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Asymmetric oxidation of sulfides to sulfoxides by chiral titanium pillared montmorillonite catalyst [☆]

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Several sulfoxides with high enantiomeric purity have been synthesised using heterogeneous catalytic systems. A variety of titanium catalysts supported on Al_2O_3, SiO_2, ZrO_2 and montmorillonite, pillared clay catalysts using montmorillonite obtained from different sources and various chiral auxiliaries in presence of stoichiometric amounts of tertiary butyl hydroperoxide (TBHP) have been evaluated in asymmetric oxidation of prochiral sulfides to sulfoxides. It was found that Ti-PILC using montmorillonite K10 afforded optimum results. A probable active species responsible for high enantioselectivity is also discussed.

Keywords: Montmorillonite catalyst; chiral pillared clay catalyst; asymmetric oxidation of sulfides

1. Introduction

The synthesis of chiral sulfoxides has generated increased interest because of their wide use as chiral synthons especially in the C–C bond formation reactions [1–6]. The synthesis of chiral sulfoxides can be realised by (a) chemical synthesis via nucleophilic substitution at sulfur, (b) kinetic resolution of sulfoxides and (c) enantioselective oxidation of prochiral sulfides [6]. A variety of chiral oxidising agents derived from transition metals successfully employed in asymmetric oxidation of prochiral sulfides with the foreseeable application as catalysts made the latter a very attractive method.

Although in 1984, Kagan and coworkers [7] and Modena and coworkers [8] independently discovered a modified Sharpless reagent for the synthesis of optically active sulfoxides, Kagan's optimised homogeneous conditions involving $Ti(O\text{-}i Pr)_4$/diethyl tartrate (DET)/tertiary butyl hydroperoxide (TBHP)/H_2O in a ratio of 1 : 2 : 1 : 1 in asymmetric oxidation of sulfides gave moderate to excellent

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enantiomeric excesses (ee's). Kagan and coworkers have successfully induced enantioselective oxidation of sulfides using stoichiometric and substoichiometric amounts of Ti(O-*i*Pr)$_4$ and DET [7]. But the ee's have sharply fallen when catalytic amounts of the chiral auxiliaries were used [9].

Many times the successes in organic transformations by soluble asymmetric catalysts affording high purity optical compounds are not reflected in the industrial front due to severe limitations including lower turn over numbers, difficulties in recovery, recycling and handling of the soluble catalysts. Therefore the enantioselective heterogeneous catalysts are preferrable because of their handling and separation properties from a technical and commercial point of view, provided the catalyst performance is satisfactory. Indeed it has been demonstrated in few cases in large scale preparations already. For example, Raney nickel modified with R,R′-tartaric acid [10] and NaBr [10] has been shown to be an efficient catalyst for the asymmetric hydrogenation of prochiral β-ketoesters in the synthesis of tetrahydro-lipstatin, a pancreatic lipase inhibitor developed by Hoffman La Roche (100% chemical yield ee 92%) [10]. Whereas the Pt/Al_2O_3 modified with 10,11-dihydro-cinchonidine system is best suited for the α-ketoesters leading to angiotensin converting enzyme inhibitor benezepril [10].

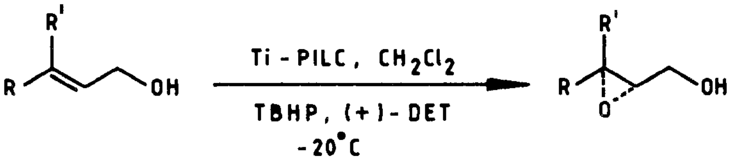
Despite inherent advantages associated with the use of heterogeneous catalysts, the progress in the area has not been as rapid as expected due to complex systems exhibiting variation in enantioselectivities depending upon the size of the metal particle agglomerated on the support, temperature etc. Thus it was conceived to use chiral pillared clay complexes by assembling transition metal oxy–hydroxy oligomers into the interlayers of the montmorillonite and complexed with chiral auxiliary, since preformed oligomers used for intercalation will have identical size. In addition to this, the pillared clay complexes retain the characteristics of homogeneous environment in liquid phase reaction conditions, and with features of solid catalysts such as ease in separation and handling.

