



From homogeneously to heterogeneously catalyzed cyclopropanation reactions: New polymeric membranes embedding cobalt chiral schiff base complexes

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ABSTRACT

In this paper we report the preparation of catalytic polymeric membranes having the complex [(N,N'-bis(3-tert-butyl-5-(heptadecafluorooctyl)salicylidene)-trans-1,2-cyclohexanediamine)Co] embedded into Hyflon AD60X, PES and PSf and their use in the cyclopropanation reaction of olefins with ethyl diazoacetate (EDA). A study of the reaction in the homogeneous phase was also performed. The kinetics of the cyclopropanation reaction is first-order in the diazoacetate and the catalyst and zero order in the olefin, but we observed a more complex dependence on the additive, NMI (N-methylimidazole). The positive effect of the additive is completely reversed at NMI concentration higher than $6 \cdot 10^{-2}$ M.

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1. Introduction

The cyclopropane moiety has always fascinated the chemist community and plays a prominent role in organic chemistry [1]. Naturally occurring and synthetic cyclopropanes are endowed with a rich spectrum of biological properties [2] and a large number of compounds carrying a cyclopropane ring have been synthesized and described in the literature. The asymmetric cyclopropanation of olefins with alkyl diazoacetates [3] represents a powerful tool in the synthesis of chiral cyclopropanes [4,5]. Nevertheless, the synthesis of these compounds remains a considerable challenge, especially due to the fact that cyclopropane rings are often found in a variety of natural products and biologically active molecules. New and more efficient methods for the preparation of cyclopropanes in an enantiomerically pure form have appeared in the last decade, clearly demonstrating the explosive growth and power of this particular field of organic chemistry [5]. Among the transition metals, the application of cobalt in synthetic organic transformation has

attracted increasing interest in the last years, especially due to its lower cost when compared with its higher homologues [6]. Since the first report by Nakamura and co-workers on the use of bis[(-)-camphorquinone- α -dioximato]cobalt(II) for the enantioselective synthesis of cyclopropane derivatives [7], cobalt complexes have played a prominent role in the asymmetric cyclopropanation reactions [8–16].

In the last three decades molecular engineering have furnished the chemist with novel materials having superior characteristics and properties and represents a rapidly growing technologie that will be pervasive in all fields of science [17]. In particular, membrane technology become available as a practical and economical technique to separate molecules in high-capacity, continuous processes. In this context, for example, the incorporation of cobalt(II) Schiff base complexes as oxygen carriers into polymeric membranes gave a significant improvement in performance in gas separation application [18].

In the field of catalysis, in spite of the general recognition that heterogeneous catalysis has practical advantages over homogeneous one, until now the heterogeneously catalyzed cyclopropanation reaction by cobalt complexes has been explored only to a lower extent. The numerous attempts to combine the best properties of homogeneous and heterogeneous systems are based on the use of either polymeric or porous inorganic solid as catalyst support [19,20]. Among the polymeric supports, polymeric membranes are innovative materials to immobilize transition metal complexes

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in which the catalyst can be dispersed into a polymer solution or co-dissolved with the polymer depending on the metal complex solubility in the preparation medium [21–23]. It is also worth noting that the use of polymeric membranes to entrap homogeneous catalysts shows several practical advantages for the fine chemical synthesis: (i) the homogeneous catalyst can be embedded in the membrane without any covalent bond formation avoiding any chemical modification of the complex; (ii) polymeric membranes show different affinities for different chemicals, therefore they can drive the reaction modulating the absorption and diffusion of the components of the reaction mixture; (iii) catalytic polymeric membranes can be prepared controlling the mechanical, chemical and thermal stability to yield the desired permeability and affinity for reagents and products; (iv) lastly, the use of polymeric catalytic membranes allows the reaction to be performed in a catalytic membrane reactor (CMR) in which the reaction and separation processes can be combined in a single stage [24].

A specific problem that can occur in liquid-phase reactions with homogeneous catalysts occluded in membranes is complex leaching out of the polymer into the liquid reaction phase. While the absence of strong interaction forces between the catalyst and the polymer is one of the practical advantages of this way of complex heterogenization, this renders at the same time the system more susceptible to leaching. The catalyst/polymer interaction is the result of van der Waals forces and steric constraints of the polymer chains on the complex. Leaching can be minimized by placing bulky groups on the catalyst or by increasing the affinity of this last for the polymer.

This paper deals with the embedding of Co(II)–salen complexes, a class of catalysts that has found a remarkable success in the cyclopropanation of olefins by diazoacetates, into polymeric membranes, affording new catalytic membranes.

2. Experimental

2.1. General procedures

^1H NMR spectra were recorded on an Avance 300-DRX Bruker instrument, operating at 300 MHz for ^1H and at 75 MHz for ^{13}C . Chemical shifts (ppm) are reported relative to TMS. The ^1H NMR signals of compounds described in the following have been attributed by COSY and NOESY techniques. Assignments of the resonances in ^{13}C NMR were made using the APT pulse sequence, HSQC and HMQC techniques. Infrared spectra were recorded on a Varian Scimitar FTS 1000 spectrophotometer. UV/vis spectra were recorded on a Agilent 8453E spectrophotometer. Elemental analyses and mass spectra were recorded in the analytical laboratories of Milan University. Unless otherwise specified, all reactions were carried out under a nitrogen atmosphere employing standard Schlenk techniques and magnetic stirring. Solvents were dried prior to use by standard procedures and stored under nitrogen. Racemic *N,N'*-bis(3-*tert*-butyl-5-(heptadecafluorooctyl)salicylidene)-*trans*-1,2-cyclohexanediamine was purchased from Aldrich. 5-Bromo-3-*tert*-

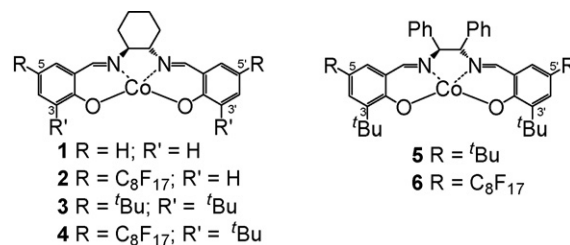


Fig. 1. Cobalt Schiff base complexes.

butyl-2-hydroxybenzaldehyde, 3-*tert*-butyl-2-hydroxy-5-*n*-heptadecafluorooctylbenzaldehyde and 2-hydroxy-5-*n*-heptadecafluorooctylbenzaldehyde were prepared according to the procedures described by Pozzi et al. [25,26]. Salen derivatives and cobalt complexes were synthesized by methods reported in the literature [8,27–29]. All other reagents were commercially available and used without further purification for the preparation of polymeric catalytic membranes. PES (Radel®), PSf (Udel®), Hyflon AD60X and Galden HT were supplied by Solvay.

2.2. Preparation of the polymeric membranes

Flat sheet PES, PSf and Hyflon AD60X based membranes were prepared by phase inversion process [30].

In Table 1 a summary of the experimental conditions for the preparation of membranes is given.

