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Ti(IV)-based catalytic membranes for efficient and selective oxidation of secondary amines

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Abstract—The incorporation of homogenous Ti(IV)/trialkanolamine catalyst in polymeric membranes provided new polymeric catalytic Ti(IV)-based membranes, stable and efficient as heterogeneous catalysts for chemoselective oxidations of secondary amines to nitrones by alkyl hydroperoxides. Polyvinylidene fluoride (PVDF)-based catalytic membranes gave the best results affording products in short reaction times, high yields and selectivity using as little as 1% of catalyst, comparable with the performances of the corresponding homogeneous system. PVDF–Ti membrane could be recycled up to five runs with no loss of activity.

Chemical processes catalysed by homogeneous transition metal complexes are increasingly utilized in the fine and basic chemical industry. The majority of such metal catalysts is often expensive, of limited environmental compatibility, or even toxic. The current trend towards a sustainable chemistry has given life to an increasing number of new strategies for catalyst immobilization, enabling an easy recovery, re-use and disposal at low costs of the catalyst.[1] A possible solution could be the use of catalytic polymeric membranes in which no catalyst recovery is required, reaction and separation of the products are coupled, catalysts may have longer life and the intact structure of the catalyst should be preserved inside the polymeric membranes, minimizing any change in activity and selectivity versus the homogeneous system.[2] As a proof of principle, Ru–BINAP,[3] Rh–DUPHOS[4] and Jacobsen catalyst for epoxidation of simple olefins[3] were entrapped in polydimethylsiloxane matrices affording performances comparable to the analogous homogeneous systems.[2] As far as oxygen transfer catalysis is concerned, the Sharpless–Katsuki epoxidation system[5] launched the rich field of titanium catalyzed asymmetric oxidations.[6] Since that breakthrough, chiral Ti(IV) alkoxides have been used to catalyze a variety of oxidative transformations affording highly stereoselective processes in the allylic alcohol epoxidation,[5] β-hydroxyamine *N*-oxidation,[7] sulfoxidation,[8] as well as in the Baeyer–Villiger oxidation of cyclobutanones.[9]

We have recently reported that tetradentate alkoxide ligands, namely C3-symmetric trialkanolamines **1**,[10] provide very stable Ti(IV) complexes (Fig. 1).[11] In the presence of alkyl hydroperoxides, such species are able to catalyze the asymmetric sulfoxidation of alkyl aryl sulfides with ee's up to 84% and with unprecedented catalytic efficiency, reaching turnover numbers (TON) of 1000[12] as well as the oxidation of secondary amines to

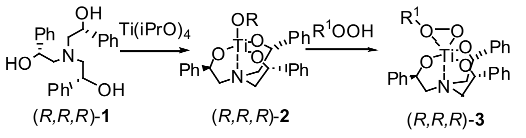

Figure 1. Synthesis of titanatrane complex (*R*,*R*,*R*)-**2** and the corresponding peroxocomplex (*R*,*R*,*R*)-**3** by reaction of (*R*,*R*,*R*)-tris-(2-phenylethanol)amine **1** with Ti(*i*-PrO)$_4$.

Keywords: Catalytic membranes; Nitrones; Ti(IV)-complexes; Trialkanolamines; *N*-Oxidation.

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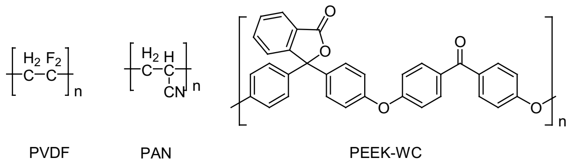
nitrones with high chemoselectivities, quantitative yields and TON up to 1400.[13]

Beside the fact that the oxygen transfer process affords in both cases the corresponding products with high chemical yields and good selectivities, the Ti(IV) catalyst was shown to be robust under the reaction conditions, which require the presence of large quantities of alkylperoxide[12] and, in the case of secondary amine oxidation, affords a stoichiometric amount of water.[13] Therefore, titanatrane complex **2** seemed to us a good candidate for preparing Ti(IV) polymeric catalytic membranes to be used in selective oxygen transfer reactions.[14] Because of their intrinsic stability they should survive the conditions required for the membrane synthesis. Once in the polymeric matrix, their stability should be even higher because secondary hydrolysis reactions will be minimized, extending catalyst life. Obviously, the effective recycling of the catalytic membrane will increase the total TON of the process.

Here we report on the successful preparation of different catalytic membranes incorporating Ti(IV)-complex **2** and their successful application for heterogeneous oxidation of secondary amines to nitrones.[15]

The preformed Ti(IV) (*R*,*R*,*R*)-tris-(2-ethanol)amine complex[11] (16%/w) has been entrapped in three different polymeric membranes using a phase inversion technique induced by a non-solvent (DMA and water, respectively).[16] Polymers characterized by a high thermal, chemical and mechanical stability were used for the preparation of catalytic membranes: polyvinylidene difluoride (PVDF),[17] a modified polyether-etherketone (PEEK-WC)[18] and polyacrylonitrile (PAN).[19]



The screening of activity of the different catalytic membranes [PVDF–Ti, PEEKWC–Ti, PAN–Ti] has been assessed in the oxidation to nitrones of dibenzylamine, chosen as a model substrate (Fig. 2).

