Enantioselectivities of chiral Ti(IV) salen complexes immobilized on MCM-41 in asymmetric trimethylsilylcyanation of benzaldehyde

Joo-Ho Kim and Geon-Joong Kim*

Department of Chemical Engineering, College of Engineering, Inha University, Inchon 402-751, Korea

Received 30 May 2003; accepted 7 November 2003

A new heterogeneous system for catalytic trimethylsilylcyanation of benzaldehyde has been developed by immobilizing Ti(IV) salen onto ordered mesoporous silica (MCM-41). The immobilization was performed according to different methods: (i) direct condensation of silanol on the silica surface with Ti(IV) salen and (ii) multigrafting of salicylaldehyde derivatives and diaminocyclohexane using 3-mercaptopropyl-functionalized MCM-41 as a starting material. The heterogenized salen catalysts showed a high enantioselectivity for the addition of trimethylsilyl cyanide to benzaldehyde.

KEY WORDS: trimethylcyanation; Ti(IV) salen; enantioselectivity; immobilization.

1. Introduction

Much effort has been devoted not only to the development of active catalysts but also to finding the ways to enable their repeated use. This is especially important for chiral catalysts, which are usually more expensive than achiral catalysts. The syntheses of optically pure chemicals have gained significant potential over recent years. Chiral salen-titanium complexes were found to be efficient catalysts for the enantioselective trimethylsilylcyanation (TMSCN) of aldehydes [1], and their bimetallic form has also been developed as an exceptionally enantioselective catalyst [2]. It is well known that optically active cyanohydrin derivatives are important and attractive synthetic intermediates. Cyanohydrins are used as starting materials for the synthesis of some pharmaceutical compounds [3]. The two functional groups can be easily manipulated into a wide range of other homochiral products, such as α-hydroxyl acids, α-hydroxyl aldehydes, β-hydroxyl amines and β-amino acid derivatives [4–7]. Therefore, many efficient methods have been developed for the synthesis of optically pure cyanohydrins by biochemical and chemical methods [8].

Belokon *et al*. have reported that a set of aromatic and α, β-unsaturated aldehydes are asymmetrically trimethylsilylcyanated over monomeric and dimeric chiral Ti(IV) salen complexes with high ee% [9,10]. As introduced by some authors, the reported papers dealt with the immobilization method of chiral salen ligands by the condensation of functional groups [11,12]. Subsequent anchoring methods of reacting a functionalized ligand with the reactive groups of organic and inorganic compounds such as MCM-41 and SBA-15, step by step, make it possible to synthesize various asymmetric chiral salens of different structures and to immobilize them onto inorganic supports. These inorganic materials would expand the areas for their application as a support. The pore system of these mesoporous materials, with a typical diameter of 3–10 nm, offers large surface areas, although molecular sieving effects become less important. Ligands bearing a trimethoxysilane function are immobilized via surface silanol groups. Surface reactions exploiting terminal silanol groups have long been performed with amorphous supports or crystalline materials for application in catalysis. By utilizing the chemical reactivity of the mesoporous host, a number of functional groups have been covalently anchored to the channel walls, including ligands intended for the attachment of metal complexes. The introduction of functional organic groups has been performed through attachment of silane-coupling agents to the mesoporous walls of the previously synthesized and calcined MCM materials. The functional group is either directly incorporated in the silane-coupling agent or grafted onto it in a second or further reaction step. Attaching the chiral ligands covalently via a suitable functional linker or tether to the support is by far the most important, because the optical purity of the product can vary with the length and the flexibility of the spacer and the pore size affects the enantioselectivity. The heterogeneous chiral catalysts offer practical advantages of facile separation from reactants and products, as well as recovery and reuse.

In the present work, we report the asymmetric catalytic activities of heterogeneous chiral salen ligands synthesized by a direct grafting method and by a stepwise condensation method, respectively, using mesoporous silica as a support. The relations between

* To whom correspondence should be addressed.
E-mail: kimgj@inha.ac.kr

1011-372X/04/0200–0123/0 © 2004 Plenum Publishing Corporation

the structural features of salen ligands and the enantioselectivities were evaluated in this study. Conventional homogeneous chiral salen ligands were also used as catalysts to compare the enantioselectivities in the trimethylsilylcyanation of aromatic aldehydes.

2. Experimental

2.1. Synthesis of homogeneous chiral Ti(IV) salen complexes

The homogeneous symmetric and asymmetric chiral salen complexes were synthesized to evaluate and to compare the enantioselectivity in the asymmetric trimethylsilylcyanation of benzaldehyde respectively. The procedure for the synthesis of homogeneous complexes is shown in scheme 1.

