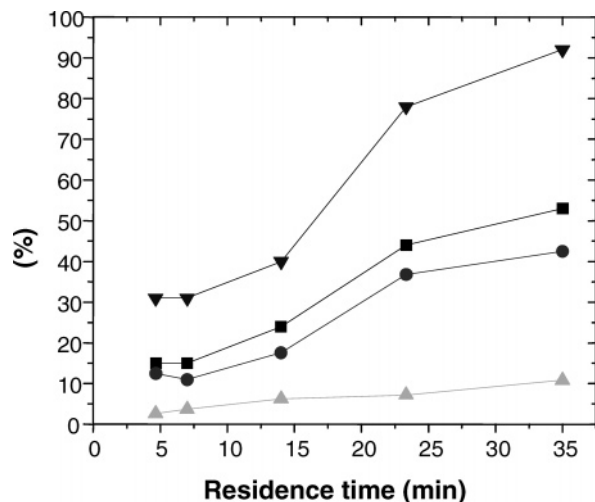
traces of moisture and/or oxygen during recycling.<sup>7b</sup> The monolithic miniflow reactors minimized those effects. In fact, the catalyst can be used in several runs (5–8 h per run) or performed in different days with up to 33 h operation time, showing a similar catalytic performance. These results are in good agreement with the long-term stability observed for the monolithic Ti-TADDOLates minireactors.<sup>5b,5d</sup>

The influence of the morphology of the chiral supported catalyst on activity and selectivity at equivalent residence times for the different monolithic miniflow reactors prepared was also observed (entries 2–5, Table 2). The polymerization conditions, such as temperature, solvent, concentration, and ratio of monomers, are determining for the performance of the final catalyst as they control both the accessibility and nature of the microenvironment of the chiral centers. Thus, an increase of the cross-linking from 20% to 51% yielded not only a more active catalyst but also a more chemoselective one (compare entries 2 and 3, Table 2). The intrinsic activity (TOF, (mol CP/mol pybox) h<sup>-1</sup>) of the catalyst **M-fm-R-1-Ru** with 51% crosslinking was twice the one found for catalysts with a lower degree of crosslinking (**M-fm-R-2-Ru**). This higher efficiency led also to an improvement on the chemoselectivity from 50% to 73%. The introduction of an aryl spacer between the polymeric backbone and the active sites produced a slight decrease in catalytic activity but did not show a big influence on the other parameters under study. On the other hand, the enantioselectivity of the reaction was not strongly influenced by the morphology of the supported catalyst. It seems clear that this cyclopropanation reaction catalyzed by Ru-pybox monolithic miniflow reactors can be efficiently performed in a continuous flow mode in CH<sub>2</sub>Cl<sub>2</sub>, with good yields and chemo-, regio-, and enantioselectivities.

An important factor to achieve stereodiscrimination is the choice of solvent. However, the solvent in which a good enantioselectivity is achieved may not always be the most environmentally benign one. In this regard, there are important limitations associated with the use of halogenated solvents; for example, CH<sub>2</sub>Cl<sub>2</sub> is the most common solvent used for our benchmark reaction. Thus, in the search of more environmentally friendly protocols, the continuous setup based on monolithic miniflow catalytic reactors allowed us to perform the reaction



**FIGURE 1.** Continuous-flow cyclopropanation reaction between VB and EDA, catalyzed by Ru-Pybox miniflow reactor.



**FIGURE 2.** Evolution of the cyclopropanation reaction between 5 and 6 vs residence time in DCM (0.25 mol/L of 5 in DCM, rt, catalyst **M-fm-R-1-Ru**, all calculated as in Table 2). (▼) % conversion EDA; (■) % yield cyclopropanes (7 + 8); (●) % yield CP trans (7); (grey ▲) % yield CP cis (8).

either under solventless conditions or using neoteric solvents and in particular supercritical fluids.