Dense symmetric polymeric membranes were prepared by phase inversion induced by solvent evaporation. For each polymer, the metal complex (24 mg) was solubilized in the solvent (2.7 g) then the polymer was added (0.3 g). The resulting solution was stirred at room temperature for 24 h and cast on a Petri disk for 12 h. Then the membrane was dried in an oven at 100 °C under vacuum for 24 h. The solvent used for PES and PSf was CH₂Cl₂. In the case of Hyflon AD60X, Galden HT was used. In this case, to evaluate the effect of solvent in the polymeric matrix, in addition to Hyflon based dried membrane, a membrane sample without solvent removal has been prepared (4-HF.D1S, Table 1 and Fig. 1).

Asymmetric membranes were prepared by phase inversion induced by a non-solvent. For PES and PSf polymers, the cobalt complex was solubilized in the solvent then the polymer was added. The resulting solution was stirred at room temperature for 24 h and casted on a glass support and immediately immersed for 2 h in a coagulation bath containing acetonitrile. Then, the resulting membranes have been washed in ethanol and dried in an oven at 100 °C under vacuum for 24 h.

2.3. Membrane characterization

The polymeric catalytic membranes were characterized by the following methods:

Table 1
Summary of the experimental conditions for catalytic membrane preparation.

Membrane	Polymer	Solvent	Cobalt complex	cat wt%	Non-solvent	PS induced by
4-PES.D	PES (9.92 wt%)	CH ₂ Cl ₂ (89.3 wt%)	(±)-4 (0.79 wt%)	7.4	-	Solvent evaporation
4-PES.A	PES (9.92 wt%)	CH ₂ Cl ₂ (89.3 wt%)	(±)-4 (0.79 wt%)	7.4	Acetonitrile	Non-solvent
4-PSf.D	PSf (9.92 wt%)	CH ₂ Cl ₂ (89.3 wt%)	(±)-4 (0.79 wt%)	7.4	-	Solvent evaporation
4-PSf.A	PSf (9.92 wt%)	CH ₂ Cl ₂ (89.3 wt%)	(±)-4 (0.79 wt%)	7.4	Acetonitrile	Non-solvent
4-HF.D1 ^a	Hyflon (9.92 wt%)	Galden HT (89.3 wt%)	(±)-4 (0.79 wt%)	7.4	-	Solvent evaporation
(<i>R,R</i>)-4-HF.D1	Hyflon (9.92 wt%)	Galden HT (89.3 wt%)	(<i>R,R</i>)-4 (0.79 wt%)	7.4	-	Solvent evaporation
4-HF.D2	Hyflon (9.84 wt%)	Galden HT (88.6 wt%)	(±)-4 (1.57 wt%)	15	-	Solvent evaporation
4-HF.A	Hyflon (9.92 wt%)	Galden HT (89.3 wt%)	(±)-4 (0.79 wt%)	7.4	<i>n</i> -Hexane	Non-solvent

^a By using these same experimental conditions, a membrane sample without solvent removal has been prepared, 4-HF.D1S.

Table 2
Cyclopropanation of α -methylstyrene by diazoacetates catalyzed by cobalt(II)–salen complexes in the homogeneous phase^a.

Entry	Catalyst	Diazoacetate	Time (h)	Diazoacetate conv. (%) ^b	Yield ^c (ee) ^d cis	Yield ^c (ee) ^d trans
1	(R,R)- 1	EDA	10	90	43 (38)	42 (26)
2	(R,R)- 2	EDA	5	>99	33 (67)	65 (24)
3	(R,R)- 3	EDA	1	>99	55 (93)	45 (54)
4	(R,R)- 4	EDA	3	>99	60 (80)	31 (58)
5	(R,R)- 5	EDA	2	>99	53 (87)	44 (52)
6	(R,R)- 6	EDA	4	>99	63 (75)	34 (61)
7	(R,R)- 4	^t BDA	3	94	56 (81)	17 (65)
8	(R,R)- 6	^t BDA	4	90	62 (79)	19 (59)

^a General procedure for cyclopropanation reactions: catalyst (1.5×10^{-2} mmol) in benzene (10 mL) at room temperature; mol ratios catalyst/NMI/diazoacetate/olefin 1:3:15:120.

^b The diazoacetate conversion was monitored by IR spectroscopy, measuring the intensity of the absorption of the N₂ group.

^c Isolated yields with respect to EDA.

^d Determined by chiral HPLC (DAICEL CHIRALPAK AD, *n*-hexane/*i*-PrOH = 9:1); absolute configurations: *cis*-cyclopropanes were (1*R*,2*S*), *trans* cyclopropanes were (1*R*,2*R*). The opposite enantiomers were obtained in the same ee when employing (*S,S*)-complexes.

- (1) The morphology of the membranes was evaluated by means of SEM at 20KV (Cambridge Instruments Stereoscan 360).
- (2) The success of cobalt based catalyst entrapment and its uniform dispersion in the polymeric membranes was evaluated by EDX (Philips EDAX analysis system) and BSE (Cambridge Instruments Stereoscan 360) techniques.
- (3) The membrane swelling was investigated by the following procedure:

Dried samples of membranes were immersed at 25 °C in benzene or *n*-hexane and in solutions of the substrate (α -methylstyrene, 0.1 M; ethyl diazoacetate, 0.01 M) in the same two solvents. Samples were withdrawn from the solvent every now and then, and weighed after removal of the surface solvent by light blotting with a filter paper. Membrane swelling was monitored until the film had reached a constant weight.

2.4. UV calibrating curves

The UV calibrating curve in benzene was determined by measuring the absorbance at 411 nm of five solutions of **4** in benzene. (1) 1.00×10^{-6} mol/L, $A = 1.54 \times 10^{-2}$; (2) 5.00×10^{-6} mol/L, $A = 6.78 \times 10^{-2}$; (3) 1.00×10^{-5} mol/L, $A = 1.32 \times 10^{-1}$; (4) 5.00×10^{-5} mol/L, $A = 5.83 \times 10^{-1}$; (5) 1.00×10^{-4} mol/L, $A = 1.14$.

The UV calibrating curve in 1,2-dichloroethane (1,2-DCE) was determined by measuring the absorbance at 408 nm of five solutions of **4** in 1,2-dichloroethane. 1) 1.00×10^{-6} mol/L, $A = 1.15 \times 10^{-2}$; 2) 5.00×10^{-6} mol/L, $A = 6.68 \times 10^{-2}$; 3) 1.00×10^{-5} mol/L, $A = 1.31 \times 10^{-1}$; 4) 5.00×10^{-5} mol/L, $A = 5.77 \times 10^{-1}$; 5) 1.00×10^{-4} mol/L, $A = 1.13$.

Due to the extremely poor solubility of complex **4** in *n*-hexane, the UV calibrating curve was not determined in this last solvent.

2.5. Catalytic reactions (homogeneous phase)

In a typical run the catalyst (1.5×10^{-2} mmol) was added to the solution of the olefin and NMI (NMI = *N*-methylimidazole) in benzene (10 mL). Then the diazoacetate was added and the reaction was stirred at room temperature for the time needed to consume all the starting diazoacetate. The catalyst/NMI/diazoacetate/olefin molar ratio was 1:3:15:120. The consumption of the diazoacetate was monitored by IR spectroscopy, following the disappearance of the band due to the stretching of the N₂ moiety at 2114 cm⁻¹. The reaction was considered to be finished when the absorbance of the diazoacetate band in the IR spectrum of the solution, measured with a 0.5 mm thick cell, was at or below 0.03. At this point the reaction mixture was analyzed by GC–MS, the mixture was evaporated to dryness in vacuo and the residue purified by chromatography on silica gel (eluant AcOEt/*n*-hexane = 0.7:10). Reagent amounts are given in Table 2.