The half unit (**1**) for the synthesis of asymmetric salen (**2**) was obtained by condensation of (1*R*,2*R*)-(-)-1,2-diaminocyclohexane and salicylaldehyde. This half unit (**1**) was salted with dibenzoyl-D-tartaric acid, and then the asymmetric salen (**2**) was synthesized by reaction between the salt of (-)-*N*, *N*′-*trans*-1-(salicylidene)-2-(dibenzoyl-D-tartrate)-cyclohexanediamine and salicylaldehyde derivatives in EtOH [13]. The symmetric chiral salen (**3**) was obtained from Aldrich Co. and used without further purification. Then, the chiral Ti(IV) salen complex was readily prepared by refluxing a salen ligand with $TiCl_4$ in methylene chloride solvent. The dimeric forms of Ti(IV) salen catalysts (**C-1**) and (**D-1**) were synthesized by the same method as reported in the literature, treating with H_2O and Et_3N [14].

2.2. Immobilization of chiral Ti(IV) salen complexes on MCM-41

The synthesis of one chiral half unit, as shown in scheme 2, is needed as an intermediate to construct the desired compounds by reacting the remaining free amine with other salicylaldehyde derivatives. Scheme 2 shows the procedures for the syntheses of various chiral salen complexes immobilized on MCM-41 by multistep anchoring method using 3-mercaptopropylsilyl-functionalized MCM-41 as a starting material. 3-Mercaptopropylsilyl-functionalized MCM-41 was synthesized according to the procedure reported by Lim *et al.* [15]. The synthesized samples were characterized by XRD analysis and N_2 adsorption for determination of pore-size distribution. The 3-mercaptopropyl groups on MCM-41 were submitted to synthesize the chiral half unit immobilized on MCM-41 **(4).** Salicylaldehyde **(5)** and 3,5-di-*tert*-butyl salicylaldehyde **(6)** were obtained from Aldrich Co. and used without purification. The compounds **(7, 8)** were prepared by the reaction of the chiral half unit immobilized on MCM-41 **(4)** with corresponding excess salicylaldehyde derivatives (**5, 6**) in boiling ethanol by the same method as that reported in the preceding publication. The loading of chiral salen unit per gram of MCM-41 support (**8**) was determined as 0.13 mmol. Then, the chiral Ti(IV) salen complexes immobilized on MCM-41 (**A-2, B-2**) were readily produced by contacting a salen ligand **(7, 8)** with 1 equiv of $TiCl_4$ in refluxing methylene chloride under nitrogen for 4 h. In order to avoid the catalytic role of remaining OH-groups of the support, the sample was treated with hexamethyldisilazane (HMDZ) before a titanium source was added [16]. The resulting red powder was filtered and washed for several times with methylene chloride and methanol. In addition, another method for immobilization of chiral salen complexes is shown in scheme 3. Chiral Ti(IV) salen complexes containing chloride (**B-1, C-1**) were directly immobilized on MCM-41 by condensation between chloride and silanols on MCM-41 in a dioxane solvent.