First, the reaction was assayed under solventless conditions at room temperature by pumping mixtures of pure reagents (solutions of VB/EDA with molar ratios ranging from 38.5/1 to 1/1) at constant flow (0.02 mL/min).<sup>13</sup> Some of the results achieved for the catalysts **M-fm-R-1-Ru** and **M-fm-R-2-Ru** are summarized in Figure 3. For the catalyst **M-fm-R-1-Ru**, the best results in terms of both yield and chemoselectivity were observed for mixtures VB/EDA with a 7/1 molar ratio (see Figure 3a). Besides, the enantioselectivities for both *trans* and *cis* isomers were similar than those observed for same catalyst in DCM (see entries 2 and 5 from Table 2). When a reaction mixture with a lower amount of EDA (38.5/1 VB/EDA) was used, a significant reduction of yield was observed (from 72% to 37%). Indeed, the final productivity experienced a 9.5-fold decrease, the TOF value for this catalyst being reduced from 4.361 to 0.458 (mol CP/mol pybox) h<sup>-1</sup>. The use of either 4/1 or equimolar VB/EDA solution showed a detrimental effect on the reaction in terms of chemoselectivity, leading to lower cyclopropanes yield and to higher amounts of fumarates and maleates. The enantioselectivities for both *trans* and *cis* isomers were lower than those found for the reaction using a mixture of VB/EDA 7/1. Catalyst **M-fm-R-2-Ru** showed similar trends

(13) The different VB/EDA molar ratios correspond with different solutions of EDA in VB of 0.22 M, 1.1 M, 1.7 M, and 4.4 M for 38.5/1, 7/1, 4/1, and 1/1, respectively.

with the variation of VB/EDA ratio as those observed for **M-fm-R-1-Ru**, although the lower crosslinking degree led to a higher global efficiency for the catalytic process, as it was previously found in DCM.

Thus, it is possible to avoid the use of a potentially harmful solvent without sacrificing the overall efficiency of the process. As a matter of fact, the final productivity of the solventless process experienced an increase in both efficiency and chemoselectivity compared with those achieved under similar conditions using CH<sub>2</sub>Cl<sub>2</sub> as the reaction medium (compare entries 2–5 and 3–6 of Table 2). The elimination of the solvent allows the use of more concentrated EDA solutions, leading to a better space time yield, as an evidence of the higher TOF values, and yields achieved for the same residence time. The better chemoselectivity can be explained by taking into account that the catalysts are based on PS-DVB monolithic polymers. Therefore, the use of VB as a “solvent” and reagent should favor the diffusion of the reagents to the active sites. Indeed, the local concentration of VB in the surroundings of the active site should be maximized, and in this way, the side reaction due to homocoupling of EDA is minimized.

Once the efficiency of Ru-pybox monolithic miniflow reactors was proved for the solventless process, we decided to evaluate the behavior of our catalysts in scCO<sub>2</sub>, which is an excellent green solvent with significant potential for both synthesis and separation of chemicals.<sup>14</sup> ScCO<sub>2</sub> represents an interesting alternative to organic solvents, because it provides a clean, nontoxic, non-flammable, and tunable solvent system, which is easily removed leaving reaction products free from undesirable organic residues.<sup>15,16</sup> The cyclopropanation benchmark reaction between VB and EDA was performed at 40 °C by pumping, at different flow rates, a solution of VB and EDA in scCO<sub>2</sub>. The reaction pressure and the ratio of CO<sub>2</sub>/organic were kept constant for all of the conditions assayed (8 MPa, the volumetric flow of organic stream was 10% of the total flow). Figure 4 summarizes the results found for the two different catalysts **M-fm-R-1-Ru** and **M-fm-R-3-Ru** assayed in scCO<sub>2</sub>. The results show that the continuous cyclopropanation reaction can be performed in a monolithic miniflow reactor using scCO<sub>2</sub> as a solvent. To the best of our knowledge, this is the first

(14) Jessop, P. G.; Leitner, W. *Chemical Synthesis using Supercritical Fluids*; VCH/Wiley: Weinheim, 1999.

