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Assembled enantioselective catalysts for carbonyl-ene reactions

Hongchao Guo, Xingwang Wang and Kuiling Ding*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China

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Abstract—A new strategy for generating assembled polymeric chiral titanium complexes using linked bis-BINOL ligands have been developed, and the assembled catalysts showed excellent enantioselectivity (up to 96.5% ee) for carbonyl-ene reaction under heterogeneous conditions to afford corresponding α-hydroxy esters in high yield. The linkers between two BINOL units of the ligands in the assembled catalysts were found to have significant impact on the enantioselectivity of reaction, which demonstrated the importance of the supramolecular structures of the assemblies for their catalytic behaviours.

Asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry.[1] The development of chiral catalysts for the enantioselective reactions is one of the most fundamental aspects in asymmetric catalysis.[2] Homogeneous asymmetric catalysis has the advantages of high enantioselectivity and catalytic activity in a variety of asymmetric transformations under relatively mild reaction conditions. The catalyst loadings employed in most cases were in the range from 5 to 10 mol %,[2] which remains impractical in terms of high costs of noble chiral catalysts and difficulty for recovery and reuse.[3] The immobilization of homogeneous catalysts using organic and inorganic supports could resolve this problem to some extent.[4] However, the immobilized catalysts often demonstrated reduced enantioselectivity and less efficiency in the catalysis in comparison with their homogeneous counterparts.

Metal–organic self-assembled frameworks have been shown to exhibit permanent porosity and absorption capacity for organic guest molecules.[5] Therefore, design and synthesis of chiral metal–organic frameworks (chiral zeolite) might provide a new strategy for asymmetric heterogeneous catalysis, because the chiral ligand can spontaneously form chiral environment and the metal ion acts as the catalytically active centre. Such kind of molecular assemblies not only have the advantage of robust chiral frameworks, but also high density of the catalytic active units. Seo and co-workers have demonstrated the enantioselective activity of a homochiral metal–organic porous material composed of tartaric acid derived ligands and Zn ion for transesterification despite of low enantioselectivity (~8% ee).[6] More recently, Lin and co-workers reported the heterogenization of Noyori's catalyst with Zr phosphonate framework, which promotes the asymmetric hydrogenation of aromatic ketones with remarkably high activity, enantioselectivity and reusability.[7] As a continuous effort for the development of practical asymmetric catalysis of organic reactions,[8] in this letter we reported our primary results on the development of a new type of assembled catalytic materials of chiral titanium complex, which demonstrated high efficiency and enantioselectivity for asymmetric carbonyl-ene reaction, one type of important C–C bond formation protocols in organic synthesis.

Among various chiral Lewis acids, such as Al, Ti, Ni, Pt, Pd, Yb and Cu metallic complexes, titanium complexes of BINOL derivatives are prominent for asymmetric carbonyl-ene reaction.[9] According to Mikami's asymmetric activation concept, enantiopure (*R*)-BINOL-$Ti(O^iPr)_2$ (10 mol %) catalyst could be activated by further addition of (*R*)-BINOL, affording the product in carbonyl-ene reaction in higher enantioselectivity (96.8% ee vs 94.5% ee).[10a] Kinetic study disclosed that the reaction catalyzed by (*R*)-BINOL-$Ti(O^iPr)_2$/(*R*)-BINOL complex was 25.6 times as fast as that catalyzed by the (*R*)-BINOL-$Ti(O^iPr)_2$.[10a] We have demonstrated that the catalysts prepared by homocombination of

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* Corresponding author. Tel.: +86-21-6416-3300; fax: +86-21-6416-6128; e-mail: kding@mail.sioc.ac.cn