2.3. TMSCN addition reaction

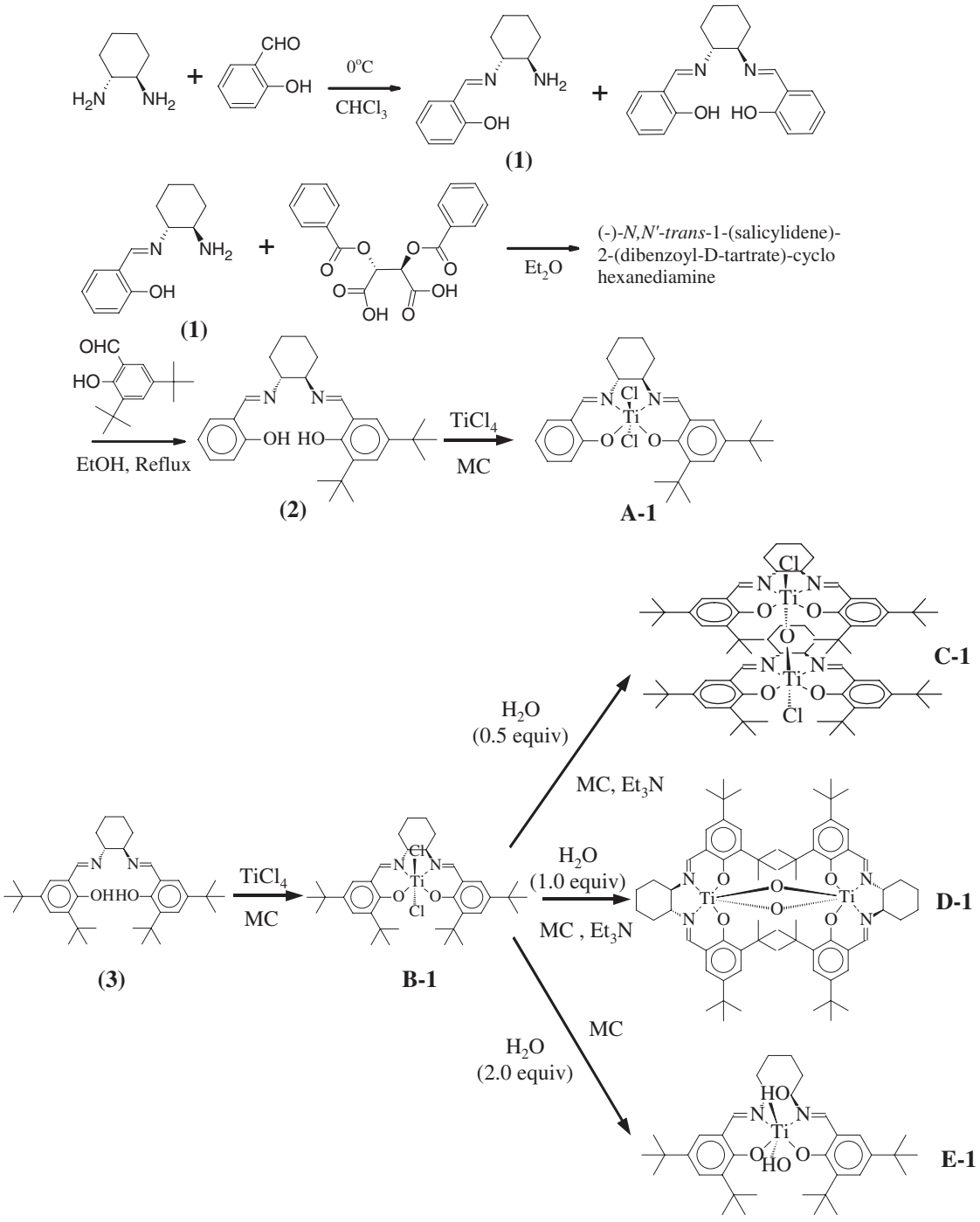
The general procedure for the asymmetric TMSCN addition reaction is as follows: Trimethylsilylcyanide was added dropwise to a mixture of the aldehyde (1.25 mmol) and catalyst in dry dichloromethane (1.5 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 24 h at the selected reaction temperature. The product was filtered through silica pad eluting with a mixture of hexane/ethyl acetate (mole ratio: 5). Concentration of the resulting solution in vacuum gave the cyanohydrin silyl ethers. The ee% values were determined by capillary GC using a chiral column (CHIRALDEXTM, gamma-cyclodextrin trifluoroacetyl, 40 m × 0.25 mm i.d.(Alltec)).

3. Results and discussion

The organofunctional MCM-41 sample has an ordered pore system. The mean pore size determined by N_2 adsorption was 4.0 nm. Its X-ray powder diffractogram showed a very intense (100) peak with three weak but well resolved (110), (200) and (210) peaks, indicating the well-developed mesopore structure.

The homogeneous chiral salen ligands (**A-1, B-1, C-1, D-1**) and heterogenized salens (**A-2, B-2, A-3, B-3, C-3**) of Ti(IV) form showed broad bands near 400 nm on the UV spectra, whereas $TiCl_4$-anchored MCM-41 and MCM-41 itself showed no absorption peaks above 300 nm. The broad bands near 400 nm are probably due to charge-transfer transitions between metal and ligand. This result indicates that the chiral salen ligands were successfully anchored onto the MCM-41 surfaces.