Recently we have successfully heterogenised Sharpless homogeneous system in the form of titanium pillared montmorillonite catalyst (Ti-PILC) [11] and employed for the asymmetric epoxidation of allylic alcohols using DET as chiral auxiliary. This afforded comparable ee's and chemical yields to the one reported by Kagan and coworkers [7] (scheme 1).

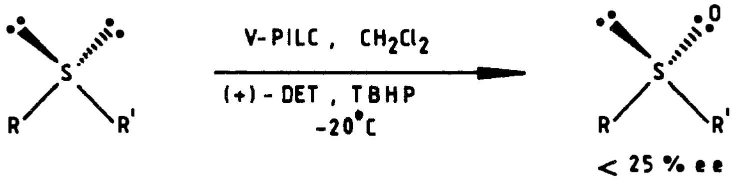
More recently vanadium pillared catalyst developed in our laboratory for the epoxidation of allylic alcohols [12] was subjected to the asymmetric oxidation of sulfides but <25% ee was observed [13] (scheme 2).

Thus the success of Ti-PILC catalyst in the asymmetric epoxidation of allylic alcohols prompted us to try the catalytic system for the asymmetric sulfoxidation successfully [14] (scheme 3).

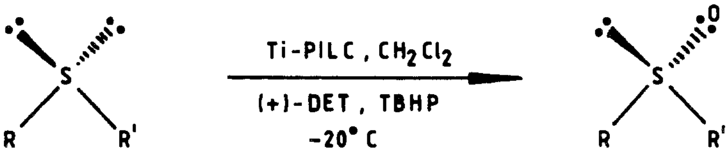
In the present paper we report the enantioselective oxidation of prochiral sulfides to sulfoxides in detail using Ti-PILC as a catalyst, DET as chiral auxiliary and TBHP as oxidant and compared with various calcined and uncalcined catalysts supported on SiO_2, ZrO_2, montmorillonite, Al_2O_3 and different chiral auxiliaries in



Scheme 1.



Scheme 2.



Scheme 3.

order to understand and optimise the active species involved in chiral induction and better chemical yields.

2. Experimental

Montmorillonite obtained from three different sources is used for the preparation of pillared catalysts. (a) K10 montmorillonite pretreated with acid (Fluka), (b) Missorie clay (Clay Mineral Society), (c) ACC clay (American Colloidal Company).

Montmorillonite prior to use suspended as 1% weight slurry and was allowed to sediment for 24 h to remove the denser impurities like silicates, quartz and calcite. The Na^+-montmorillonite was then prepared by the procedure of Posner and Quirk [15] by suspending the sedimented montmorillonite as obtained above in excess of saturated aqueous NaCl solution for 24 h. The sodium exchanged clay was then separated by centrifugation and washed free of chlorides by deionised water as indicated by an $AgNO_3$ test. Finally, it was dried in air.

Ti-PILC$_1$ was prepared by the procedure reported by Yamanaka et al. [16]. Ti(O-*i*Pr)$_4$ (11.37 g, 40 mmol) was added dropwise to vigorously stirred 1 M HCl (163 ml). The resulting slurry was stirred for 3 h to give a clear titania sol and then mixed with an aqueous suspension of 1 wt% Na$^+$-montmorillonite (1.0 g) which was prepared from K10 montmorillonite. The suspension was then stirred for 3 h at 50°C. The clay was washed with deionised water, the mixture centrifuged, and the sample dried in air at room temperature. X-ray diffraction of the resulting Ti-PILC has a basal spacing of 24 Å.

Ti-PILC$_2$ and Ti-PILC$_3$ catalysts were also prepared by the same procedure described above using Missorie and ACC clay respectively.

