Bifunctional catalytic membrane containing Brønsted acids and sites for enantioselective hydrogenation

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The hydrogenation of methyl acetoacetate to give optically pure methyl 3-hydroxybutyrate is performed heterogeneously with high activity and enantioselectivity under mild reaction conditions due to the combination of Brønsted acid and Ru–binap sites in a polydimethylsiloxane membrane matrix.

Binap based complexes are among the most versatile and selective catalysts used to produce chiral compounds.[1] Given their extremely high cost, immobilization of the catalyst is highly desirable to allow regeneration of the catalyst.

The first attempt at immobilization consisted of a triphasic approach in which the sulfonated form of the complex was dissolved in an ethylene glycol phase which adhered on one side to a support, with the other side in contact with an immiscible phase containing the substrate.[2] The system, however, is restricted in the choice of possible substrates and solvents. Recently, we reported a new, more versatile method to immobilize binap based complexes by simple occlusion in a polydimethylsiloxane (PDMS) membrane.[3]

The hydrogenation of β-keto esters, catalyzed by binap based complexes, is a very important class of enantioselective reaction. Unfortunately, it suffers from the need for high reaction temperatures (> 60 °C) and high hydrogen pressures (> 6 MPa).[4] In homogeneous reaction conditions, King *et al.* discovered that the addition of small amounts of strong inorganic acids allows the reaction to occur at 40 °C using reduced hydrogen pressures.[5] This, however, requires the separation of the acid from the products after reaction to keep the catalyst active and enantioselective.

In the present work, both a Ru–binap complex and toluene-*p*-sulfonic acid (PTSA) have been immobilized in a PDMS membrane *via* the same technique and used in the enantioselective hydrogenation of β-keto esters. This acidic chiral membrane shows substantially enhanced enantioselectivity and activity at room temperature, allowing catalyst separation and reuse after simple filtration.

Typically, binap–chloro(*p*-cymene)–ruthenium chloride was occluded in an elastomeric-type PDMS membrane together with PTSA. To do so, the PDMS membrane was synthesized in the presence of the binap complexes and the organic acid. A 20 vol% solution in chloroform of appropriate amounts of the prepolymer (RTV-615 A) and crosslinker (RTV-615 B) from General Electric was stirred in a 10 : 1 weight ratio together with an appropriate amount of PTSA (typically, 5 wt%) at room temp. for 1 h. The chiral complex (obtained from Aldrich) was then added (0.25 wt%), and the mixture was further stirred at room temp. for 1 h under a nitrogen atmosphere. After casting the mixture in a Petri dish, the solvent was allowed to evaporate for 18 h under nitrogen flux. The membrane was precured under vacuum at room temperature for 4 h, followed by curing under vacuum at 150 °C for 1 h. The catalyst membrane showed an average thickness of 0.2 mm, corresponding to a coverage of *ca.* 0.054 μmol cm^{-2} for the Ru–binap complex. The complex and the acid are both wrapped in the elastomer network and retained by steric restrictions, in combination with van der Waals interactions between the occluded compounds and polymer chains.

Hydrogenation of methyl acetoacetate (MAA) (molar ratio MAA : Ru : solvent = 2500 : 1 : 25000) with the occluded Ru–binap complex was performed in a batch reactor at a pressure of 6 MPa at room temp. (RT), 40 or 60 °C.

An overview of the catalytic results obtained with the membrane occluded Ru–(*R*)-binap complex is given in Table 1. Entries 1–3 show that the Ru–binap PDMS membrane requires hydrogenation temperatures of at least 60 °C to exhibit reasonable activity and moderate enantioselectivity. Literature data show that the same is true for the homogeneous case.[4] Entries 4 and 5 show that strong organic acids like PTSA exert a comparable effect on catalyst activity as inorganic acids, allowing room temp. hydrogenation of methyl acetoacetate with high enantioselectivity. PTSA, added to the reaction mixture containing a Ru–binap membrane, activates the heterogeneous catalyst yielding good activity (entry 6). At the same time, a very significant increase in enantioselectivity from 61 to 93% is observed compared to the acid-free system at 60 °C (entry 3). However, this system still requires removal of PTSA from the reaction medium.