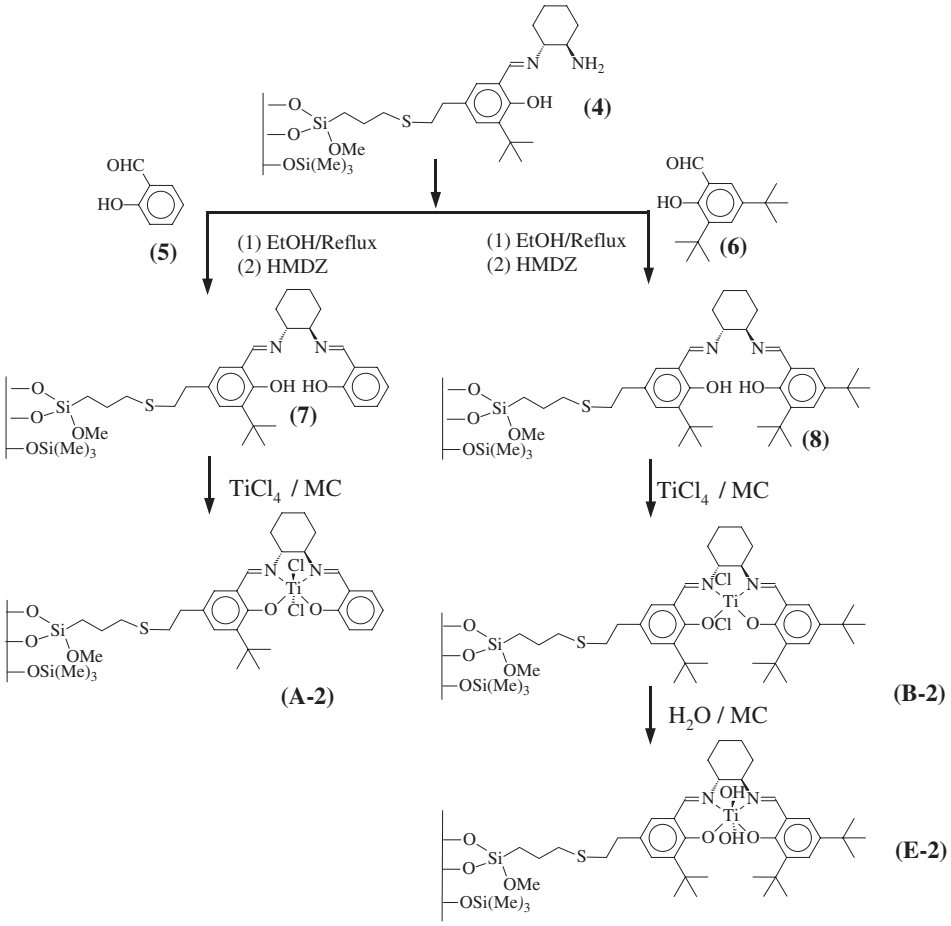
The homogeneous monomeric Ti(IV) salens (**A-1, B-1**) having two chlorines showed characteristic peaks at 2950, 1630, 1550, and 1460 cm^{-1} and these absorption bands were also found at the same position for the two



Scheme 1. The synthesis of homogeneous chiral Ti(IV) salen complexes.

different dimeric Ti(IV) salens (**C-1, D-1**). The homogeneous Ti(IV) salen (**B-1**) itself has no hydroxyl groups in the structure, and no peaks near 3500 cm^{-1} were found on IR spectra as shown in figure 1. When 1 mmol of monomeric salen (**B-1**) was treated with 2 mmol of water, the obtained sample (**E-1**) exhibited new peaks at 3400 cm^{-1}, suggesting the replacement of chlorine with hydroxyl group in the salen structure.

The various solid samples, such as pure siliceous MCM-41, MCM-41 end-capped with HMDZ, and chiral salen–immobilized MCM-41, were characterized by FT-IR analysis; the results are shown in figure 2. The presence of hydroxyl groups on the as-synthesized MCM-41 surfaces is confirmed by the IR analysis showing the band near 3400 cm^{-1}. The acid-extracted MCM-41 containing organic functional groups shows a strong peak around 3400 cm^{-1} on the IR spectra due to the presence of silanol groups on the surfaces. This band disappears from the spectrum of the organofunctionalized MCM-41 after treatment with HMDZ for the removal of silanols (end-capping). After formation of salen structures by multistep anchoring on the support,



Scheme 2. The synthesis of chiral Ti(IV) salen complexes immobilized on MCM-41 (multigrafting method).