(15) (a) Beckman, E. J. *J. Supercrit. Fluids* **2004**, *28*, 121. (b) Cole-Hamilton, D. J. *Adv. Synth. Catal.* **2006**, *12–13*, 1341. (c) Jessop, P. G. *J. Supercrit. Fluids* **2006**, *38*, 211.

(16) CO<sub>2</sub> has been considered a “green” alternative solvent as a result of its properties (non-toxic, non-flammable, and tunable solvent system). However, to consider that a process is more environment-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 a study is out of the scope of this paper, but it should be kept in mind for possible implementation of this process in CO<sub>2</sub>.

TABLE 2. Continuous Cyclopropanation Reaction between VB and EDA Catalyzed by Ru-Pybox Monolithic Flow Minireactors

entry	catalyst	solvent	% conversion EDA <sup>d</sup>	% yield <sup>e</sup>	TOF <sup>f</sup>	% chemoselectivity <sup>g</sup>	trans/cis	% ee cis	% ee trans
1	pybox	CH <sub>2</sub> Cl <sub>2</sub> <sup>a</sup>	81	44		68	87:13	48	77
2	<b>M-fm-R-1-Ru</b>	CH <sub>2</sub> Cl <sub>2</sub> <sup>b</sup>	92	53	0.736	73	80:20	48	79
3	<b>M-fm-R-2-Ru</b>	CH <sub>2</sub> Cl <sub>2</sub> <sup>b</sup>	70	23	0.367	50	85:15	45	82
4	<b>M-fm-R-3-Ru</b>	CH <sub>2</sub> Cl <sub>2</sub> <sup>b</sup>	55	20	0.319	46	85:15	39	76
5	<b>M-fm-R-1-Ru</b>	solventless <sup>c</sup>	92	72	4.361	88	83:17	43	79
6	<b>M-fm-R-3-Ru</b>	solventless <sup>c</sup>	68	48	3.373	83	82:18	41	76
7	<b>M-fm-R-1-Ru</b>	scCO <sub>2</sub> <sup>h</sup>	41	22	5.299	71	85:15	56	89
8	<b>M-fm-R-3-Ru</b>	scCO <sub>2</sub> <sup>h</sup>	51	29	7.860	73	89:11	59	83

<sup>a</sup> Reaction was carried out in batch with 5 mol % RuCl<sub>2</sub>(pybox-ip)(C<sub>2</sub>H<sub>4</sub>). <sup>b</sup> All data are average numbers of aliquots, determined every 30 or 60 min by means of GLC analysis with a Cyclodex-B column. The reaction was carried out at rt and at a constant residence time of 35 min; flow rate 20 μL/min; reactor volume 700 μL. Solution: 0.25 mol/L EDA and 1.5 mol/L VB in CH<sub>2</sub>Cl<sub>2</sub>. <sup>c</sup> Solution: VB/EDA ratio 7/1, 1.1 mol/L EDA in VB. <sup>d</sup> Percent conversion EDA = [(mmol CP + mmol ethyl fumarate + mmol ethyl maleate)/[initial mmol EDA]] × 100. <sup>e</sup> Percent yield = (mmol CP/initial mmol EDA) × 100. <sup>f</sup> TOF (mol CP/mol pybox) h<sup>-1</sup> = [(conv EDA (mmol/mL) × flow (mL/min) × 60 (min) × (% yield/100)]/[loading (mmol/g) × g catalyst (g)]; **M-fm-R-1-Ru** 0.54 mequiv/g, 0.4 g of monolithic catalyst; **M-fm-R-2-Ru** 0.47 mequiv/g, 0.4 g of monolithic catalyst. <sup>g</sup> Chemoselectivity % = [mmol CP/(mmol CP + mmol ethyl fumarate + mmol ethyl maleate)] × 100. <sup>h</sup> 40 °C, 8 MPa, total flow rate 550 μL/min, residence time 1.27 min, solution of 1.73 mol/L EDA in VB pumped at 0.05 mL/min.

