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Enantioselective carbonyl-ene reaction on BINOLate/titanium catalyst encapsulated in magnetic nanoreactors[†]

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An asymmetric multicomponent catalyst, BINOLate/titanium, successfully encapsulated in the nanocages of mesoporous silicas exhibits much higher activity than the homogeneous counterpart in quasi solvent-free enantioselective carbonyl-ene reaction, owing to the confinement effect of the nanoreactor.

Asymmetric multicomponent catalysts that consist of two or more chiral ligands and/or metals have attracted much research attention in the asymmetric catalytic transformations due to the synergistic cooperation among different components. For example, the titanium complex of BINOL (1,1-bis-2-naphthol) and its derivatives are among the most widely used asymmetric multicomponent catalysts for a wide variety of enantioselective reactions.¹⁻⁸ For BINOLate/titanium catalyst, the catalytic species is usually generated in situ and subtle changes in reaction conditions (ligand-to-Ti ratio, solvent, addition sequence, and so on) may have a big influence on the catalytic performance of BINOLate/titanium catalyst.^{1,9} This is due to the co-existence of different kinds of species during the catalytic process as a result of a dynamic mixture of BINOLate/titanium species equilibrating with each other in solution.^{10,11} This makes the usage of asymmetric catalysts inefficient and the mechanistic study of the asymmetric catalysis difficult.

Immobilization of asymmetric multicomponent catalysts on solid supports may help to keep most multicomponent complexes in their active forms by carefully fixing two or more chiral ligands and/or metals in proper position, which will favor the usage efficiency of asymmetric catalysts and the research on the catalytic mechanism. Moreover, the transformation of homogeneous asymmetric catalysts into heterogeneous ones would benefit the economic and green process for the production of chiral chemicals.¹² Several strategies have been developed for immobilization of the asymmetric multicomponent catalysts. Sasai and co-workers immobilized bisBINOL ligands on the polymersupport *via* a "catalyst analogue" concept, in which the proper

proximity of the ligands in the monomer was controlled.¹³ Ding and co-workers demonstrated a successful immobilization of multicomponent metal complexes *via* a self-supporting strategy for the heterogeneous asymmetric catalysis.¹⁴ Although the methods mentioned above are efficient, the immobilization of asymmetric multicomponent catalysts that consist of two or more chiral ligands and/or metals still remains a difficult task due to the difficulty in controlling the proper proximity of two or more catalytic centers needed for the generation of active species on a solid catalyst.

Herein, we report an efficient and facile strategy for the heterogenization of the multicomponent metal complex, BINOLate/ titanium, by its encapsulation in the magnetic nanocages of mesoporous silicas. The confinement effect of the nanoreactor prohibits the formation of a dynamic mixture of BINOLate/ titanium species. Consequently, BINOLate/titanium encapsulated in the nanoreactor exhibits higher activity than the homogeneous counterpart for the quasi solvent-free enantioselective carbonyl–ene reaction. The comparison results of varying the BINOL-to-Ti molar ratio in the nanoreactor from 1 to 3 suggest that Ti(BINOLate)₂ species are the active catalysts for the carbonyl–ene reaction. This work demonstrates a new strategy to realize the heterogenization of asymmetric multicomponent catalysts and also a new method for elucidation of active species among a dynamic mixture evolved in the catalytic process.

Mesoporous silicas, FDU-12 with cage-like pore structure, were used as nanoreactors for encapsulation of the BINOLate/titanium complex. With an aim of obtaining solid asymmetric catalysts which could be easily separated from the reaction system, the magnetic nanoreactor was prepared by putting Fe₃O₄ nanoparticles on the surface of the as-synthesized FDU-12. The as-synthesized FDU-12 containing magnetic Fe₃O₄ nanoparticles was carbonized under inert gas conditions and F127 surfactant in the nanocages could generate a thin layer of carbon species. This synthetic method can selectively modify the inner surface of the mesoporous FDU-12, which is important for microenvironment modification of the mesoporous materials and difficult to be achieved using other synthetic strategies. The synthetic process for this bifunctionalized mesoporous materials, FDU-CM (C and M refer to the thin layer of carbon species and magnetic property, respectively), is outlined in Scheme 1A (for details of synthesis and characterization see ESI⁺, Fig. S1-S4).