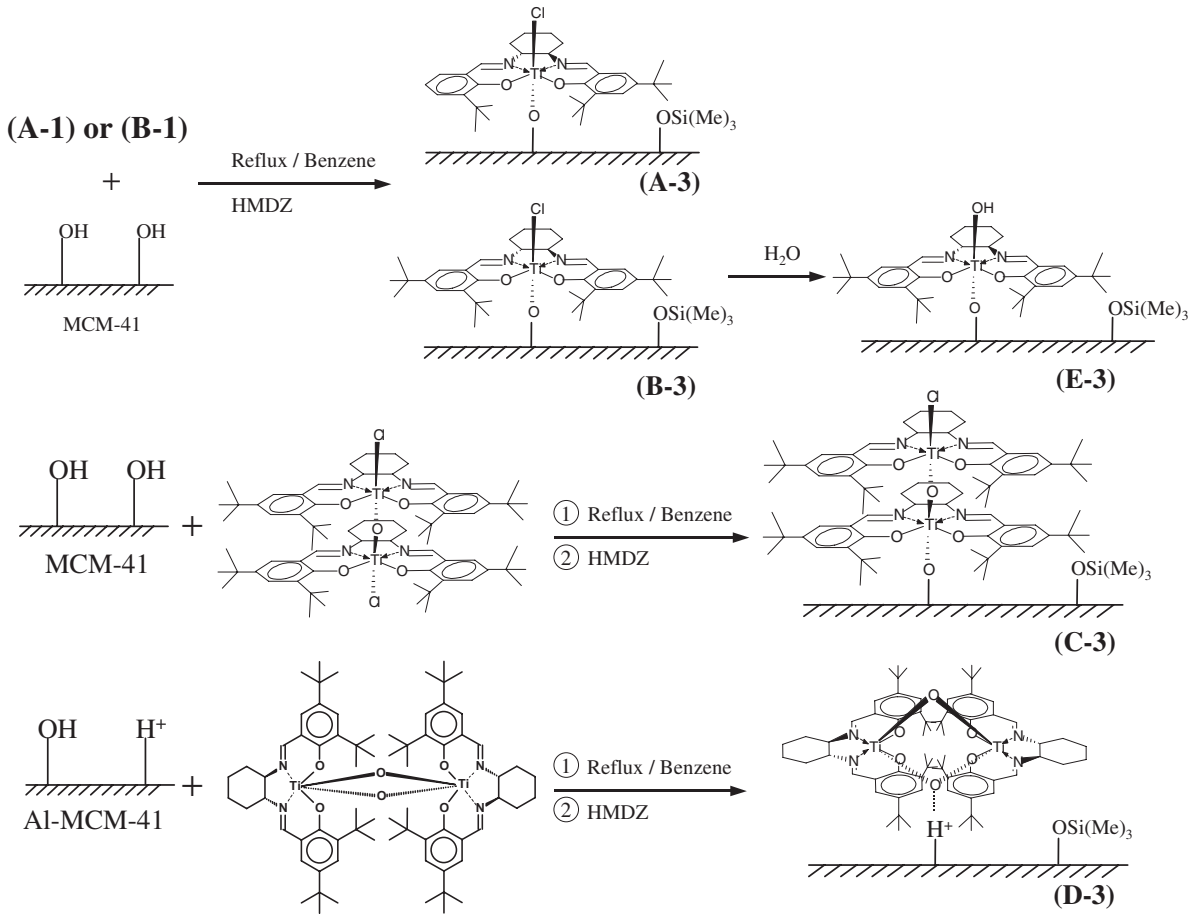
the peak for silanol group was also found. This silanol peak finally disappeared after HMDZ treatment as can be seen in figure 2. Furthermore, when the heterogenized salen was treated with excess water, the samples (**E-2**) exhibited new peaks at 3400 cm^{-1}, indicating the formation of hydroxyl groups in the structure as in the case of homogeneous salen (**E-1**). The appearance of the bands near 2950 and 2873 cm^{-1} due to -CH_3, -CH_2- groups indicates the presence of salen ligands immobilized on the support. These peaks were increased as the amount of salen immobilized on the solid support increased.

3.1. The catalytic activity of homogeneous chiral salen

The synthesized homogeneous or heterogeneous chiral titanium salen complexes were applied as catalysts for the enantioselective addition of trimethylsilyl cyanide to benzaldehyde. The enantioselectivity was dependent on the structure of Schiff base ligands, as can be seen in table 1. The salen catalyst having no bulky groups at para or ortho position to the salen oxygens showed moderate enantioselectivity for this reaction. The introduction of *tert*-butyl groups at para and ortho position as in the catalyst (**A-2**) resulted in an improvement of enantiomeric excess. However, the catalytic activities of asymmetric chiral titanium salen catalyst (**A-1**) containing salicylaldehyde and 3,5-di-*tert*-butylsalicylaldehyde units afforded very high enantioselectivities.

The use of *p*-methoxybenzaldehyde and 2-chlorobenzaldehyde as substrates was also investigated. The results shown in table 1 indicate that good enantioselectivities are obtained with benzaldehyde. *p*-Methoxybenzaldehyde and 2-chlorobenzaldehyde gave lower enantiomeric excess than benzaldehyde under the same reaction conditions.

The good enantiomeric excess was obtained with the electron-rich aromatic aldehydes, while electron-deficient aromatic aldehydes gave lower enantioselectivities in the enantioselective addition of trimethylsilyl cyanide to benzaldehyde derivatives using chiral salen catalyst (**A-2**), as reported by Belokon *et al.* [2] In addition, they investigated a relationship between the steric properties of aromatic aldehydes and ee% of the product, showing that the ortho-substituted aromatic aldehydes generally gave lower ee values than the meta and the para isomers. However, the highest enantiomeric excess was obtained using benzaldehyde as a reactant (tables 1 and 2), and this substrate was used mainly to investigate the activities of other salen catalysts.



Scheme 3. The synthesis of chiral Ti(IV) salen complexes immobilized on MCM-41 (direct-anchoring method).