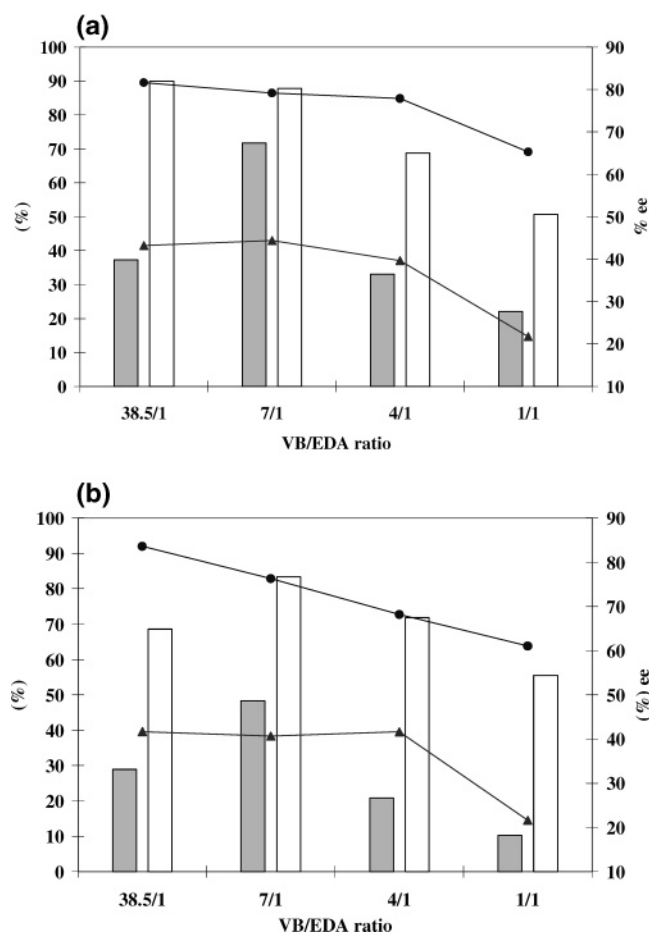


FIGURE 3. Evolution of continuous flow cyclopropanation solventless reaction between 5 and 6 vs VB/EDA ratio at room temperature and 20 μL/min. (a) **M-fm-R-1-Ru**: 1/VB/DVB 7/42/51. (b) **M-fm-R-2-Ru**: 1/VB/DVB 7/73/20. (gray bars) % yield, (white bars) % conversion EDA, (▲) % ee (cis), (●) % ee (trans) (calculated as in Table 2).

example of asymmetric cyclopropanation reaction being conducted in flow conditions in scCO<sub>2</sub>.<sup>17</sup>

In general, the results followed trends similar to those observed in the halogenated solvent and for solventless conditions. The shorter residence time, tested in supercritical fluid,

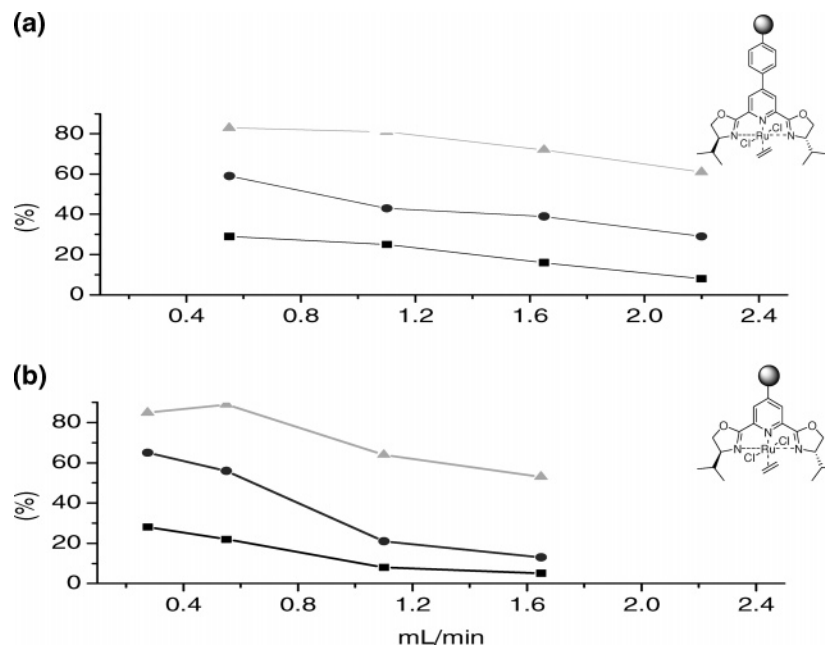
led to a lower conversion of EDA and cyclopropane yields, namely, 47% EDA conversion and 28% yield for **M-fm-R-1-Ru** and 42% EDA conversion and 29% yield for **M-fm-R-3-Ru** for a residence time of 2.67 and 1.27 min, respectively. Furthermore, the chemoselectivity and enantioselectivity of the reaction decreased with higher flow rates. However, both catalysts gave good values for these reaction parameters at lower flow rates. The *trans/cis* ratio was similar for the two catalysts and for all of the conditions studied (ca. 85:15 *trans:cis* ratio). As a matter of fact, for a total flow rate of 0.55 mL/min (residence time 1.27 min), the outcome of the reaction in terms of regio-, chemo-, and enantioselectivity are good and comparable with the results under conventional conditions (see entries 7 and 8, Table 2).