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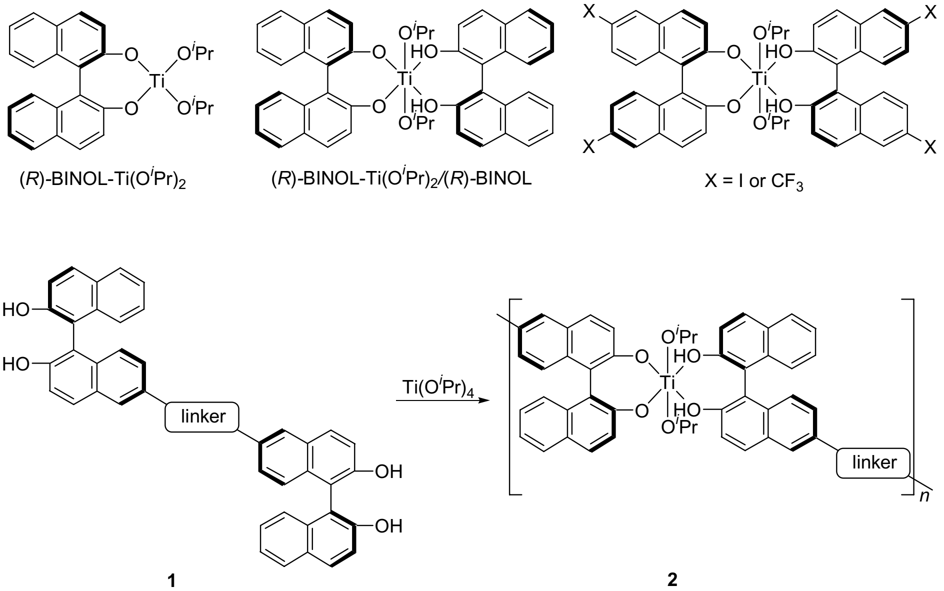
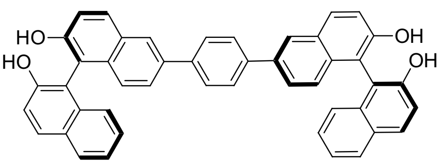


1 **2**

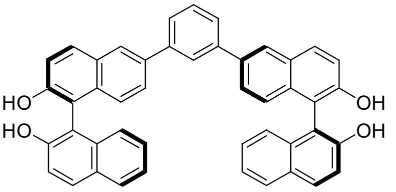
Scheme 1. The strategy for the molecular assembly of heterogeneous chiral catalyst with linked BINOL derivatives.

(*R*)-6,6′-I$_2$-BINOL with Ti(O^{i}Pr)$_4$ or heterocombination (*R*)-6,6′-I$_2$-BINOL and (*R*)-6,6′-(CF$_3$)$_2$-BINOL with Ti(O^{i}Pr)$_4$ showed exceptional efficiency for carbonyl-ene reaction under nearly solvent-free conditions to afford α-hydroxy ester derivatives in good yields and excellent enantioselectivities.[8b] These phenomena provided an excellent opportunity for design of assembled catalysts for this reaction by using linked BINOL[11] ligands with Ti(O^{i}Pr)$_4$, which is shown in Scheme 1.