TiO_2–SiO_2 catalyst was prepared by the "coprecipitation method" [17] in which the coprecipitate of $Ti(OH)_4$–$Si(OH)_4$ was obtained by adding ammonia slowly into a mixed aqueous solution of titanium tetrachloride and sodium silicate solution at room temperature with stirring until the pH of the mother liquor reached 8. The dried coprecipitate was again washed with successive portions of a 5% ammonium nitrate solution and then with hot distilled water to remove sodium ion in the coprecipitate. Similarly $ZrOCl_2$ and K10 montmorillonite were used along with $TiCl_4$ for the preparation of TiO_2–ZrO_2 and TiO_2–montmorillonite catalysts.

TiO_2/SiO_2 catalyst was prepared by the "wet-impregnation" method [18] where Ti(O-*i*Pr)$_4$ (170 mg; 0.18 mmol), silica (72 mg) were mixed in pentane in nitrogen atmosphere and refluxed for 5–6 h. The impregnated catalyst thus formed was filtered and dried for 4 h in an oven at 60° which contains 28% or 0.6 mmol of titanium. The same method was adopted for the preparation of TiO_2/ZrO_2, TiO_2/Al_2O_3 and TiO_2/montmorillonite catalysts.

General procedure for the oxidation of prochiral sulfides

Ti-PILC containing titanium (0.18 mmol), (+)-DET (0.36 mmol) in dry CH_2Cl_2 (50 ml) were stirred at room temperature under nitrogen atmosphere for 20 min. Then prochiral sulfide (5 mmol) was added and cooled to −20°C and azeotropically dried TBHP (2 M, 5 mmol) in toluene was then introduced. The reaction mixture was stirred at −20°C for 3 h. The catalyst was filtered after the completion of the reaction which was periodically monitored by thin layer chromatography (TLC). The filtrate was concentrated and chromatographed on silica gel (ethylacetate : hexane; 1 : 1) gave chiral sulfoxide. The ee's of the chiral sulfoxides thus synthesised are calculated from $[\alpha]_D^{20}$ obtained by polarimeter and reconfirmed by ^1H NMR (200 MHz) using chiral shift reagent (R)-(−)-N-(3,5-dinitrobenzyl)-α-phenylethylamine [19] in the case of *p*-tolyl methyl sulfoxide (table 1, entry No. 2).

3. Results and discussion

The present heterogenised system possesses the following advantages over the homogeneous system reported by Kagan and coworkers:

Table 1
Asymmetric oxidation of prochiral sulfides into R $\overset{*}{S}$(O) R′ by Ti-PILC$_1$ catalyst

Entry No.	R	R′	Time (h)	Chemical yield (%)	$[\alpha]_D^{20}$ (in acetone)	ee (%) (configuration)
1	phenyl	CH$_3$	3	80	+131.5°(c 1)	90 (R)
2	*p*-tolyl	CH$_3$	3	85	+130.5°(c 1)	90 (R)
3	*p*-nitrophenyl	CH$_3$	3.5	72	+83°(c 1.5)	83 (R)
4	*p*-bromophenyl	CH$_3$	3	75	+89.5°(c 1)	92 (R)
5	*p*-hydroxyphenyl	CH$_3$	12	89	+107.2°(c 2)	80 (R)
6	*p*-methylphenyl	CH$_3$	10	70	+97.9°(c 1)	81 (R)
7	*p*-chlorophenyl	CH$_3$	12	90	+110.6°(c 1)	89 (R)
8	phenyl	vinyl	5	90	+40.9°(c 1)	9 (R)
9	phenyl	allyl	4	92	+30.5°(c 1)	nd[a]
10	phenyl	propargyl	3	89	+26.8°(c 1)	nd
11	octyl	CH$_3$	24	70	−49.5°(c 1)	80 (R)
12	benzyl	CH$_3$	4	75	−44.6°(c 1.5)	77 (R)
13	cyclohexyl	CH$_3$	24	60	−61.5°(c 1.5)	75 (R)
14	Cl–CH$_2$–CH$_2$	CH$_3$	12	80	−30.5°(c 1)	nd

[a] nd: not determined.