2.6. Catalytic reactions (heterogeneous phase)

In a typical run the catalytic membrane, cut into slices (171 mg membrane containing complex **4**, 7.4 wt%, 12.6 mg; 9.53×10^{-3} mmol) was stirred with NMI (7.0 mg, 8.58×10^{-2} mmol), EDA (EDA = ethyl diazoacetate) (16.3 mg, 0.140 mmol) and α -methylstyrene (112.5 mg, 9.53×10^{-1} mmol) in distilled benzene (10 mL). The catalyst/NMI/EDA/olefin molar ratio was 1:9:15:100. The consumption of the EDA was monitored by IR spectroscopy, following the disappearance of the band due to the stretching of N₂ moiety at 2114 cm⁻¹. The reaction was considered to be finished when the EDA absorbance band in the IR spectrum of the solution, measured with a 0.5 mm thick cell, was at or below 0.03. At this point the amount of complex **4** leached into the solution was measured by UV spectroscopy and the reaction mixture was analyzed by GC–MS. Then the reaction mixture was removed *via* cannula under dinitrogen, evaporated to dryness in vacuo and the residue purified by chromatography on silica gel (eluant AcOEt/*n*-hexane = 0.7:10).

In order to recycle the catalytic membrane, it was washed with freshly distilled benzene and then a benzene solution containing the required amounts of the reagents (calculated with respect to the amount of catalyst remained in the membrane) was added.

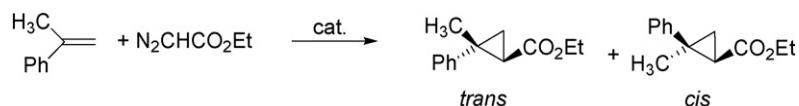
2.7. Membrane reactor

The catalytic reactions were also performed in a membrane reactor, where a peristaltic pump fed the permeation cell with the feed solution containing the reagents. The membrane in the permeation cell had an exposed surface area of 13.2 cm². The catalytic tests in the membrane reactor were carried out employing the following procedure: a benzene solution (50 mL) of EDA (0.161 mg, 1.41×10^{-3} mol), NMI (31 mg, 3.76×10^{-4} mol) and α -methylstyrene (2 mL, 1.5×10^{-2} mol) was pumped in the permeation cell containing the catalytic membrane. The catalyst/NMI/diazoacetate/olefin molar ratio was 1:90:350:3750. The consumption of the diazoacetate was monitored by IR spectroscopy, following the disappearance of the band due to the stretching of N₂ moiety at 2114 cm⁻¹, the amount of complex **4** leached into the solution was measured by UV spectroscopy and the reaction mixture was analyzed by GC–MS.

3. Results and discussion

3.1. Preparation of the catalysts and catalytic activity in homogeneous phase

The synthetic route to salen ligands is straightforward and can easily be adapted to the preparation of chiral compounds



Scheme 1. Cyclopropanation reaction catalyzed by cobalt(II) Schiff base complexes.

[29]. This offers the possibility to increase the number of conceivable ways to prepare a ligand suitable for heterogenization process. For this reason we turned our attention to salen complexes (Jacobsen-Katsuki catalysts) with different substituents on the aryl moieties. The ligands employed and the cobalt complexes thereof have been prepared in multigram-scale by condensation of commercially available, enantiomerically pure diamines (*i.e.* *trans*-1,2-diaminocyclohexane or 1,2-diphenylethylenediamine) with the substituted benzaldehydes followed by reaction with hydrated cobalt acetate. Fluorous benzaldehydes were prepared according to the procedures described by Pozzi et al. [25,26]. The long fluorous chains were introduced in the salen skeleton in order to enhance the affinity of the catalyst for Hyflon AD60X polymeric membrane. The cobalt complexes synthesized in the present study are reported in Fig. 1.

Before embedding the catalyst into the polymeric membrane, a study of the catalytic cyclopropanation reaction in the homogeneous phase was undertaken. In fact, despite cobalt–salen catalysts have been widely used in this class of reactions, the conditions normally employed (THF as solvent) are not the best suited for running the reaction in polymeric membranes due to polymer swelling and probable leaching of the catalyst. Moreover, although excellent papers have appeared on the subject [9–11], to the best of our knowledge, no clear data concerning the reaction kinetic have been reported. As model reaction we chose the cyclopropanation of α -methylstyrene, an olefin which is known to give cyclopropanes with low diastereoselectivity [10] and that undergoes polymerization less easily with respect to styrene, with EDA (Scheme 1). With all the cobalt(II) complexes tested we observed a complete conversion of the starting EDA at room temperature in 1–10 h, in the presence of NMI as additive [31]. Catalytic reactions were run by adding EDA to a benzene solution containing the olefin, the cobalt complex and NMI (catalyst/NMI/EDA/olefin ratio 1:3:15:120, see footnote of Table 2 for conditions), following by IR spectroscopy the disappearance of the band due to the stretching of the N_2 moiety ($\nu = 2114\text{ cm}^{-1}$).

The results in Table 2 compare well with what reported in the literature for related complexes, although some observations are worth to be made. It is well known that metallo–salen complexes are flexible and can adopt various ligand conformations, depending on the ligand substituents [32]. Katsuki et al. have elegantly shown that the presence or absence of C3 and C3' groups (Fig. 1) does not affect the direction of enantioselection [10]. In our catalytic system, it is clear that the presence of the bulky *tert*-butyl groups in the 3 and 3' position has proved beneficial in both enantioselectivity (compare entry 1 with entry 3, Table 2) and the catalyst stability. The activity of the fluorous cobalt(II)–salen complex **4** in benzene is superior to that reported by Pozzi and O'Hagan for the same complex in the cyclopropanation of styrene with EDA employing THF as solvent [33]. But more surprisingly, the diastereoselection of the reaction is strongly affected by the presence of the fluorous chain in the 5 and 5' position. In the case of **2** the *trans* cyclopropane was obtained as the major diastereoisomer (*trans/cis* ≈ 2), although with low enantiomeric excess (entry 2). On the other hand a *cis/trans* ratio of ca. 2 was observed employing complexes **4** and **6**. The reason for such a behavior is not clear at the present stage, but it is evident that the presence of electron withdrawing substituents in 5 and 5' positions affects more the diastereoselectivity and the activ-

ity of the catalyst than the enantioselectivity, as already pointed out in the literature [33].

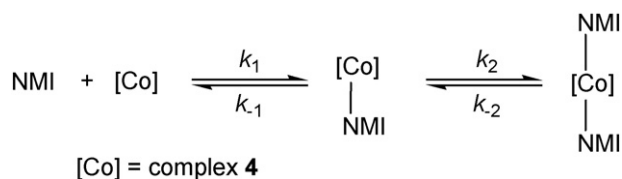
In general, the stereoselectivity of the asymmetric cyclopropanation increases as the steric requirement of the ester alkyl group of the α -diazoacetate becomes larger. When we examined the catalytic reactions with *tert*-butyl diazoacetate (*t*BDA), catalyzed by **4** and **6**, again we observed a slight increase in diastereoselectivity (*cis/trans* ≈ 3 , compare entries 7 and 8 with entries 4 and 6 respectively), but the enantioselectivities remained almost unchanged.

