Catalytic Carbonyl-Ene Reaction

Quasi Solvent-Free Enantioselective Carbonyl-Ene Reaction with Extremely Low Catalyst Loading**

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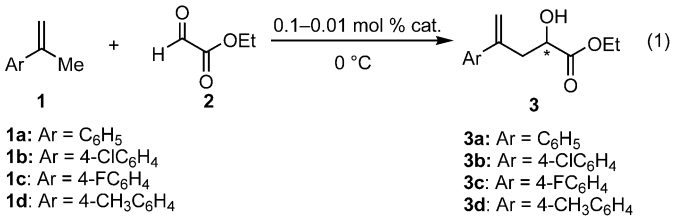
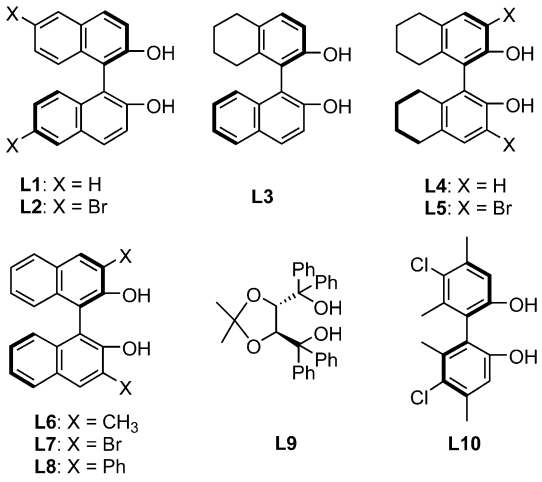
Asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry.[1] The development of chiral catalysts for the enantioselective carbon–carbon bond-forming reactions is a fundamental topic in asymmetric catalysis.[1] However, many currently accessible methods are impractical, for example, in terms of efficiency and environmental considerations.[2] Therefore the development of truly efficient and practical synthesis has been one of the greatest challenges for synthetic chemists. As part of our continuing effort in this area,[3] we report in this communication the first quasi solvent-free enantioselective carbonyl-ene reaction. The reaction of ethyl glyoxylate with a variety of olefins could be carried out with 0.1–0.01 mol % of catalysts to give α-hydroxy esters in good to excellent yields and up to 99 % *ee* [Eq. (1)].



For practical synthesis, solvent-free processes are ideal in terms of volumetric productivities and environmental safety.[4] Although most catalytic asymmetric processes are highly sensitive to the polarity of solvent and the concentration of substrates, a solvent-free procedure might be suitable for an asymmetric reaction with a concerted mechanism[3] because its transition state is less influenced by the polarity of the solvents. The thermal pericyclic ene reaction represents a typical concerted pathway involving six electrons with a suprafacial orbital interaction,[5] and its asymmetric version has been achieved with various chiral Lewis acids including Al, Ti, Ni, Pt, Pd, Yb, and Cu complexes.[6,7] The catalyst loadings employed in most cases were in the range from 1 to 10 mol %. In our experiments we employed binolate-Ti, which was prepared in situ by the reaction of (*R*)-binol (2,2′-dihydroxy-1,1′-biphenyl) and titanium isopropoxide (2:1 molar ratio in dichloromethane/toluene). Under nearly solvent-free conditions (the solvent volume from the catalyst was about 13 % of the whole system) and with a catalyst loading of 0.1 mol %, α-methylstyrene (**1a**) reacted with ethyl glyoxylate (**2**) [Eq. (1)] efficiently at room temperature to give α-hydroxy ester (*R*)-**3a** in quantitative yields and good enantioselectivity (90 % *ee*). The practical advantages of this strategy—the easy preparation of the catalyst, the nearly solvent-free conditions, the high yield and enantiopurity of the product, and the extremely low catalyst loading—make this protocol attractive for the preparation of enantiomerically enriched α-hydroxy esters of biological and synthetic importance.

Tuning the sterics and electronics of the diol ligands in their metal complexes is essential to achieving highly efficient catalysts for asymmetric reactions, and the combinatorial-chemistry approach may be a powerful strategy for this purpose.[8] We searched for more efficient catalysts for the reaction of **1a** with **2** by high-throughput screening of a catalyst library generated from the parallel combination of any two of the ligands shown in Scheme 1 with titanium isopropoxide. We found that both the electronic effect and the steric bulk of the substituents of these binol derivatives have significant impact on the catalytic activity and enantioselectivity of the binol-Ti catalysts (see the Supporting Information). The serious steric hindrance of the substituents (e.g. CH_3, Ph, Br) at the 3,3′-positions of binol proved to be disadvantageous for the reaction. The partially reduced binaphthyl ligands **L3** and **L4** were inferior to the parent ligand **L1**. The modification of diol ligand at the 6,6′-positions of binol with Br (**L2**) is quite effective for enhancing both the reactivity and the enantioselectivity of the reaction.



Scheme 1. Chiral ligands employed for asymmetric induction.