To increase the yield of cyclopropanes, a catalyst with a higher pybox loading (**M-fm-R-4-Ru** 1.07 mequiv pybox/g) was used. Its catalytic behavior was tested at 8 MPa, 40 °C at a total flow rate of 0.165 mL/min. As it was expected, better EDA conversion and yields were achieved (ca. 90% EDA conversion and a 65% yield). The catalyst provided good levels of chemoselectivity (ca. 82%) and enantioselectivity (77% ee *trans* and 50% ee *cis*). Besides, the catalyst was found to be stable under these reaction conditions, with minimal degradation of performance over a period of 5 h (see Figure 5). Metal analysis of the product stream by ICP-MS showed levels of leached total metals <1 ppm. It is important to note that for the scCO<sub>2</sub> process a temperature of 40 °C is required, but room temperature was used with conventional or solventless conditions.

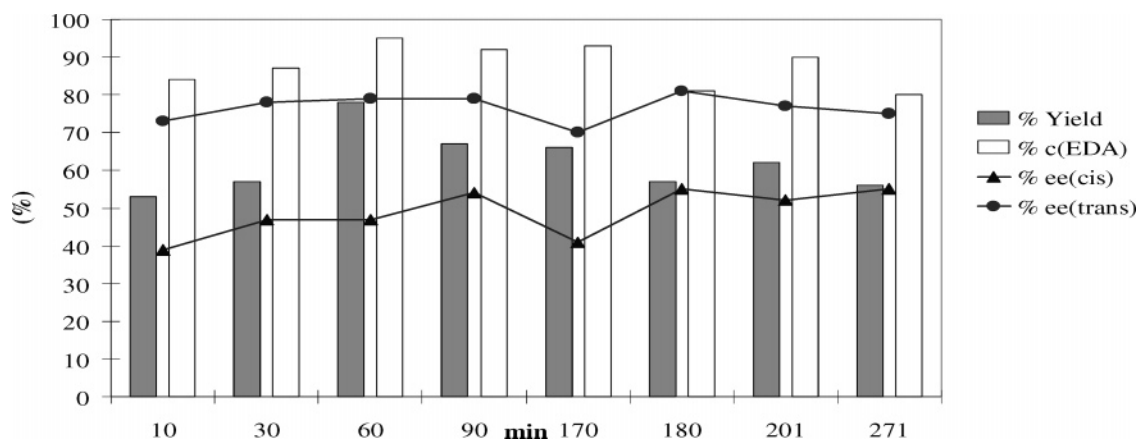
An additional set of experiments was conducted exploring the effect of pressure on the cyclopropanation. The reactions were carried out for the catalyst **M-fm-R-2-Ru** at 40 °C and different pressures by pumping 0.05 mL/min of a solution of VB/EDA (4:1, 1.7 M of EDA) and 0.5 mL/min of CO<sub>2</sub>. It is clear from Table 3 (entries 1–4) that no significant variation of the reaction parameters such as yield or chemoselectivity was observed with the increase of the pressure. However, a slight decrease in regio- and enantioselectivity was found for higher pressures. As was pointed out by Jessop et al., this is presumably due to the fact that the dielectric constant of scCO<sub>2</sub> increases only slightly with pressure. Thus, varying the pressure and density has little effect on asymmetric cyclopropanation in the absence of a drastic dielectric constant change.<sup>17,18</sup>