The (*R*)-6,6'-Br₂-BINOL–Ti complex (simplified as B_n Ti, where *n* refers to the molar ratio of (*R*)-6,6'-Br₂-BINOL-to-Ti)

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[†] Electronic supplementary information (ESI) available: Experimental details, nitrogen adsorption isotherms, TEM images, Raman spectrum, solid state ¹³C and ²⁹Si NMR, UV-vis spectra, and recyclability of solid catalyst. See DOI: 10.1039/c2cc17950d



Scheme 1 Schematic description for synthesis process of FDU-CM with Fe_3O_4 nanoparticles on the outer surface and carbon species on the inner surface of the nanoreactor (A) and encapsulating the chiral (*R*)-6,6'-Br₂-BINOL-Ti complex with different ratios of ligand to metal in the nanoreactor through the silylation method (B).

was encapsulated in the nanocage of FDU-CM and FDU-12 according to a modified method based on our previous reports using propyltrimethoxysilane (C3) as silylation reagent to reduce the pore entrance size (Scheme 1B).^{15,16} Solid catalysts with the confined molecular complexes are denoted as $B_nTi@FDU-CM$ and $B_nTi@FDU-12$, respectively, using FDU-CM and FDU-12 as starting materials (for the preparation details and characterizations of the solid catalysts see the ESI[†], Fig. S5–S7). The characterizations of UV-vis diffuse reflectance spectroscopy and ¹³C CP/MAS NMR spectrum confirm that the homogeneous catalyst is successfully encapsulated in the nanoreactor (Fig. S8 and S9, ESI[†]).

The asymmetric carbonyl-ene reaction catalyzed by titanium complexes of BINOL derivatives is an important approach for C-C bond formation in organic synthesis.^{3,17} The catalytic performance of B_nTi@FDU-CM and B_nTi with different (R)-6,6'-Br₂-BINOL-to-Ti ratios for quasi solvent-free enantioselective carbonyl-ene reaction is summarized in Table 1. B₂Ti@FDU-CM could smoothly catalyze the asymmetric carbonyl-ene reaction with up to 95% yield and 92.1% ee at an S/C of 1000 (Table 1, entry 2). However, low product yield and ee were obtained for B₁Ti@FDU-CM (6% yield with 27.3% ee, Table 1, entry 1) and B₃Ti@FDU-CM (4% yield with 34.6% ee, Table 1, entry 3) with (R)-6,6'-Br₂-BINOL-to-Ti molar ratio other than 2. This result suggests that the B₂Ti complex is the active catalyst for the carbonyl-ene reaction.3,8 Similar to the results of solid catalysts, the homogeneous catalyst, B2Ti, showed the highest product yield and ee among B_nTi (Table 1, entry 2). It is interesting to find that B₂Ti@FDU-CM showed much higher yield (95% versus 58%) than and comparable ee to B₂Ti under similar conditions. However, B1Ti@FDU-CM and B3Ti@ FDU-CM showed lower product yield and ee than the homogeneous counterparts (Table 1, entry 1 and 3).

For enantioselective carbonyl–ene reaction, the active species is the B₂Ti complex. The ¹H NMR spectrum of B_nTi (n = 1, 2, 3) in C₆D₆ showed broad bulge-like resonances at the aromatic region (Fig. S10, ESI[†]), indicating the existence of a mixture of slowly equilibrating aggregates or oligomeric species.¹ Consequently, the presence of slowly equilibrating aggregates or oligomeric species

Table 1 The catalytic performance of the solid catalyst with different ratios of (R)-6,6'-Br₂-BINOL to Ti $(OiPr)_4$ for the quasi solvent-free enantioselective carbonyl–ene reaction^{*a*}

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Entry	п	S/C	$\operatorname{Yield}^{b}(\%)$	ee^{c} (%)
1	1:1	1000	6 (14)	27.3 (43.1)
2	2:1	1000	95 (58)	92.1 (94.7)
3	3:1	1000	4 (31)	34.6 (84.3)
4^d	2:1	5000	71 (53)	91.7 (94.4)
5^d	2:1	10 000	55 (22)	92.3 (94.6)

^{*a*} Unless otherwise stated, ethyl glyoxylate was 2.0 molar equivalents to α-methylstyrene; room temperature; 48 h. Ti contents for solid catalysts $B_n Ti@FDU-CM$ with *n* of 1, 2 and 3 are 0.154, 0.142, 0.130 wt%, respectively. The values in the parentheses are for homogeneous catalysts. ^{*b*} Isolated yields. ^{*c*} ee value of the product was determined by HPLC analysis using a Chiralcel OJ column. ^{*d*} The reaction time was 96 h.

may contribute to the catalytic activity and enantioselectivity of homogeneous B₁Ti and B₃Ti. The fact that B₁Ti@FDU-CM and B₃Ti@FDU-CM are almost inactive for the carbonyl-ene reaction and B₂Ti@FDU-CM shows very high activity and ee under quasi solvent-free conditions suggests that little equilibrating aggregates or oligomeric species exist in the nanoreactor and most of the B_nTi complexes remain in the form of B_nTi . Therefore, most of the B₂Ti complexes in the nanoreactor keep in their active forms, which results in much higher activity than the homogenous catalyst. At an S/C ratio as high as 5000, B₂Ti@ FDU-CM could smoothly catalyze the reaction with product yield of 71% with 91.7% ee, while homogeneous B₂Ti showed only 52% product yield with 94.4% ee. Even at an S/C of 10000, 55% product yield with 92.3% ee could still be obtained with solid catalysts and the homogeneous catalyst only showed 22% product yield. The above results show that B₂Ti encapsulated in the nanoreactor is more active than the homogeneous counterpart. As far as we know, B₂Ti@FDU-CM is among the few solid catalysts that can catalyze the carbonyl-ene reaction at such low amounts of catalyst usage. This result suggests that the free transformation of different species of BINOLate/Ti is difficult in the confined space of the nanoreactor due to the spatial limitation. The encapsulation of metal complexes in the nanoreactor may be an efficient method for immobilization of metal complexes with ligand/metal ratio more than 1.