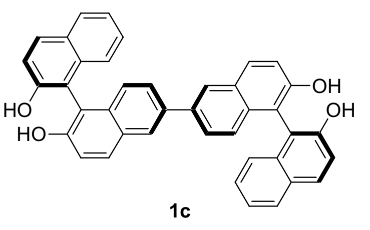
In order to demonstrate the applicability of our strategy, three linked BINOL ligands (**1a**–**c**) (Scheme 2) were synthesized by Suzuki coupling reactions. Ligands **1a**–**b** were obtained by the reaction of *para*- and *meta*-phenylene-diboronic acid with (*S*)-6-bromo-2,2′-dimethoxymethoxy-1,1′-binaphthyl, followed by acidic deprotection of methoxymethyl groups, and ligand **1c** was prepared by coupling of (*S*)-6-bromo-2,2′-dimethoxymethoxy-1,1′-binaphthyl with (*S*)-6-(MeO)$_2$B-2,2′-dimethoxymethoxy-1,1′-binaphthyl, followed by acidic deprotection of methoxymethyl groups. The catalysts **2a**–**c** were prepared by mixing the ligands **1a**–**c** and Ti(O^{i}Pr)$_4$ (1:1 molar) in CHCl$_3$. The mixtures were stirred at room temperature for 4 h and then the solvent was removed under the reduced pressure. The resulting orange solids were submitted to the carbonyl-ene reaction of α-methylstyrene (**3**) with ethyl glyoxylate (**4**). The reaction was carried out in toluene or in the absence of solvent and the catalyst loading employed in the reaction was 1 mol %. As shown in Table 1, the carbonyl-ene reaction proceeded smoothly at room temperature under the catalysis of **2a** to give α-hydroxy ester (*S*)-**5** in 91% yield and 94.4% ee (entry 1). Lowering the reaction temperature to 0 °C only resulted in the decrease of reactivity with slight improvement of the enantioselectivity (entry 2 vs entry 1). The addition of 4 Å molecular sieve (MS) has no significant impact on the catalysis in terms of both enantioselectivity and reactivity of the reaction (entrie 4–5 vs entries 1–2). The reaction could be also carried out under solvent-free conditions with the catalysis of **2a**, affording the product (*S*)-**5** in 75% yield with 94.4% ee (entry 6). On the contrary, the catalyst **2b** prepared from the ligand **1b** having meta-phenylene linker showed poor catalytic activity and enantioselectivity (entries 7 and 8) under the same experimental conditions, which demonstrated the change of the linker probably significantly altered the supramolecular structure of the assemblies. It is interesting to note that the catalyst **2c** obtained from a simple



1a



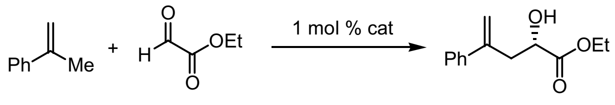
1b



1c

Scheme 2. The linked BINOL ligands employed for assembling the catalysts with titanium isopropoxide.

Table 1. Enantioselective catalysis of carbonyl-ene reaction with assembled catalysts **2a**–**c**[a]



3 **4** **5**

Entry	Catalyst	Toluene[b]	4 Å MS[c]	Stirring	Temperature (°C)	Time (h)	Yield (%)[d]	Ee (%)[e]
1	**2a**	+	–	+	rt	48	91	94.4
2	**2a**	+	–	+	0	120	85	95.4
3	**2a**	+	–	–	0	120	96	95.6
4	**2a**	+	+	+	rt	120	93	92.1
5	**2a**	+	+	+	0	120	65	92.5
6	**2a**	–	–	–	0	120	75	94.4
7	**2b**	+	–	+	rt	48	32	9.8
8	**2b**	+	–	+	0	120	9	24.2
9	**2c**	+	–	+	rt	30	>99	96.5
10	**2c**	+	–	+	0	96	95	91.5
11	**2c**	+	+	+	rt	96	85	92.4
12	**2c**	+	+	+	0	96	90	95.5
13	**2c**	–	–	+	0	96	90	92.7

[a] The reaction was carried out with the ratio of **3**/**4**/**2** = 1:2:0.01 in a 1.25 mmol scale of **3**.[12]

[b] 0.05 mL of toluene was added to the reaction system.

[c] 15 mg of 4 Å MS (dried in vacuo at 400 °C for 8 h) was added.

[d] Isolated yield.

[e] The ee was determined by HPLC on a Chiralcel OJ column and the absolute configuration was assigned to be *S* by comparing their optical rotations with that of literature.[8b]

dimmer of BINOL (**1c**) showed enhanced enantioselectivity and dramatically increased catalytic activity, giving product (*S*)-**5** in >99% yield and 96.5% ee (entry 9). Similarly, addition of 4 Å MS and decreasing the reaction temperature did not shown any advantages over the cases of room temperature reaction in the absence 4 Å MS. Again, the reaction under the solvent-free condition could proceed smoothly under the catalysis of **2c** to afford the product in slightly decreased yield and enantioselectivity (entry 13). The solids of the catalyst **2c** gradually dissolved in the reaction mixture under the solvent-free condition, which implies a homogeneous catalysis of reaction in this case.