To better study the role of the olefin, we have studied the cyclopropanation of other substrates. Good results (in all cases conversion >99% in 1.5 h, *cis/trans* ≈ 2 , when two diastereoisomers could be obtained) have been obtained by using (*R,R*)-**6** as catalyst and EDA in the optimized conditions, when employing terminal styrene derivatives, like styrene, *p*-chlorostyrene, *p*-methylstyrene and 1,1-diphenylethylene. In all cases the enantiomeric excesses were similar to those observed with α -methylstyrene. The reaction becomes instead extremely slow when non-terminal olefins, like *cis*-stilbene (less than 35% conversion of the starting EDA after one week), β -methylstyrene and dihydronaphthalene, are employed.

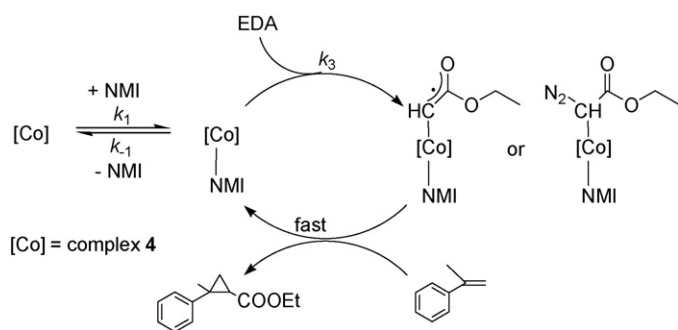
3.2. Kinetic studies

To clarify the mechanism of the cyclopropanation reactions we performed a kinetic study. The reaction between EDA and α -methylstyrene catalyzed by cobalt(II)–salen complexes was followed by IR spectroscopy, monitoring the intensity of the 2114 cm^{-1} absorption of the N_2 moiety. All reactions were conducted at room temperature and showed an excellent first-order dependence of the rate on EDA concentration ($R^2 > 0.99$ for all reactions). The kinetics is also first-order with respect to the catalyst, as shown by a series of experiments run by employing different amounts of **3**. We can rule out any term independent from the catalyst in the reaction rate since the fitting for the plot of k_{obs} versus the **3** concentration can be forced to pass through the origin without affecting to a large extent the R^2 value ($R^2 = 0.99$). On the other hand, a zero order dependence of the reaction rate on α -methylstyrene ($k_{obs}/[\text{Co}]$) concentration was observed. The reaction rate depends also on NMI concentration, but in this case a more complex behavior was observed. The reaction, very slow in the absence of any additive (more than 6.5 h at 50°C with complex **4** as catalyst under otherwise identical conditions as those reported in Table 2 footnote), becomes fast upon the addition of 3 equivalents of NMI ($[\text{NMI}] = 1.05 \times 10^{-2}\text{ M}$) with respect to the catalyst ($[\text{Co}] = 3.5 \times 10^{-3}\text{ M}$) ($k_{obs}/[\text{Co}] = 6.86\text{ M}^{-1}\text{ s}^{-1}$). A remarkable increase of the reaction rate is observed upon the addition of 5 and 10 equivalents of NMI ($[\text{NMI}] = 1.73 \times 10^{-2}\text{ M}$ and $[\text{NMI}] = 3.50 \times 10^{-2}\text{ M}$, respectively), but no linear correlation is observed when increasing the amount of the additive. The positive effect of such an addition is completely reversed at NMI concentration higher than $6 \times 10^{-2}\text{ M}$. It is reasonable to assume that under these conditions two molecules of NMI can coordinate to the central metal atom forming a catalytically inert species (Scheme 2).

Such a dependence of the reaction rate on the added nitrogen ligand concentration has been recently proposed by our group to occur in the asymmetric cyclopropanation of olefins catalyzed by chiral cobalt(II)–binaphthyl porphyrins [34].



Scheme 2. Proposed formation of the NMI cobalt complexes.



Scheme 3. Suggested catalytic cycle for cyclopropanation.

In the commonly accepted mechanism of cobalt catalyzed cyclopropanation reaction, the cobalt–carbene intermediate is considered to be generated from the starting cobalt(II) complex with diazoacetate and then to react with the alkene to afford the resulting cyclopropane. The presence of the ethylene bridge in salen complexes has been proposed, on the basis of DFT calculations, by Yamada et al. to favor the reaction to proceed via a concerted mechanism [35]. Theoretical analysis of the effect of the axial ligand for 3-oxobutylideneaminatocobalt(II) catalyzed cyclopropanation reaction has shown that NMI should coordinate the cobalt atom to reduce the activation energy of the formation of the cobalt(II)–carbene complex [36]. The occurrence of such a cobalt–carbene complex has been confirmed by the same group by FAB-mass spectroscopy [37]. The observed kinetic data, together with the synthetic results, are in agreement with a reaction for which the rate determining step is the formation of an adduct between the diazoalkane and the metal complex that can lead to the formation of the cobalt–carbene complex. This cobalt–carbene complex should transfer the carbene moiety to the incoming olefin in a fast reaction step, which becomes very slow for non-terminal – sterically hindered alkenes (Scheme 3). Such a picture would imply that the incoming olefin approaches the carbene intermediate in an end-on fashion.

3.3. Membrane preparation and characterization

The catalytic membranes based on polyethersulfone (PES), polysulfone (PSf) and a fluorinated polymer, Hyflon AD60X (HF) were prepared by phase inversion methods [30] to yield, depending on the used technique, two different kinds of catalytic membranes. The first one, dense and symmetric, was prepared by phase inversion induced by solvent evaporation and the second one, asymmetric with a dense skin layer and a porous sublayer, was prepared by non-solvent induced phase inversion using *n*-hexane or acetonitrile as external non-solvent. In both cases, the occlusion of catalytic complexes in polymeric membranes did not involve strong interaction forces between the complex and the polymer.

In Fig. 2 SEM analyses of membrane surfaces of symmetric membranes 4-HF.D1 and 4-HF.D2 are shown. It is evident a very good dispersion of the catalytic complex for the first membrane, whilst for the second one (prepared by increasing the catalyst concentration from 0.79 to 1.57 wt%) agglomerates are visible.

The catalyst has also been dispersed successfully in PES and PSf matrix by using a low catalyst loading of 0.79 wt%. As for Hyflon AD60X, the membranes prepared with these two polymers showed a uniform surface. The main differences of membranes 4-PES.A, 4-PSf.A and 4-HF.A compared to the analogue membranes prepared by using solvent evaporation (Table 1), concern the cross-section. In Fig. 3 SEM analyses of cross-sections of asymmetric membranes 4-PES.A, 4-PSf.A and 4-HF.A are shown and compared with 4-HF.D1. Voids of different sizes from top to membrane bottom characterize the membrane cross-sections of the asymmetric membranes.

To evaluate any interaction between the material of the catalytic membranes and the solvent and reagents used in the catalytic tests, the membranes prepared by using PSf, PES and Hyflon AD60X have been characterized by means of sorption analysis in two different organic solvents (*n*-hexane and benzene). The same sorption experiments have been repeated also in presence of both reagents used in the catalytic reactions, namely α -methylstyrene (0.1 M solution in the solvent) and ethyl diazoacetate (0.01 M). In Fig. 4, the results of these analyses are shown.