(17) For homogeneous cyclopropanation reaction in scCO<sub>2</sub> see: Wynne, D. C.; Olmstead, M. M.; Jessop, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7638.

(18) Moriyoshi, T.; Kita, T.; Uosaki, Y. *Ber. Bunsen. Ges. Phys. Chem.* **1993**, *97*, 589.



**FIGURE 4.** Evolution of cyclopropanation reaction between 5 and 6 vs total flow rate in scCO<sub>2</sub> (40 °C, 8 MPa, all calculated as in Table 2). (a) **M-fm-R-3-Ru**. (b) **M-fm-R-3-Ru**. (■) % yield, (●) % ee (cis), (gray ▲) % ee (trans).



**FIGURE 5.** Performance of the catalyst **M-fm-R-4-Ru** for the continuous cyclopropanation reaction between 5 and 6 in scCO<sub>2</sub> at 40 °C and 8 MPa vs reaction time.

**TABLE 3.** Continuous Cyclopropanation Reaction between VB and EDA Catalyzed by Ru-Pybox Monolithic Flow Minireactors in scCO<sub>2</sub><sup>a</sup>

entry	<i>T</i> (°C)	<i>P</i> (MPa)	catalyst	org flow (μL/min)	CO <sub>2</sub> flow (μL/min)	% conv EDA <sup>b</sup>	% yield <sup>c</sup>	TOF <sup>d</sup>	% chemo-selectivity <sup>e</sup>	<i>trans/cis</i>	% ee <i>cis</i>	% ee <i>trans</i>
1	40	8	<b>M-mf-R-2</b>	0.05	0.5	30	16	4.340	72	82/18	33	66
2	40	11	<b>M-mf-R-2</b>	0.05	0.5	21	12	3.254	74	84/16	22	61
3	40	15	<b>M-mf-R-2</b>	0.05	0.5	28	15	4.068	68	78/22	20	60
4	40	20	<b>M-mf-R-2</b>	0.05	0.5	25	13	3.526	68	79/21	21	57
5	40	8	<b>M-mf-R-4</b>	0.015	0.15	91	63	2.251	82	87/13	47	77

<sup>a</sup> All data are average numbers of aliquots, determined every 30 or 60 min by means of GLC analysis with a Cyclodex-B column, reactor volume 700 μL, solution of 1.73 mol/L EDA in VB. <sup>b</sup> Percent conversion EDA = ([mmol CP + mmol ethyl fumarate + mmol ethyl maleate] / [initial mmol EDA]) × 100. <sup>c</sup> Percent yield = [mmol CP / initial mmol EDA] × 100. <sup>d</sup> TOF (mol CP/mol pybox h<sup>-1</sup>) = [(conv EDA (mmol/mL) × flow (mL/min) × 60 (min) × (% yield/100)] / [loading (mmol/g) × g catalyst (g)]; **M-mf-R-2-Ru** 0.47 mequiv/g, 0.4 g of monolithic catalyst; **M-mf-R-4-Ru** 1.07 mequiv/g, 0.4 g of monolithic catalyst. <sup>e</sup> Chemoselectivity % = [mmol CP / (mmol CP + mmol ethyl fumarate + mmol ethyl maleate)] × 100.