– Comparable chemical yields and enantioselectivities in case of aromatic sulfoxides (table 1, entries Nos. 1–7) and higher ee's in case of aliphatic compounds (table 1, entries Nos. 11–14).

– Catalytic amounts of Ti-PILC.

– Easy work up by simple filtration and possible reusability.

Selective oxidation of vinyl phenyl sulfide, allyl phenyl sulfide and propargyl phenyl sulfide with good chemical yields is a significant achievement with the present catalytic system. But vinyl phenyl sulfoxide exhibited poor enantioselectivity.

Various titanium catalysts both calcined and uncalcined, supported on Al$_2$O$_3$, SiO$_2$, ZrO$_2$ and montmorillonite prepared by coprecipitation or wet-impregnation and pillared montmorillonite clay catalysts using montmorillonite obtained from various sources have been evaluated in asymmetric oxidation of prochiral sulfides in order to screen and identify the best catalyst and understand the nature of the active species responsible for the activity and enantioselectivity (table 2). Ti(O-*i*Pr)$_4$ as such and both the calcined and uncalcined samples of Ti supported on Al$_2$O$_3$, SiO$_2$ and ZrO$_2$ are inactive in the oxidation of sulfides at −20°C in the presence of chiral auxiliary and stoichiometric amounts of TBHP. It should also be noted that titanium exchanged or impregnated on montmorillonite displayed negligible performance in the oxidation of sulfides under identical conditions. On the other hand, the samples of titanium pillared clay prepared by the intercalation of oxy–hydroxy oligomers into montmorillonite obtained from various sources before thermal treatment have shown better chemical activity. However, the natural montmorillonites obtained from Clay Mineral Society and American Colloidal Company showed poor enantioselectivity. The excellent enantioselectiv-

Table 2
Asymmetric oxidation of phenyl methyl sulfide to sulfoxide by different catalytic systems

Entry No.	Catalyst	Chemical yield[a]	ee (%) (configuration)
1	$Ti(O\text{-}i Pr)_4$	90	89 (R)
2	montmorillonite	15	–
3	Ti-$PILC_1$ [b]	80	90 (R)
4	Ti-$PILC_1$ [c]	–	–
5	Ti-$PILC_2$ [b]	60	25 (R)
6	Ti-$PILC_3$ [b]	65	29 (R)
7	TiO_2–montmorillonite [d]	5	–
8	TiO_2–SiO_2 [d]	10	–
9	TiO_2–ZrO_2 [d]	10	–
10	TiO_2–SiO_2–ZrO_2 [d]	5	–
11	TiO_2/montmorillonite [d]	15	–
12	TiO_2/ZrO_2 [d]	5	–
13	TiO_2/Al_2O_3 [d]	–	–
14	TiO_2/SiO_2 [d]	5	–

[a] Reaction conditions: catalyst (0.18 mmol of Ti), TBHP (5 mmol), sulfide (5 mmol), (+)-DET (0.36 mmol), CH_2Cl_2 (50 ml), at −20°C.
[b] Before calcination.
[c] After calcination.
[d] Before and after calcination.

ity under identical conditions was displayed only by the acid treated montmorillonite K10 obtained from Fluka. The same catalyst upon calcination lost its activity in sulfoxidation reactions.