Hyflon AD60X showed the best resistance in both solvents *n*-hexane and benzene. Using *n*-hexane as solvent, the sorption for the membranes based on PES and PSf was again nearly absent. On the contrary, the polymers PES and PSf containing an aromatic moiety showed significant sorption in benzene (Fig. 5a). The addition of either α -methylstyrene or ethyl diazoacetate changes somewhat the observed results. In particular the presence of the former caused an increase in the sorption value compared to the pure solvent.

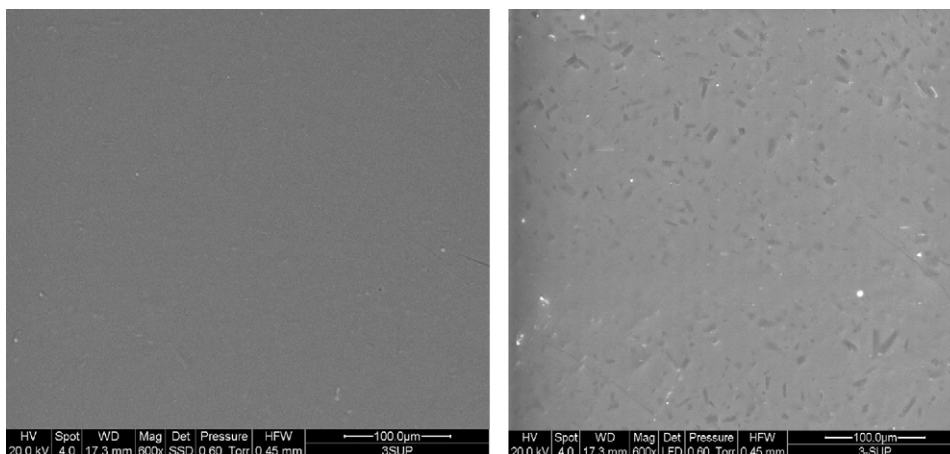


Fig. 2. SEM analyses of top surfaces of 4-HF.D1 (left) and 4-HF.D2 (right).

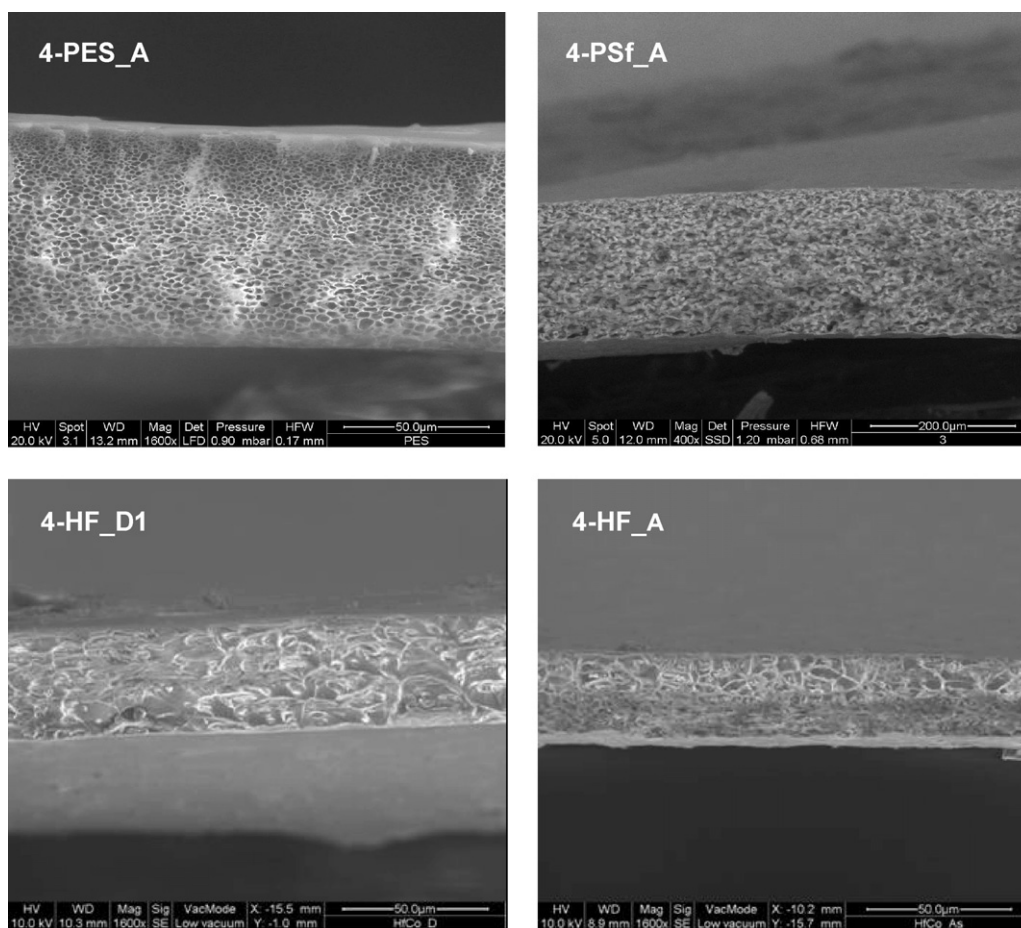


Fig. 3. SEM analyses of cross-section of **4**-PES.A (top left), **4**-PSf.A (top right), **4**-HF.A (bottom left) and **4**-HF.D (bottom right).

For Hyflon AD60X based membranes, no catalyst leaching was observed at the end of the sorption experiments, while a significant leaching was measured for PES and PSf membranes using benzene as solvent.

3.4. Catalytic activity

Before exploring the catalytic activity of membranes based on PES, PSf and on Hyflon AD60X we have investigated the suitability of these polymeric materials as support for the cyclopropanation reactions. To this aim, we have performed a reaction between α -methylstyrene and EDA in the presence of a membrane prepared without the occlusion of the catalyst and using the same experimental conditions (benzene as solvent) used for the homogeneously catalyzed reactions. No reaction was observed (see entry 1, Table 3 for an example using Hyflon AD60X). Similar results in *n*-hexane, due to swelling problems in benzene, *vide supra*, have been obtained employing PES or PSf). This proves that PSf, PES and Hyflon AD60X membranes are stable under the catalytic conditions and that they are not responsible for any chemical transformation of the reaction components.

The preliminary reactions described here were performed by cutting the membrane into slices, as often done in the literature [22], and suspending it into the solvent in a magnetically stirred glass flask. However, this procedure causes problems in the reproducibility of the reaction, since the membrane pieces tend to adhere to the walls of the flask and moreover the occasional mechanical friction of the membrane with the stirring bar may contribute to their degradation. Such an approach, still, allowed

us to perform several catalytic tests to select the better polymeric support to embed the catalyst before performing the reaction in the designed membrane reactor (see later). For practical reasons the optimization study of the heterogeneously catalyzed cyclopropanation reaction has been performed embedding into the membranes the more readily available racemic complex **4**.