## Conclusion

The monolithic miniflow reactors here presented showed a high potential for practical application in continuous enantioselective asymmetric catalytic cyclopropanation reactions. Besides, we have been able to design a more environmentally friendly chemical reaction by replacing a toxic solvent by using

solventless or scCO<sub>2</sub> conditions. A “greener” process should not only be based on replacement of toxic solvent but also should have additional advantages. In this sense, not only is the continuous flow operation based on the combined use of the Ru-pybox monolithic miniflow reactor with more environment-friendly conditions an easy methodology for the separation

of catalyst and product, but also the total number of turnovers the catalyst makes before it must be replaced is greatly increased. For instance, for an operation time of 8 h the productivity of the process is highly enhanced by the use of solventless or  $\text{scCO}_2$  conditions. Thus, the productivity for the solventless process experiences a 5.8-fold increase relative to the reaction in DCM ( $\text{TON}_{(\text{DCM})}$  6 mol CP/mol pybox vs  $\text{TON}_{(\text{solventless})}$  35 mol CP/mol pybox). Further improvements were observed for the  $\text{scCO}_2$  process, with a 7.7-fold increase in productivity ( $\text{TON}_{(\text{DCM})}$  6 mol CP/mol pybox vs  $\text{TON}_{(\text{scCO}_2)}$  46 mol CP/mol pybox).<sup>19</sup> The methodology here reported represents a simple and straightforward strategy to improve the efficiency of catalytic process by the combined use of continuous flow reactions and non-conventional conditions, allowing the development of more efficient synthetic chemical asymmetric processes.

## Experimental Section

**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 meets the necessary safety requirements.

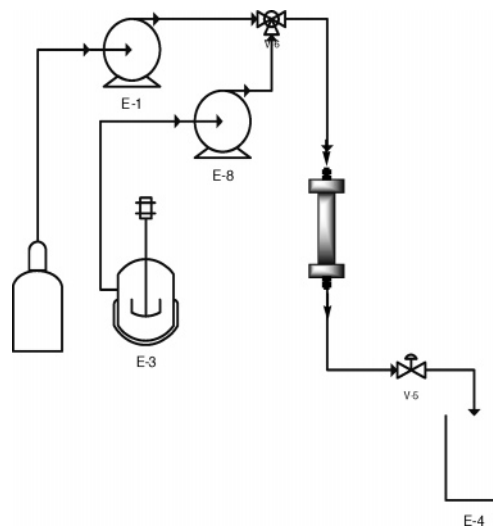
The monomers 2,6-bis[(*S*)-4-isopropylloxazolin-2-yl]-4-vinylpyridine (**1**) and 2,6-bis[(*S*)-4-isopropylloxazolin-2-yl]-4-(4-vinylphenyl)-pyridine (**2**) were synthesized as previously reported.<sup>7</sup> Styrene, DVB (80% grade), and EDA were purchased from Aldrich and used without further purification. The cyclopropanes used for analytical determinations have been synthesized as previously reported.<sup>7</sup>

**Preparation of Monolithic Miniflow Reactors.** Monoliths were molded into a stainless steel column (15 cm  $\times$  1/4 in.). **M-mf-R-1** was prepared using a solution of 0.01 g of azobisisobutyronitrile (AIBN) and **1** (0.07) in styrene, and divinylbenzene a (80% w/w, 0.6 g), toluene (0.25 g), and 1-dodecanol (1.25 g). The polymerization mixture was stirred and purged with nitrogen for 3 min and poured into the mould. The stainless steel tubular mould was sealed at the two ends and placed in a vertical position into a water bath. The polymerization was allowed to proceed for 24 h at 70 °C. The seals were then removed, the tube was provided with fittings, attached to a high-pressure pump, and THF was pumped through the column to remove the porogenic solvents and any other soluble compounds.

Polymers **M-mf-R-2**, **M-mf-R-3**, and **M-mf-R-4** were prepared with similar preparation protocols using the monomeric mixture showed in Table 1.

**Cyclopropanation under Batch Conditions.** To a solution of  $\text{Ru-Cl}_2$ -(2,6-bis[(*S*)-4-isopropylloxazolin-2-yl]-pyridine)-(C<sub>2</sub>H<sub>4</sub>) (5 mol %), styrene, and *n*-decane (25 mg) in methylene chloride (3 mL) was added a slution of ethyl diazoacetate in methylene chloride (3 mL) during 6 h using a syringe pump. The concentration of both solutions was such that at the end of the addition the concentration of EDA and VB were 0.25 and 1.25 M, respectively. The reaction was monitored by HPLC employing a C18 column.