In TMSCN of aldehydes, water plays a key role since under strictly anhydrous conditions, much lower enantiomeric excesses are produced. The role of water has been shown to generate the dimeric form of $[(salen)Ti(\mu\text{-}O)]_2$ complex, which is the real catalyst precursor. The dimeric complexes are known to be more active than the monomeric Ti(IV) salen precursors, showing very high enantiomeric excess under high substrate/catalyst mole ratio [2]. Belokon *et al.* suggested that in the transition state for asymmetric

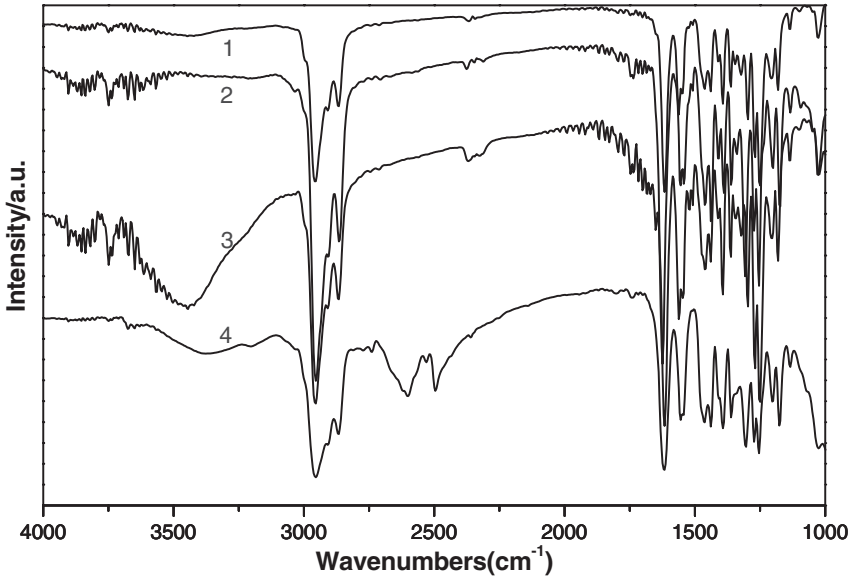


Figure 1. FT-IR spectra of homogeneous Ti(IV) salens; (1) B-1, (2) D-1, (3) E-1, and (4) C-1.

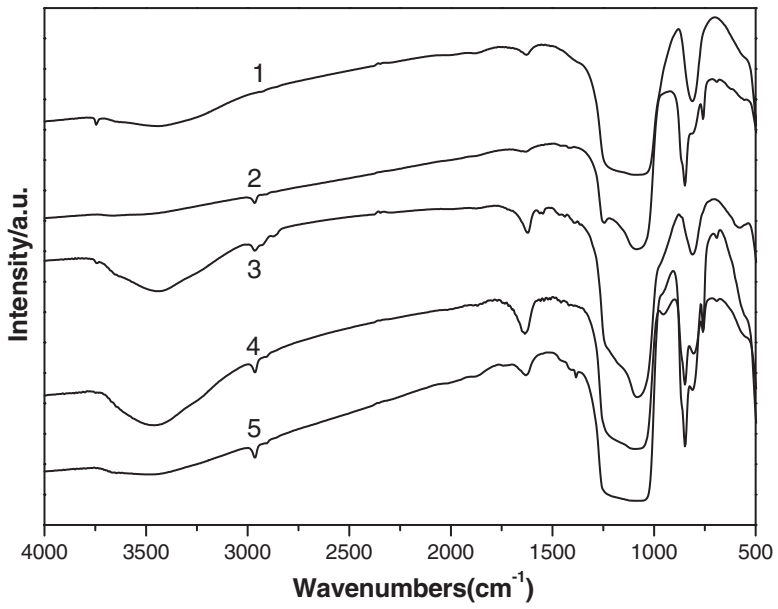


Figure 2. FT-IR spectra of (1) pure MCM-41, (2) MCM-41 end-capped by HMDZ, (3) salen complex immobilized MCM-41, (5) HMDZ-treated sample (B-2), and (4) sample E-2.

Table 1
Enantioselective trimethylsilylcyanation of benzaldehyde catalyzed by homogeneous catalysts (room temperature)

Entry	Substrate	Catalyst	Conversion (%)	ee (%)
1	Benzaldehyde	A-1	100	87
2	Benzaldehyde	B-1	100	75
3	*p*-Methoxybenzaldehyde	B-1	100	58
4	2-Chlorobenzaldehyde	B-1	100	69
5	Benzaldehyde	D-1	100	86
6	Benzaldehyde	E-1	100	78
7	Benzaldehyde	C-1	100	72
8	Benzaldehyde	C-1[a]	100	75

Note: Reaction was carried out using 10 mol% of catalyst, time = 24 h, reaction temperature: room temperature.[a]Catalyst(C-1) was treated with 2 equiv H_2O.

Table 2
Enantioselective trimethylsilylcyanation of benzaldehyde catalyzed by homogeneous catalysts

Entry	Substrate	Temperature (°C)	Catalyst	Conversion (%)	ee (%)
1	Benzaldehyde	−80	A-1	47	92
2	Benzaldehyde	−80	D-1	44	93
3	Benzaldehyde	0	D-1	72	89
4	Benzaldehyde	−80	C-1	48	88
5	Benzaldehyde	0	C-1	76	81
6	Benzaldehyde	−80	B-1	53	82
7	*p*-Methoxybenzaldehyde	−80	B-1	48	65
8	2-Chlorobenzaldehyde	−80	B-1	78	76

Note: Reaction was carried out using 10 mol% of catalyst, time = 24 h.