Before using a symmetric Hyflon AD60X membrane at 7.4 wt% loading of **4** (**4**-HF.D1S) in a catalytic reaction, the latter was stirred in benzene at 75 °C for 2 h to wash out any salen complex not firmly fixed to the polymeric material. A catalyst leaching of 3.6% (corresponding to a 3.5×10^{-5} mol/L solution) was calculated using the UV calibrating curve reported in Section 2.

Then the solvent was removed and the membrane **4**-HF.D1S was used as catalyst in benzene for the reaction between α -methylstyrene and EDA.

Best results have been obtained using **4**-HF.D1S in benzene, with a complete conversion of the starting EDA in 26 h and an almost quantitative yield in cyclopropanes (99%) (Entry 2, Table 3). The same ratio *cis/trans*=2 that was observed in the homogeneous phase was found even in this case. As reported in entry 2 of Table 3, the leaching of **4** gave a 5.0×10^{-6} mol/L solution of the catalyst. When a homogeneous catalytic reaction was performed with a concentration of **4** equal to that lost in solution we did not observe any significant EDA conversion after 24 h, under otherwise similar catalytic conditions. These data indicate that the cyclopropane formation is due to the activity of the catalytic membrane rather than to that of complex **4** present in solution. The efficiency of NMI in promoting cyclopropanation reactions has been verified even in the heterogenized system. In fact, in the absence

Table 3
Cyclopropanation of α -methylstyrene by EDA catalyzed by polymeric membrane catalysts^a.

Entry	cat	Solvent	Time (h)	EDA conv. (%) ^b	Yield (%) ^c	cis/trans ^c	cat leached (mol/L) ^d
1	HF	Benzene	1st run 240	<5	–	2:3	–
2	4-HF_D1S	Benzene	1st run 26	>99	99	2:1	5.0×10^{-6}
3 ^e	4-HF_D1S	Benzene	1st run 72	<10	–	2:3	2.1×10^{-6}
4 ^f	4-HF_D1	Benzene	1st run 48	>99	99	2:1	$<10^{-6}$
			2nd run 96	80	75	2:1	$<10^{-6}$
			3rd run 96	50	25	1:1	$<10^{-6}$
5	4-HF_D1S	<i>n</i> -Hexane	1st run 72	45	20	1:1	n.d.
			6	4-HF_D1S	1,2-DCE	1st run 72	40
2nd run 72	<15	–	2:3			$<10^{-6}$	
7	4-HF_D2	Benzene	1st run 96	<15	–	2:3	7.9×10^{-5}
8	4-HF_A	Benzene	1st run 96	<15	–	2:3	1.8×10^{-5}
9	4-PES_D	Benzene	1st run 96	60	45	2:1	2.6×10^{-6}
			2nd run 96	50	30	2:1	$<10^{-6}$
10	4-PES_D	<i>n</i> -Hexane	1st run 96	70	40	1:1	n.d.
			11 ^g	4-PSf_D	<i>n</i> -Hexane	1st run 24	45

^a General procedure for cyclopropanation reactions: **cat** (9.53×10^{-3} mmol) in the solvent (10 mL) at room temperature; mol ratios **cat**/NMI/EDA/ α -methylstyrene = 1:9:15:100.

^b The EDA conversion was monitored by IR spectroscopy, measuring the intensity of the absorption of the N₂ group.

^c Determined by GC–MS (yield refer to the sum of cyclopropanes).

^d Molar concentration of **cat** in solution at the end of each run measured by UV spectroscopy.

^e Without the addition of NMI.

^f Before use the membrane was kept under vacuum at 90 °C to remove any solvent used in the preparation.

^g The reaction was run at 45 °C.

of the additive the reactions becomes extremely slow (Entry 3, Table 3).

Particular attention has been given to the preparation of the polymeric membrane and to the solvents employed for this purpose. A perfectly homogeneous membrane, that is well suited for the catalytic reaction, could be obtained by using as solvent Galden HT, a mixture of oligomeric perfluorinated ethers that can be represented by the general

formula $\text{CF}_3-(\text{CF}_2-\text{CF}(\text{CF}_3)-\text{O})_m-(\text{CF}_2-\text{O})_n-\text{CF}_3$, that has the effect of enhancing the hydrophobicity and lipophilicity of the membrane [38]. It is reasonable to assume that a more lipophilic membrane should show a better affinity for the diazoalkane. When the membrane was kept under vacuum at 90 °C to remove the solvent Galden HT used for its preparation before use, the amount of **4** leached was below the detectability limit but the catalytic activity was decreased and the time needed for the quantitative conversion of the starting EDA almost doubled (Entry 4, Table 3).

In order to recycle the catalytic membrane, it was washed with freshly distilled benzene and then a benzene solution containing the required amounts of the reagents was added. A quite fast degradation of the catalytic membrane, probably due to partial oxidation of the cobalt metal ions, was observed and already at the third recycle the membrane was much less active. This can be explained with a catalyst deactivation but any attempt to recover the catalyst from the membrane after its use met with failure and uncharacterizable mixtures of cobalt containing complexes were always obtained.

Cobalt salen complexes are almost insoluble in *n*-hexane and this renders this solvent not suitable for running homogeneous

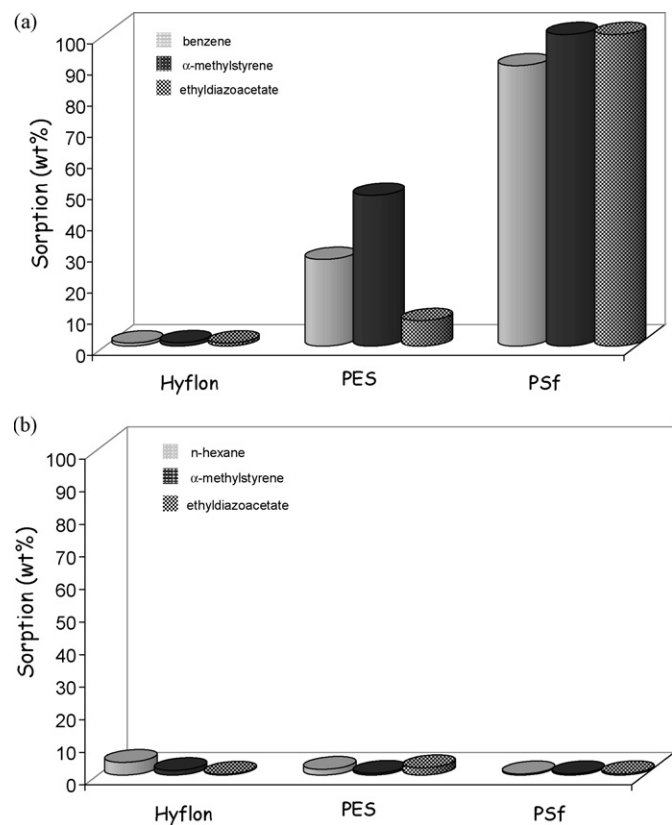


Fig. 4. Room temperature sorption experiments for: (a) benzene, α -methylstyrene (0.1 M) and EDA (0.01 M) in benzene and (b) *n*-hexane, α -methylstyrene (0.1 M) and EDA (0.01 M) in *n*-hexane.