(19) For 8 h of reaction time, the process in DCM has a TOF of 0.763 (mol CP/mol pybox) h<sup>-1</sup> (at 0.02 mL/min, 35 min of residence time), which corresponds to a TON per catalytic cycle or bed volume of 0.429 (mol CP/mol pybox) per cycle and ca. 13.7 catalytic cycles. For the solventless process, in a similar try (at 0.02 mL/min, 35 min of residence time) a TOF of 4.361 (mol CP/mol pybox) h<sup>-1</sup> corresponds to a TON 2.544 (mol CP/mol pybox) per cycle or bed volume and ca. 13.7 catalytic cycles. Finally for the  $\text{scCO}_2$  (at 0.165 mL/min, 1.27 min of residence time) a TOF of 5.299 (mol CP/mol pybox) h<sup>-1</sup> corresponds to a TON 0.122 (mol CP/mol pybox) per cycle or bed volume and ca. 377 catalytic cycles.



**FIGURE 6.** E-3, reagents feed vessel and CO<sub>2</sub> feed vessel; E-8, reagents feed pump (HPLC Jasco pump, Gilson model 304, flow rate = 0.01–5 mL/min, maximum allowed pressure ( $P_{\text{max}}$ ) = 40 MPa); E-1, CO<sub>2</sub> feed pump (Jasco, 304, flow rate = 0.25–1 mL/min,  $P_{\text{max}}$  = 40 MPa); V-8, mixer (Gilson); monolithic microreactor (1/4 in. AISI 316 tubing, 15 cm, heat supplied by a band heater (Watlow, 240 V, 200 W, NTB25X6UA3, 47 02 DM)); V-5, back pressure regulator (Jasco  $P_{\text{max}}$  = 42 MPa,  $C_v$  < 0.01).

Conditions: CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% v/v TFA) 60:40; 30 °C; flow rate 1 mL/min; 3.3 min (EDA), 4.4 min (ethyl maleate), 7.4 min (ethyl fumarate), 11.4 min (ethyl benzoate, internal standard), 14.1 (cyclopropane, *cis*), 16.6 min (styrene), 19.4 min (cyclopropane, *trans*). Assay of enantiomeric purity was performed by gas chromatography with a Cyclodex-B column: 30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ , FID detector; helium as carrier gas, 20 psi; injector temperature 230 °C; detector temperature 250 °C; oven temperature program 125 °C isotherm. Retention times: (1*S*,2*R*)-cyclopropane 14*S*, 28.3 min; (1*R*,2*S*)-cyclopropane 14*R*, 29.1 min; (1*R*,2*R*)-cyclopropane 13*R*, 33.9 min; (1*S*,2*S*)-cyclopropane 13*S*, 34.3 min.

**Cyclopropanation under Continuous Flow Conditions.** A fresh reaction mixture of styrene (1.25 M), ethyl diazoacetate (0.25 M), and *n*-decane (as internal standard) in anhydrous degassed methylene chloride was pumped through the monolithic column at different flow rates using a HPLC pump (Figure 6). Samples were taken every 30 or 60 min and analyzed by GC. Experiments were started when product streams were stabilized after the initiation period (ca. 1 h). For the solventless reaction the solution was prepared without the addition of methylene chloride (1.78 M EDA in VB/EDA). For SCF runs the SCF was pressurized and delivered by a Peltier cooled pump running in constant flow mode, and the organic substrates (4:1 VB/EDA, 1.7 M EDA in VB/EDA) were delivered at a constant rate via a standard HPLC pump. All feed streams were mixed by a dynamic mixer before being passed through the monolithic catalytic bed. Products were collected after a single stage depressurization of the fluid mixture by an electronic backpressure regulator and analyzed by GC.

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