Table 3
Enantioselective trimethylsilylcyanation of benzaldehyde catalyzed by heterogeneous catalysts

Entry	Substrate	Catalyst	Conversion (%)	ee (%)
1	Benzaldehyde	A-1/MCM-41	38	67
2	Benzaldehyde	A-2/MCM-41	26	93
3	Benzaldehyde	B-2/MCM-41	23	87
4	Benzaldehyde	E-2/MCM-41	28	89
5	Benzaldehyde	B-3/MCM-41	36	60
6	Benzaldehyde	B-3/silica gel	34	52
7	Benzaldehyde	C-3/MCM-41	39	59
8	Benzaldehyde	C-3/silica gel	31	48
9	Benzaldehyde	D-3/MCM-41	38	43
10	Benzaldehyde	E-3/MCM-41	40	64

Note: Reaction time = 24 h, room temperature.

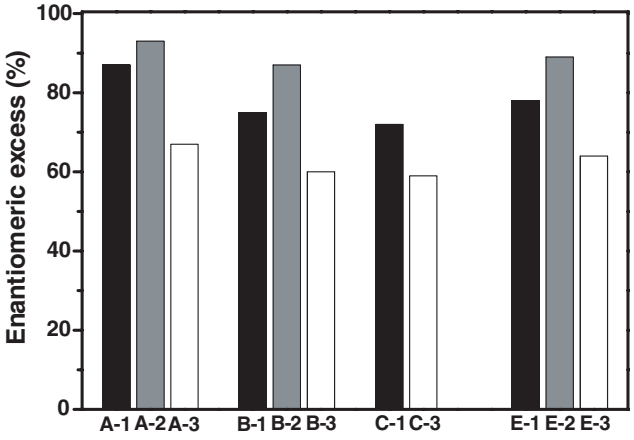


Figure 3. The enantioselectivities of homogeneous (A-1, B-1, C-1, and E-1) and heterogenized chiral salen catalysts for TMSCN of benzaldehyde at room temperature (same reaction conditions as in table 1).

cyanohydrin synthesis using Ti(IV) salen catalyst of dimeric form, the aldehyde is coordinated to one of the titanium ions and is oriented so that the small hydrogen atom is located near the cyclohexanediamine unit. The larger substituent on the aldehyde is located well away from the backbone of the salen ligand. Cyanide is then delivered intramolecularly to the Re-face of the coordinated aldehyde, resulting in the formation of the (*S*)-enantiomer of the product [14]. In our work, two dimeric forms of chiral salen also showed a very high enantioselectivity for the addition of trimethylsilyl cyanide to benzaldehyde at an ambient temperature. The effect of the reaction temperature on the enantioselectivity is summarized in table 2. The results show that lower reaction temperature favors higher enantioselectivity.

When the chiral TI(IV) salen catalysts were treated with H_2O, the ee% value improved slightly (for **E-1** and **E-2**). This catalyst is presumed to have OH groups instead of chlorine in the structure.

3.2. The catalytic activity of heterogeneous chiral salen

Results for the enantioselective addition of trimethylsilyl cyanide (TMSCN) to benzaldehyde by chiral Ti(IV) salen complexes immobilized on mesoporous material are summarized in table 3. In addition, the catalytic activities of homogeneous and heterogeneous salens are presented graphically in figure 3. The catalytic activities of supported chiral salen catalysts can be compared with those obtained using the analogous homogeneous catalysts. Table 3 also includes comparative results obtained with catalysts supported on silica gel. Table 3 and figure 3 show that the ee% values obtained on the immobilized catalysts are slightly higher than those over homogeneous catalysts. Furthermore, the enantioselectivities of the heterogenized Ti(IV) salens synthesized by multistep condensation were almost the same as those obtained over homogeneous catalysts. As shown in table 3, the enantioselectivity was also strongly dependent on the structure of salens as can be seen in the case of homogeneous catalysts. The salen catalysts prepared by multistep anchoring method (**A-2, B-2**) show higher enantioselectivities than those obtained by simple direct anchoring method (**B-3**), even though they have the same structures.

Attaching the chiral ligands covalently via a suitable functional linker to the support is shown to be important in this work. The optical purity of the product for TMSCN reaction varied with the presence of the spacer between the support and the salen complexes.