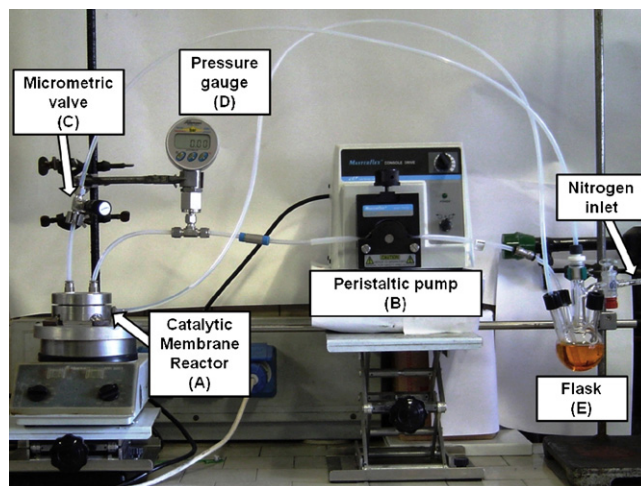


Fig. 5. Picture of the Catalytic Membrane Reactor (A) equipped with a peristaltic pump (B) employed to perform catalytic reactions.

reactions. Considering that the choice of the reaction solvent is not limited any more by the solubility of cobalt complexes, we have decided to explore the use of the more eco-friendly *n*-hexane for performing the catalytic reaction. Unfortunately, with this last solvent we observed a dramatic decrease in the reactivity of the catalytic membrane and after 72 h, only 45% of the starting EDA was converted and, together with the desired cyclopropanes, large amounts of fumarate and maleate, the coupling products of EDA, were obtained. We next monitored the reaction in 1,2-dichloroethane (1,2-DCE), a solvent that has been used in our group with success in the copper catalyzed cyclopropanation [39]. The amount of **4** leached in the solution was almost negligible, but even in this case the catalytic outcome of the reaction was unsatisfactory and the membrane lost any catalytic activity already in a second run (Entry 6, Table 3).

We next monitored the activity of the catalytic membrane **4**-HF.D2, prepared in the same manner but increasing the catalyst loading from 7.4 to 15 wt%. A catalytic activity (<15% EDA conversion with *cis/trans* ratio 2:3 in 96 h) was observed, even if the catalyst leaching was only slightly increased if compared to that of the membrane at 7.4 wt% loading of **4**. The surface analysis of **4**-HF.D2 membrane revealed an inhomogeneous dispersion of the catalyst and the formation of aggregated structures therefore an increase of the catalyst loading from 7.4 to 15 wt% did not produce a better membrane performance. Again any attempt to recycle the membrane was unsuccessful. To increase the catalyst accessibility, we decided then to move from dense symmetric membranes, in which the activity of surface layer is more prominent than the catalytic activity of the bulk material because the transport of the components follows the solution-diffusion model, to asymmetric ones in which a dense skin layer is supported on a porous sublayer. For instance, the membrane **4**-HF.A, has been prepared occluding 7.4 wt% of **4** in Hyflon AD60X by phase inversion technique induced by a non-solvent (*n*-hexane, see Table 1). Although the catalyst leaching was again negligible, in contrast to what expected, no catalytic activity was observed (Entry 8, Table 3). We have noticed that this last membrane is more sensible toward oxidation and that at the end of the reaction the orange colour due to the presence of the cobalt(II) complex disappeared to give a brownish colour typical of cobalt(III) species. This can explain the low reactivity observed.

We next studied the catalytic activities of the membranes prepared with PES and PSf. The membrane **4**-PES.D is not very stable in benzene due to partial swelling, that is anyway reduced in the presence of EDA, and the quantity of **4** leached was <0.3%, but again the catalytic activity was poorer (Entry 9, Table 3). A conversion of 70% of the starting EDA with a 57% cyclopropanes selectivity in 96 h was observed in *n*-hexane, the other products being fumarate and maleate (Entry 10, Table 3).

On the other hand, **4**-PSf.D is not stable in benzene, due to swelling, and is almost catalytically inactive at room temperature in *n*-hexane. We observed a catalytic activity only after increasing the temperature at 45 °C (Entry 11, Table 3).

Since the best catalytic results have been obtained with **4**-HF, our study has focused on this particular catalyst to study the asymmetric version of the reaction by embedding the enantiopure (*R,R*)-**4** at 7.4 wt% into the Hyflon AD60X membrane. A catalytic reaction was then performed using the same experimental conditions reported for entry 2 in Table 3 but with (*R,R*)-**4**-HF.D1 as catalyst. After separation of the membrane and purification by column chromatography of the crude, we determined by chiral HPLC a 60% and a 39% enantiomeric excesses for the *cis* and *trans* cyclopropanes respectively. The catalytic membrane was washed with freshly distilled benzene and then the required amounts of the reagents and benzene were added again. However, only a modest catalytic activity was observed after 48 h, and almost racemic cyclopropanes were recovered after purification of the crude.

As already pointed out in the introduction, the use of polymeric catalytic membranes allows the reaction to be performed in a catalytic membrane reactor (CMR) in which the reaction and separation processes can be combined in a single stage. For this reason we have designed the apparatus depicted in Fig. 5, in which a stainless steel reactor (A) is equipped with a peristaltic pump (B), a micrometric valve (C), a pressure gauge (D) and a four necked flask with a nitrogen inlet (E). The reactor is constructed having a sample inlet and a sample outlet at the top and a sample outlet at the bottom to allow the permeate solution to be collected. The permeation ratio, that is, the rate of permeation/introduction, can be adjusted by means of the micrometric valve (C). At this stage, both the permeate and the retentate were recirculated to the reservoir flask. The membrane in the reactor was supported on a porous stainless steel disk. The membrane reactor has an effective area of 13.2 cm² (membrane diameter of 42 mm). All the connections were made with PTFE tubing to avoid any contact of the reagents with potentially reactive surfaces. A similar membrane reactor, employed in the oxidation of benzene to phenol under mild conditions, has been recently reported by Molinari and Poerio [40].

We first monitored the system without the catalytic membrane by placing a Teflon foil on the porous stainless steel disk and charging the flask with the minimum amount of benzene (50 mL, enough to fill all the reactor and connections to the flask). We next introduced the reagents (EDA and α -methylstyrene in the same ratio and concentration used for the previously described tests) and the reaction mixture was circulated for 96 h. No reaction was observed. Then several tests were performed by using the (*R,R*)-**4**-HF.D1 membrane. Firstly, the membrane stability was checked and benzene (50 mL) was circulated in the system for several hours. A leaching of less than 10⁻⁶ mol/L was calculated using the UV calibrating curve reported in the Experimental. Then the pressure was increased by means of the micrometric valve (C) up to 0.5 bar. Under these conditions a permeation ratio of ca. 0.5 was observed. The solvent was allowed to circulate for 96 h and then the membrane was analyzed and confirmed to be unchanged. The concentration of the catalyst leached in solution was again lower than 10⁻⁶ mol/L. A similar test was repeated by introducing also α -methylstyrene and NMI into the apparatus. The same results were observed. Finally a catalytic test was run. Due to the surface area of the membrane reactor only 4.10⁻⁶ mmol of the actual catalyst could be charged into the reactor and at the same time the volume needed for the system to circulate was fivefold the volume in the previously described batch reactions. That means that the ratios employed in the membrane reactor were actually **cat**/NMI/EDA/ α -methylstyrene = 1:90:350:3750. Under these conditions the catalytic reaction at room temperature becomes very slow and after 8 h only 17% of the starting EDA was converted. GC-MS analysis revealed a 50% yield in cyclopropanes derivatives with a *cis/trans* ratio 2:3. Along with minor amounts of maleate and fumarate (20%), we observed also the formation of 2,4,6-cycloheptatriene-1-carboxylic acid, ethyl ester (25%), derived from the attack of EDA on the solvent. This was the only case in which we observed such a side product and we do not have a rationale explanation of such an observation at the present stage. The reaction products were isolated and the cyclopropanes derivatives were analyzed by chiral HPLC. Both derivatives were recovered with only 20% of enantiomeric excess.