An acid/Ru–binap membrane, containing equal molar amounts of PTSA and Ru, shows a four-fold increase in activity at 40 °C while maintaining the high enantiomeric excess (entry 8) compared to the previous case (entry 6) in which PTSA was added to the reaction medium. The acid/Ru–binap membrane shows good activity and enantioselectivity at room temperature as well (entry 7). The ratio of PTSA to Ru–binap in the catalytic membrane was found to have a pronounced effect on the system's activity (Fig. 1). After an initial steep rise in activity resulting from an increase in concentration of the incorporated acid, an optimum activity is obtained at a molar ratio of H^+/Ru of about 10 (entry 9). The activity decrease at higher ratios is

Table 1 Influence of PTSA addition to a Ru–binap PDMS membrane on the activity and enantioselectivity of the hydrogenation of methyl acetoacetate[a]

Entry	Catalyst	PTSA	*T*/°C	TOF/h^{-1}[b]	Ee (%)
1	Ru–binap membrane	—	RT	—	—
2	Ru–binap membrane	—	40	—	—
3	Ru–binap membrane	—	60	9.6	61
4	Ru–binap homogeneous	0.5[c]	RT	8.2	97
5	Ru–binap homogeneous	0.5[c]	40	59.2	96
6	Ru–binap membrane	0.5[c]	40	1.8	93
7	PTSA/Ru–binap membrane	0.5[d]	RT	3.7	79
8	PTSA/Ru–binap membrane	0.5[d]	40	6.5	87
9	PTSA/Ru–binap membrane	2.0[d]	40	41.6	92

[a] Reactions (4) and (5) (homogeneous), for reasons of solubility, were carried out in methanol, whereas the membrane reactions are carried out in ethylene glycol. [b] TOF = turnover frequency, calculated as turnover number per hour, is often referred to as turnover number (TON). [c] Amount of PTSA in the homogeneous reaction mixture (g per g Ru–binap). [d] Amount of PTSA incorporated in the PDMS membrane (g per g Ru–binap).

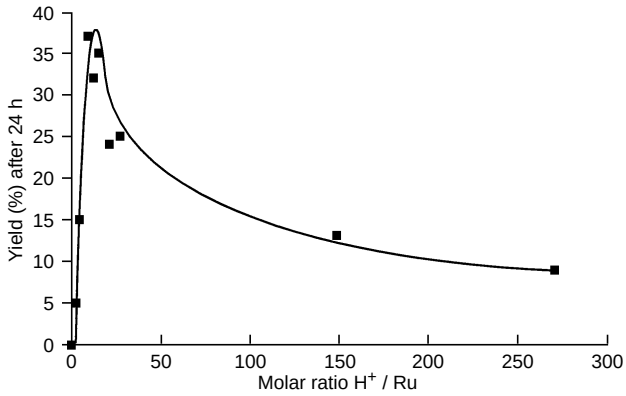

Fig. 1 Influence of the amount of PTSA in PTSA/Ru–binap PDMS membranes, on the hydrogenation of methyl acetoacetate at 40 °C. The ee in all cases is 90 ± 3%.

probably due to a decreasing degree of crosslinking in the PDMS membrane when increasing amounts of acid are present. It seems that this results in moderate to severe leaching of the acid from the membrane, implying a decreasing concentration of incorporated acid and thus a drop in hydrogenation activity. Complex leaching is absent in all reported cases as measured by atomic absorbance spectrophotometry. The ruthenium content of the reaction mixture is lower than the detection limit of 0.16 ppm. Furthermore, after removing the membrane, the reaction mixture did not show any activity upon addition of fresh substrate. Up to the optimum point of activity, catalyst reuse after filtration is possible without loss of activity or enantioselectivity. These results clearly prove the heterogenity of the reported system.

In conclusion, a new highly active and enantioselective heterogeneous hydrogenation catalyst is presented, allowing room temp. hydrogenation of β-keto esters. The system consists of a Ru–binap complex, occluded in a PDMS membrane together with toluene-*p*-sulfonic acid activating the complex. The new catalyst has superior activity compared to its homogeneous equivalent. Moreover, reuse of the catalyst is possible after filtration.

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Footnote and References

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