The performance of the catalytic membranes was investigated under batch conditions using an equal active surface and comparable total catalyst loading. In order to have a better comparison of the results, the reactions were carried out under the best conditions selected for the homogeneous reactions. Due to the solubility of PEEK-WC in chlorinated solvents, which are the most suitable ones for the homogeneous reactions, the reactivity was initially explored in acetonitrile and the course of the reactions was monitored via ^{1}H NMR. Preliminary tests on the catalytic membranes indicated that catalyst leaching was not a severe problem.[20]

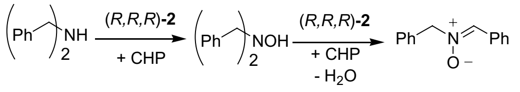
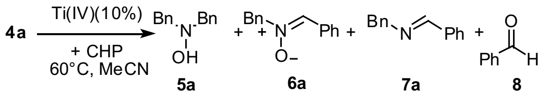


Figure 2. Chemoselective oxidation of dibenzyl amine by cumyl hydroperoxide (CHP) catalyzed by Ti(IV) complex (*R*,*R*,*R*)-**2**.

Table 1. Effect of the catalyst on reaction times and product distribution in the Ti-catalyzed oxidation of dibenzylamine with CHP[a]



Time (h)	Catalyst (product ratio: **4a**:**5a**:**6a**:**7a**:**8**)			
	Ti-**2**	PVDF–Ti	PAN–Ti	PEEKWC–Ti
3	4:5:74:5:3	38:12:44:6:0	54:6:25:11:4	92:1:6:1:0
7	1:4:78:4:13	0:7:82:5:6	49:6:27:12:7	82:1:14:3:0
25			9:0:40:18:33	58:1:34:7: 0
117				43:2:34:14:6

[a] Reaction conditions: $[\text{substrate}]_0 = 0.1$ M; $[\text{CHP}]_0 = 0.4$ M, catalyst = 10%mol; CD_3CN; $T = 60$ °C. ms.

In Table 1 the product distributions at increasing reaction times for the oxidations catalyzed by PVDFD–Ti, PEEKWC–Ti, PAN–Ti and by the Ti-**2** homogeneous system are reported.

Significantly, all three Ti-based catalytic membranes could activate CHP for the oxygen transfer process although the polymeric matrix plays an important role in determining performance and product distribution.

Reactions performed with PAN–Ti and PEEK-WC–Ti gave slow conversions of the reagent affording the nitrone in comparable amounts with *N*-benzylidene benzylamine and benzaldehyde. Furthermore, at long reaction times high amount of benzaldehyde were recovered due to further oxidation/hydrolysis of the products. On the contrary, PVDF–Ti efficiently catalyses the oxidation affording the nitrone in good yields (82%) in reasonable reaction times, almost comparable to the ones of the homogeneous system.[21]

The oxidation with catalytic membrane PVDF–Ti was also tested in chloroform. The kinetic profile of the reaction is reported in Figure 3.

In chloroform the reaction occurs much faster [$t_{1/2}$ ($CDCl_3$) = 65 min vs $t_{1/2}$ (CH_3CN) = 140 min] and the nitrone was recovered in high chemical yield (92%) with almost complete chemoselectivity (only traces of imine and hydroxylamine were detected).

The performance of the PVDF–Ti catalytic membrane has been also evaluated on the basis of system recycling. A set of experiments was carried out in order to examine its activity along five oxidation runs. After each experiment the membrane was removed from the reaction vessel, washed in chloroform in order to remove adsorbed

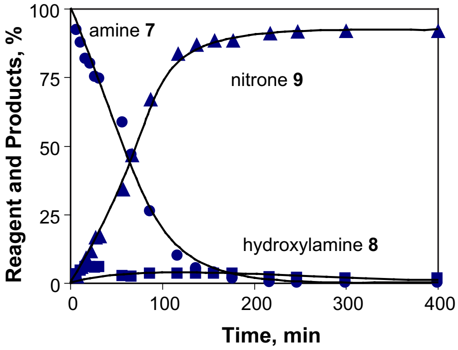


Figure 3. Oxidation of dibenzylamine with CHP catalyzed by PVDF–Ti catalytic membrane: $[\text{substrate}]_0 = 0.1\,\text{M}$; $[\text{CHP}]_0 = 0.4\,\text{M}$, catalyst = 10%mol; $T = 60\,°\text{C}$, ms = 250 mg/mmol in $CDCl_3$: (●) dibenzylamine; (■) dibenzylhydroxylamine; (▲) nitrone.