4. Conclusions

In this paper we have reported a new catalytic method to obtain cyclopropanes using cobalt Schiff base complexes embedded in PES, PSf or Hyflon AD60X membranes. A complete study of the reaction in the homogeneous phase was undertaken, that allowed us to clarify some aspect of the reaction mechanism. The data of the catalytic

membrane system indicated that the results obtained in the homogeneous phase can be in part reproduced also in the heterogeneous phase, with an easier catalyst separation, recovery and recycling. Moreover, it should be emphasized that the heterogeneous system allows the reaction to be performed in a more friendly solvent as *n*-hexane. The results in the enantioselective version of the reaction have been also reported, clearly indicating that a moderate asymmetric induction can be obtained even in these conditions. Obviously there are still a lot of improvements to be done before the catalytic membrane reactor proposed can be competitive with the homogeneous catalyst. More efficient catalysts should be tested. However, in our opinion several points have been highlighted in the work presented here. While the activity of the catalyst seems to be a major problem, leaching is not, showing that the interaction between the polymeric material and the organic ligand is well matched. A new reactor has been designed and realized and we have shown that the system is working and this will help for future applications. It is intuitive to understand that the development of this innovative catalytic method should improve the synthesis of useful fine chemicals as cyclopropanes using environmentally benign technologies.

Acknowledgements

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References

- [1] M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* 107 (2007) 3117.
- [2] J. Salaun, *Top. Curr. Chem.* 207 (2000) 1.
- [3] T. Uchida, T. Katsuki, *Synthesis* (2006) 1715.
- [4] H. Lebel, J.-F. Marcoux, C. Molinaro, A.B. Charette, *Chem. Rev.* 103 (2003) 977.
- [5] H. Pellissier, *Tetrahedron* 64 (2008) 7041.
- [6] W. Hess, J. Treutwein, G. Hilt, *Synthesis* (2008) 3537.
- [7] A. Nakamura, A. Konishi, Y. Tatsuno, S. Otsuka, *J. Am. Chem. Soc.* 100 (1978) 3443.
- [8] T. Fukuda, T. Katsuki, *Tetrahedron* 53 (1997) 7201.
- [9] T. Niimi, T. Uchida, R. Irie, T. Katsuki, *Tetrahedron Lett.* 41 (2000) 3647.
- [10] T. Niimi, T. Uchida, R. Irie, T. Katsuki, *Adv. Synth. Catal.* 343 (2001) 79.
- [11] T. Uchida, B. Saha, T. Katsuki, *Tetrahedron Lett.* 42 (2001) 2521.
- [12] L. Huang, Y. Chen, G.-Y. Gao, X.P. Zhang, *J. Org. Chem.* 68 (2003) 8179.
- [13] B. Saha, T. Uchida, T. Katsuki, *Tetrahedron: Asymmetry* 14 (2003) 823.
- [14] Y. Chen, K.B. Fields, X.P. Zhang, *J. Am. Chem. Soc.* 126 (2004) 14718.
- [15] Y. Chen, X.P. Zhang, *Synthesis* (2006) 1697.
- [16] Y. Chen, X.P. Zhang, *J. Org. Chem.* 72 (2007) 5931.
- [17] V. Balzani, A. Credi, F.M. Raymo, J.F. Stoddart, *Angew. Chem. Int. Ed.* 39 (2000) 3349.
- [18] Z.Y. Zhang, S.G. Lin, *J. Appl. Polym. Sci.* 74 (1999) 1071.
- [19] B.M.L. Dooos, I.F.J. Vankelecom, P.A. Jacobs, *Adv. Synth. Catal.* 348 (2006) 1413.
- [20] C. Baleizao, H. Garcia, *Chem. Rev.* 106 (2006) 3987.
- [21] S.S. Ozdemir, M.G. Buonomenna, E. Drioli, *Appl. Catal., A* 307 (2006) 167.
- [22] I.F.J. Vankelecom, P.A. Jacobs, *Catal. Today* 56 (2000) 147.
- [23] M. Carraro, M. Gardan, G. Scorrano, E. Drioli, E. Fontananova, M. Bonchio, *Chem. Commun.* (2006) 4533.
- [24] I.F.J. Vankelecom, *Chem. Rev.* 102 (2002) 3779.
- [25] G. Pozzi, M. Cavazzini, F. Cinato, F. Montanari, S. Quici, *Eur. J. Org. Chem.* (1999) 1947.
- [26] M. Cavazzini, A. Manfredi, F. Montanari, S. Quici, G. Pozzi, *Eur. J. Org. Chem.* (2001) 4639.
- [27] J.F. Larrow, E.N. Jacobsen, Y. Gao, Y. Hong, X. Nie, C.M. Zepp, *J. Org. Chem.* 59 (1994) 1939.
- [28] E. Szlyk, A. Surdykowski, M. Barwiolek, E. Larsen, *Trans. Met. Chem.* 25 (2000) 670.
- [29] P.G. Cozzi, *Chem. Soc. Rev.* 33 (2004) 410.
- [30] M. Mulder (Ed.), *Basic Principles of Membrane Technology*, Second edition, 1996.
- [31] T. Yamada, T. Ikeno, H. Sekino, M. Sato, *Chem. Lett.* (1999) 719.
- [32] T. Katsuki, *Adv. Synth. Catal.* 344 (2002) 131.
- [33] I. Shepperson, S. Quici, G. Pozzi, M. Nicoletti, D. O'Hagan, *Eur. J. Org. Chem.* (2004) 4545.
- [34] S. Fantauzzi, E. Gallo, E. Rose, N. Raoul, A. Caselli, S. Issa, F. Ragaini, S. Cenini, *Organometallics* 27 (2008) 6143.
- [35] I. Iwakura, T. Ikeno, T. Yamada, *Org. Lett.* 6 (2004) 949.
- [36] T. Ikeno, I. Iwakura, S. Yabushita, T. Yamada, *Org. Lett.* 4 (2002) 517.
- [37] T. Ikeno, I. Iwakura, T. Yamada, *J. Am. Chem. Soc.* 124 (2002) 15152.
- [38] M.G. Buonomenna, E. Gallo, F. Ragaini, A. Caselli, S. Cenini, E. Drioli, *Catal Appl.* A 335 (2008) 37.
- [39] A. Caselli, F. Cesana, E. Gallo, N. Casati, P. Macchi, M. Sisti, G. Celentano, S. Cenini, *Dalton Trans.* (2008) 4202.
- [40] R. Molinari, T. Poerio, *Appl. Catal. A—Gen.* 358 (2009) 119.