The proper proximity of BINOL ligands can be adjusted by the loadings of (R)-6,6'-Br₂-BINOL-Ti complexes in the nanoreactor. The catalytic performance of B2Ti@FDU-CM with different metal complex loadings encapsulated in the nanoreactor is summarized in Table 2 for the carbonyl-ene reaction. The yield and ee of products increased as the Ti content increased and reached the maximum at a Ti content of 0.142 wt% (Table 2). Further increasing the Ti content above 0.142 wt% led to the decreasing of yield and ee. The "volume active site density" of the nanoreactor can be used to explain this tendency.¹⁶ With the increase of catalyst loadings in the nanoreactor from 0.064 to 0.211 wt%, the molecular number of the metal complex in each cage increases from 5 to 17 (Table 2). Consequently, the contact frequency between substrates and catalysts becomes increased and the activity of the solid catalyst increases. At high catalyst loading, the nanoreactor becomes crowded, which makes the

Table 2 The catalytic performance of solid catalysts with different contents of B_2 Ti for the quasi solvent-free enantioselective carbonyl–ene reaction^{*a*}



 a S/C = 1000; ethyl glyoxylate is 2.0 molar equivalents to α -methylstyrene; no solvent was added; room temperature; 48 h. b For calculation of number of catalyst molecules in each nanocage see ESI. c Isolated yields. d HPLC analysis using a Chiralcel OJ column. e The catalyst is B₂Ti@FDU-12.

diffusion of reactants and products in the nanoreactor difficult and reduces the activity of the solid catalyst. The "volume density of the active site" has great influence on the proximity of BINOL ligands and can change the coordination status between ligand and metal, which may cause the changes in ee of the solid catalysts with encapsulation of different B_2Ti contents. The activity and ee of encapsulated molecular catalysts could be improved by adjusting the "volume density of the active site" in the nanoreactors.

In addition, if B_2Ti was encapsulated in the nanocage of FDU-12 without inner surface modification of carbon, only 79% yield with 61.3% ee was obtained in CH₂Cl₂ (Table 2, entry 6), which was lower than that of $B_2Ti@FDU-CM$ with almost the same catalyst loading (Table 2, entry 3). This is probably due to the strong interaction of (*R*)-6,6'-Br₂-BINOL-Ti species with the pore wall of FDU-12. Careful screening of the modification of the microenvironment of the nanoreactors is important to acquire high activity and enantioselectivity for the heterogeneous asymmetric catalysis.

The substrate scope of enantioselective carbonyl-ene reaction was investigated under optimized conditions using B2Ti@FDU-CM as a model catalyst (Table S2, ESI[†]). Higher catalytic activity and enantioselectivity (95.5%-94.9% ee) were obtained for F- and Cl-substituted olefins than those for CH₃-substituted olefin. The result exhibits that B₂Ti@FDU-CM is a highly efficient asymmetric catalyst for electron-withdrawing substituents. The recycling performance of the solid catalysts was conducted by using B₂Ti@FDU-CM as the model catalyst (Fig. S11, ESI[†]). After the reaction was complete, the solid catalyst was recovered easily from the reaction system through magnet and was washed thoroughly with CH₂Cl₂. The separated solids were recharged with toluene and substrates for the next run. As shown in Fig. S11, the catalyst was used for three cycles in the enantioselective carbonyl-ene reaction. However, longer time was needed to obtain higher yield and the enantioselectivity dropped slightly from 92.0% to 86.4%. In order to determine the heterogeneity of the reaction,

the activity of filtrate was investigated. The solid catalyst, $B_2Ti@$ FDU-CM, was filtrated out after the product yield reached 23%. The filtrate was continuously stirred. After 48 h, the product yield was about 26%. This indicated that the enantioselective carbonyl–ene reaction was mainly catalyzed by the solid catalyst.

In summary, we have demonstrated the successful encapsulation of asymmetric multicomponent catalysts in the nanocage of mesoporous silicas using BINOLate/Ti complexes as a model catalyst. The solid catalyst exhibits significantly higher activity than the homogenous catalyst under quasi solvent-free conditions for enantioselective carbonyl–ene reaction. The confinement effect of the nanoreactor could effectively suppress the formation of a dynamic mixture of BINOLate/Ti species and increase the usage efficiency of the asymmetric catalysts, which mainly contribute to the high activity of the solid catalyst. It is found that the solid catalyst can catalyze the enantioselective carbonyl–ene reaction even at an S/C as high as 10 000. This work provides a new strategy to realize the heterogenization of the asymmetric multicomponent catalysts.

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