Table 2. Oxidation of dibenzylamine with CHP catalyzed by PVDF–Ti, catalyst recycling: substrate: $[\text{substrate}]_0 = 0.1\,\text{M}$; $[\text{CHP}]_0 = 0.4\,\text{M}$, catalyst = 10%mol; $T = 60\,°\text{C}$, $CDCl_3$, ms = 250 mg/mmol in run 1, 500 mg/mmol runs 2–5[a]

Run	Time$_{1/2}$ (min)	Nitrone (%)
1	39	92
2	10	90
3	14	90
4	14	90
5	23	90

[a] In the recycling, the presence of twice amount of ms proved to be beneficial in decreasing the formation of benzaldehyde.

reagent or products, and recycled. The results are reported in Table 2.

It is noteworthy that the catalytic activity of the PVDF–Ti membrane was maintained for all five runs, affording comparable yields of nitrone (90%) and that, indeed, catalyst leaching does not seem a severe problem. Interestingly, reaction rates in the recycling experiments were higher than the first one. The increased reactivity could originate from modifications of the polymeric membrane that render available a larger quantity of the catalyst or enhance the Lewis acidity of the metal complex. This important aspect will be addressed in future studies.

The effect of catalyst loading for the PVDF–Ti membrane was also tested at substrate/catalyst ratios from 10:1 to 1000:1 (Table 3).

The results reported in Table 3 show that complete conversion of dibenzylamine and >90% selectivity for the nitrone could be achieved also in the presence of 1% of catalyst. It is noteworthy that, in order to maintain the catalyst concentration at 0.01 M, these reactions were performed neat. However, further increasing the ratio to s/c = 1000 (which necessarily dropped the catalyst concentration to 0.001 M) resulted in a severe deterioration of chemoselectivity, as was also observed in the homogeneous system.[13]

Table 3. Effect of substrate/catalyst ratio on oxidation of dibenzylamine catalyzed by PVDF–Ti membrane or the homogeneous catalyst Ti(IV)-**2** in $CDCl_3$ at 60 °C[a]

$[\text{Sub}]_0$, M	Sub/cat	Catalyst	Time (h)	Nitrone (%)
0.1	10:1	Ti-**2**[b]	3	100
		PVDF–Ti	2.5	92
1.0	100:1	Ti-**2**[b]	1	100
		PVDF–Ti	3	90
1.0	1000:1	Ti-**2**[b]	100	68[c]
		PVDF–Ti	71	65[d]

[a] Conditions: dibenzylamine: CHP = 4:1, 4 Å molecular sieves in $CDCl_3$ at 60 °C.

[b] See Ref. 13.

[c] Complete reagent conversion; other products: *N*-benzylidene benzylamine (15%), PhCHO (15%).

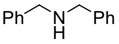
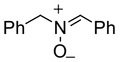
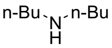
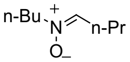
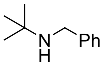
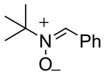
[d] Complete reagent conversion; other products: *N*-benzylidene benzylamine (10%), PhCHO (22%), 1,2-dichloroethane as solvent.

The conditions for the highest catalyst loading (10%) from Table 2 were adopted to explore the scope of the reaction with other secondary amines (Table 4).[22]

In all cases nitrones were readily isolated in synthetically significant chemical yields (80–93%) via removal of the solvent under vacuum followed by chromatography over silica gel.

In conclusion, novel heterogeneous oxidation catalysts have been synthesized by embedding Ti(IV)–trialkanolamine complexes within polymeric membranes. The reactivity studies allowed us to: (i) identify the PVDF–Ti catalytic membrane as the most reactive and stable system where the catalyst structure is preserved from hydrolysis; (ii) exclude the occurrence of competing homogeneous pathways due to catalyst leaching; and (iii) verify the stability of the embedded catalyst during recycling. We feel that the prospects for further and more general applications for the new PVDF–Ti catalytic membranes are excellent and we plan to pursue this research. Studies directed at the characterization of the catalytic membrane, especially the nature of the catalyst embedded in the polymeric matrix, are currently underway.

Table 4. Catalytic oxidation of secondary amines by CHP[a]

Substrate	Product	$T_{1/2}$ (min)	Yield (%)[b]
		39	92
		50	80
		20	93

[a] Reaction conditions: $[\text{substrate}]_0 = 0.10\,\text{M}$, $[\text{CHP}]_0 = 0.40\,\text{M}$; catalyst = 10%mol, 4 Å ms, $CHCl_3$ at 60 °C.

[b] Based on isolated product after chromatography. Reactions were carried out on mmol scale.

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22. Typical oxidation procedure with PVDF–Ti catalysis: in a 25 mL screw-cap vial, under nitrogen, containing 10 mL of $CHCl_3$ and 250 mg of 4 Å activated molecular sieves was added an amount of PVDF-membrane containing 0.1 mmol of Ti-**2**, followed by CHP (4.0 mmol, 80% in cumene) and, after 30 min, by the substrate (1.0 mmol). The solution was heated at 60 °C and the reaction course was monitored via TLC. After the disappearance of the reagent, the membrane was removed, solvent was distilled under vacuum and the reaction mixture was purified directly via radial chromatography over silica gel (gradient: ethyl ether, petroleum ether).