All these results lead to the conclusion that the $Ti(OH)_4$ predominantly present in uncalcined samples and TiO_2 formed in calcined samples on various supports such as Al_2O_3, SiO_2, ZrO_2, and montmorillonite are inactive. TiO_2 formed in pillared clays upon thermal treatment also showed inertness in terms of activity and enantioselectivity. The inertness of TiO_2 formed upon calcination on various supports and pillared clay in the sulfur oxidation, under the identical conditions is due to its inability to form complexation with the reactant, oxidant and chiral auxiliary. While the inertness of $Ti(OH)_4$ predominantly present in the uncalcined samples can be attributed to the difficulty in complexation with the participants because of facial restriction existing in the metal supported catalytic systems. The higher chemical activity by the pillared clays is due to the ease of complexation of the titanium hydroxy oligomer with the reactant, oxidant and chiral auxiliary in the interlayer space of $\sim$ 13 Å available in the pillared clays. Natural montmorillonite has a regular layered structure, while the montmorillonite K10 is left with a deformed and broken layered structure upon treatment with acid. This irregular and broken layered structure with higher Lewis acidity than natural clays [20] possesses more exposed oligomers of titanium, easily accessible for chiral auxiliary and other reacting molecules for complexation than in natural clay and thus responsible for higher enantioselectivity and activity. Further the bridging of the titanium centres by tartrate alkoxide oxygen atoms, the necessary requirement for higher enantioselectivity in case of asymmetric epoxidations [21] and sulfoxidations [7] is possible in case of oligomers only. The monoatomic species present in titanium exchanged montmorillonite which has not shown any activity supported that similar type of complexation in the homogeneous analogue is possible only in allowed space of pillared clays. Therefore, these studies indicate that the active species responsible for stereospecific delivery of oxygen in asymmetric oxidation of sulfides is likely the transient chiral complex as described in fig. 1.

The reaction was tried with different chiral auxiliaries such as (+)- or (−)-DET, (+)-DIPT, and (+)trans, α,α′-(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(disphenyl methanol) (TADOL) (table 3). DET is found to be more active than the DIPT while with TADOL there was no reaction. (+)-DET gave the product with "R" configuration, whereas (−)-DET afforded "S" product with equal but opposite rotation. The inactivity of the reaction when TADOL was used as chiral auxiliary is due to its larger dimension that precludes complex formation with titanium oligomer intercalated in montmorillonite.

The present reaction was also conducted by different substrate/catalysts ratios and it was found that the reaction conducted with 5 mol% of the catalyst to the substrate is optimum requirement for the better enantioselectivity (table 3).

On recycling of the catalyst the enantioselectivity is considerably decreased (table 3, entry 5), although d_{001} spacing of the catalyst remained the same. These results indicate that the catalyst is poisoned by the absorption of some polymeric material formed during the reaction which could not be desorbed by washing with variety of solvents.

In conclusion, the Ti-PILC derived from montmorillonite K10 possessing optimum Lewis acidity forms a complex with bridged tartrates of alkoxides, reactant

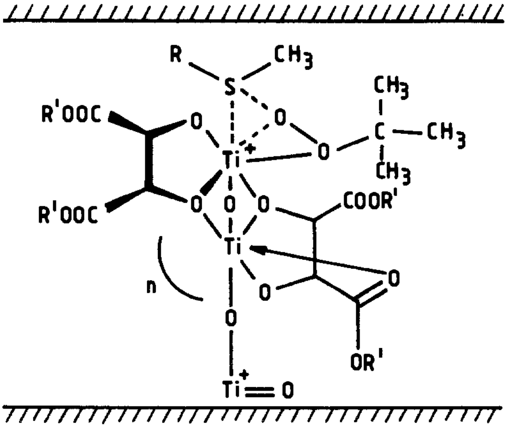


Fig. 1. Transition state of asymmetric sulfoxidation.

Table 3
Asymmetric oxidation of phenyl methyl sulfide by using different substrate/Ti-PILC$_1$ mol ratios and different chiral auxiliaries

Entry No.	Substrate/Ti-PILC$_1$ ratio (mol%)	Chiral auxiliary	Time (h)	Chemical yield (%)	ee (%) (configuration)
1	5	TADOL	12	–	–
2	5	(+)-DIPT	4	80	90 (R)
3	5	(−)-DET	3.5	86	92 (S)
4	5	(+)-DET	3.5	85	92 (R)
5	5[a]	(+)-DET	3.5	80	60 (R)
6	3	(+)-DET	3.5	80	69 (R)
7	2	(+)-DET	3.5	75	60 (R)
8	1.5	(+)-DET	3.5	60	45 (R)

[a] Reused catalyst.

and oxidant as in homogeneous analogue which facilitates the oxygen delivery stereospecifically to afford higher enantioselectivity and activity (fig. 1).

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