The heterogenized salen of unsymmetrical type (**A-2**) was also effective for this asymmetric reaction. Especially benzaldehyde was trimethylsilylcyanated to the corresponding product with an improved ee% up to 93% over heterogenized asymmetric salen catalyst. When the chiral TI(IV) salen catalysts were treated with H_2O, the ee% value resulted in a small improvement in the cases of both homogeneous and heterogeneous catalysts(**E-1, E-2)**. IR spectra of **E-2** (figure 2) suggest that these catalysts contain OH groups instead of chlorine in the structure.

MCM-41-supported chiral salens gave somewhat higher reaction rates and better asymmetric induction than the silica gel–supported catalysts. When the silica gel was used as a support to immobilize the chiral ligands, lower ee% values than with MCM-41 resulted under the same reaction conditions. The heterogenized catalyst was simply separated by filtration from the mixture of the product and could be recycled several times. However, the conversions obtained on the supported chiral salen catalysts were very low, showing the low turnover frequency.

4. Conclusion

Mesoporous MCM-41 materials functionalized with mercaptopropylsilyl groups were prepared by *in situ*

cocondensation with higher loadings of functional groups than the grafted materials. The chiral salen complexes of different structures could be readily immobilized on mesoporous MCM-41 by the multistep condensation of terminal functional groups on MCM-41 with diamines and salicylaldehyde derivatives, or by the one-step reaction between silanols and chlorine in the salen structure. In the asymmetric trimethylsilylcyanation of benzaldehyde, a high level of enantioselectivity was attained using chiral TI(IV) salen complexes immobilized onto MCM-41. The chiral salen TI(IV) complexes immobilized over MCM-41 using the multistep synthesis were stable during these reactions and exhibited relatively high enantioselectivity for reactions as compared with homogeneous ones. We conclude that chiral (salen) complexes immobilized on a mesoporous material by the multistep procedure can be applied as effective asymmetric heterogeneous catalysts.

References

[1] Y. Jiang, L. Gong, X. Feng, W. Hu, W. Pan, Z. Li and A. Mi, Tetrahedron 53 (1997) 14327.
[2] Y. Belokon, S. Caveda-Cepas, B. Green, N.S. Ikonnikov, V.N. Khrustalev, V.S. Larichev, M.A. Moscalenko, M. North, C. Orizu, V.I. Tararov, M. Tasinazzo, G.I. Timofeeva and L.V. Yashkina, J. Am. Chem. Soc. 121 (1999) 3968.
[3] K.G. Watson, Y.M. Feng, M. Gredley, G.J. Bird, W.R. Jackson, H. Gountzos and B.R. Mattews, J. Chem. Soc., Chem. Commun. (1990) 1018.
[4] B.R. Mathews, H. Gountzons, W.R. Jackson and K.G. Watson, Tetrahedron Lett. 30 (1989) 5157.
[5] T. Ziegler, B. Horsh and F. Effenberger, Synthesis (1990) 575.
[6] (a) W.R. Jackson, H.A. Jacobs, G.S. Jayatilake, B.R. Mathews and K.G. Watson, Aust. J. Chem. 43 (1990) 2045; (b) W.R. Jackson, H.A. Jacobs, G.S. Jayatilake, B.R. Mathews and K.G. Watson, Tetrahedron Lett. 31 (1990) 1447.
[7] (a) F. Effenberger and U. Stelzer, Angew. Chem. Int. Ed. Engl. 30 (1991) 873; (b) P. Zandbergen, J. Brussee, A. Van der Gen and C.G. Kruse, Tetrahedron: Asymmetry 3 (1992) 769.
[8] J. Brusee, E.C. Roos and A. Van der Gen, Tetrahedron Lett. 29 (1988) 4485.
[9] Y. Belokon, M. Moscalenko, N. Ikonnikov, L. Yashkina, D. Antonov, E. Vorontsov and V. Rozenberg, Tetrahedron: Asymmetry 8 (1997) 3245.
[10] Y. Belokon, B. Green, N.S. Ikonnikov, M. North and V.I. Tararov, Tetrahedron Lett. 40 (1999) 8147.
[11] D. Pini, A. Mandoli, S. Orlandi and P. Salvadori, Tetrahedron: Asymmetry 10 (1999) 3883.
[12] D.-W. Park, S.-D. Choi, S.-J. Choe, C.-Y. Lee and Geon-Joong Kim, Catal. Lett. 78 (2002) 145.
[13] A.M. Daly, C.T. Dalton, M.F. Renehan and D.G. Gilheany, Tetrahedron Lett. 40 (1999) 3617.
[14] Y.N. Belokon, G. Brendan, S.I. Nicolai *et al.*, Eur. J. Org. Chem. (2000) 2655.
[15] M.H. Lim, C.F. Blanford and A. Stein, J. Am. Chem. Soc. 119 (1997) 4090.
[16] J.M. Fraile, J.I. Garcia, J.A. Mayoral and A.J. Royo, Tetrahedron: Asymmetry 7 (1996) 2263.