In conclusion, we have developed a new strategy for generating polymeric chiral catalysts by in situ assembly of linked bis-BINOL ligands with $Ti(O^iPr)_4$, and the assembled catalysts showed excellent enantioselectivity for carbonyl-ene reaction of α-methylstyrene and ethyl glyoxylate under heterogeneous conditions to afford corresponding α-hydroxy esters in high yield. The linkers between two BINOL units of the ligands in the assembled catalysts have significant impact on the enantioselectivity of reaction, which demonstrated the importance of the supramolecular structures of the assemblies on their catalytic behaviours. The strategy described in this work might provide a new direction to the design of chiral catalysts for asymmetric synthesis.[13] The research on the recovery and reuse of the assembled catalysts and the application of this strategy for the design of other type of assembled enantioselective catalysts is being carried out in this laboratory and will be reported in due course.

Acknowledgements

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12. A general procedure for carbonyl-ene reaction using assembled catalysts: To a solution of ligand (for **1a** or **1b**, 8.1 mg, for **1c**, 7.1 mg, 0.0125 mmol) in CHCl$_3$ (0.2 mL) was added Ti(O^{i}Pr)$_4$ (25 μL, 0.5 M in CH$_2$Cl$_2$, 0.0125 mmol) under stirring at room temperature in the glove box. The orange solids appeared at once after addition. After stirring for 4 h, the solvent in the mixture was removed under the reduced pressure and the orange solid catalyst were obtained. The carbonyl-ene reaction was then carried out by addition of dried toluene (50 μL), α-methylstyrene (165 μL, 1.25 mmol) and freshly distilled ethyl glyoxylate (200 μL, 2.5 mmol) to the Schlenk tube containing the catalyst solids. After the heterogeneous mixture was stirred at room temperature for 48 h, freshly distilled anhydrous ethyl ether (1 mL) was added and stirred for several minutes. After staying, the clear supernatant was removed via syringe and the catalyst was remained at the bottom of the tube. The operation was repeated for three times. The combined ethyl ether solution was concentrated and purified by flash chromatography on silica (ethyl acetate/hexane = 1/5) to afford the carbonyl-ene product **5**. IR (KBr) $\nu_{\max}$ 3475, 3084, 3058, 2984, 2939, 1737, 1630, 1496, 1446, 1372, 1267, 1210, 1114, 1030, 905, 780 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.44–7.28 (m, 5H), 5.40 (s, 1H), 5.21 (s, 1H), 4.30–4.24 (m, 1H), 4.15–4.00 (m, 2H), 3.07 (dd, $J = 4.5$ Hz, 13.5 Hz, 1H), 2.84 (dd, $J = 8.1$ Hz, 13.5 Hz, 1H), 2.73 (d, $J = 6.30$ Hz, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). EIMS m/z (relative intensity): 220 (M$^+$, 38.62), 202 (25.82), 174 (11.50), 147 (45.90), 129 (100.00), 119 (63.65), 115 (41.90), 103 (42.58), 91 (88.83), 77 (45.74). The enantiomeric excess of the product was determined with HPLC on a Chiralcel OJ column (eluent, hexane/2-propanol (97:3); flow rate, 0.7 mL/min; UV detection at $\lambda = 254$ nm; $t_R = 23.37$ min (major), 30.76 min (minor), respectively).
13. After the accomplishment of preparation of this manuscript, we noticed that a paper by Sasai and co-workers appeared at the upcoming Hot Paper, homepage of *Angew. Chem. Int. Ed.*, where a similar strategy was employed for the synthesis of chiral Al-bridged and Ti-bridged polymers by a metal-mediated self-assembly of (*R*,*R*)-6,6′-bi(BINOL). These catalysts were found to promote asymmetric Michael addition and carbonyl-ene reaction with high enantioselectivity: Takizawa, S.; Somei, H.; Jayaprakash, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5711–5714.