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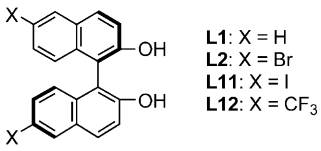
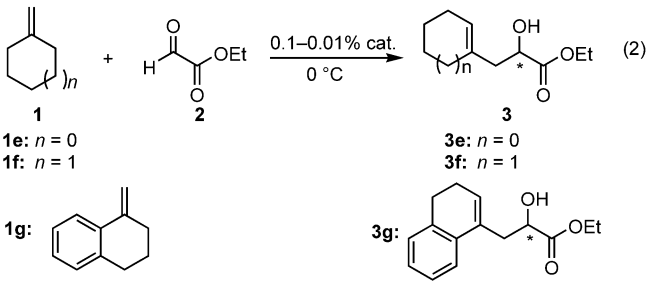
All these results demonstrated that enhancing the Lewis acidity of the titanium complexes might be a key point for achieving high efficiency and enantioselectivity in the carbonyl-ene reaction. Therefore, we decided to set up a second-generation library of chiral binol ligands with various electron-withdrawing groups (X = Br, I, CF_3) at the 6,6′-positions (Scheme 2). As we expected, the catalyst library



Scheme 2. Second-generation chiral binol ligands employed for asymmetric induction.

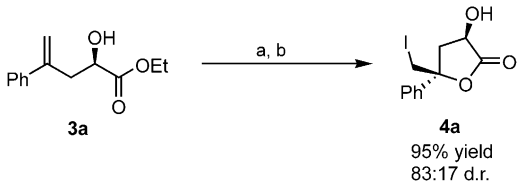
generated by either homocombination or heterocombination of these chiral ligands with titanium isopropoxide showed excellent enantioselectivity (> 94.9 % *ee*) (see the Supporting Information) under nearly solvent-free conditions even though the catalyst loading was reduced to 0.01 mol %. (The solvent volume of the catalyst system was only ca. 1.3 % of the whole system in these cases!) The catalysts formed by homocombination of **L11** or heterocombination of **L11** and **L12** with titanium isopropoxide were found to be superior to other catalysts, affording α-hydroxy ester **3a** in 97.1 % yield and 97.7 % *ee*.

The reactions promoted by the optimized catalysts (**L11**/Ti/**L11** and **L11**/Ti/L**12**) were then carried out on a gram scale with catalyst loadings of 0.1–0.01 mol % at 0 °C. We found that both **L11**/Ti/**L11** and **L11**/Ti/**L12** are highly efficient catalysts for the reactions of a variety of 2-arylpropenes (**1a–d**), including derivatives with electron-withdrawing or electron-donating substituents (Table 1). The olefin substrates could be also extended to cyclic systems (**1e,f**). The reactions of ethyl glyoxylate with methylenecyclopentane (**1e**) and methylenecyclohexane (**1f**) proceeded with excellent enantioselectivities [Eq. (2)]. Incidentally, product **3e** is a key intermediate in the synthesis of the collagenase-selective inhibitor Trocade.[9] In the case of benzocyclic olefin substrate **1g**, the corresponding α-hydroxy ester **3g** could be obtained in 94–97 % yields with 92.6–96.3 % *ee*.



(2)

To demonstrate the preparative utility of this methodology, we conducted the reaction of ethyl glyoxylate with α-methylstyrene at 0 °C on a 0.1-mole scale employing 0.05 mol % **L11**/Ti/**L12**; the desired adduct **3a** was generated in > 99 % yield and 95 % *ee*. To the best of our knowledge, this is the lowest catalyst loading for a Lewis acid catalyzed asymmetric carbonyl-ene reaction.[6h] The resulting product **3a** could be converted stereoselectively into functionalized γ-butyrolactone **4a** by iodolactionization in excellent yield with the (*R,S*) isomer as the major product (Scheme 3).[10] This is a powerful approach for the synthesis of biologically important products.



Scheme 3. Preparation of γ-butyrolactone **4a**. Conditions: a) 20 % aq KOH, CH_3OH, 40 °C, 4 h; b) I_2, $NaHCO_3$, CH_3CN, room temperature, 16 h.

Table 1: Enantioselective ene reactions between ethyl glyoxylate and representative olefins under nearly solvent-free conditions.

Olefin	Product[a]	Cat. (mol %)	*t* [h]	Yield[b] [%]	*ee* [%][c]
1a	(*R*)-**3a**	**L11**/Ti/**L11** (0.1)	48	98	98.2
1a	(*R*)-**3a**	**L11**/Ti/**L12** (0.1)	48	85	97.6
1a	(*R*)-**3a**	**L11**/Ti/**L11** (0.01)	72	76	97.2
1a	(*R*)-**3a**	**L11**/Ti/**L12** (0.01)	72	49	97.9
1b	(−)-**3b**[d]	**L11**/Ti/**L11** (0.1)	48	89	99.4
1b	(−)-**3b**[d]	**L11**/Ti/**L12** (0.1)	36	96	98.2
1c	(+)-**3c**[d]	**L11**/Ti/**L11** (0.1)	48	83	98.4
1c	(+)-**3c**[d]	**L11**/Ti/**L12** (0.1)	48	96	98.4
1d	(−)-**3d**[d]	**L11**/Ti/**L11** (0.1)	36	92	97.1
1d	(−)-**3d**[d]	**L11**/Ti/**L12** (0.1)	36	> 99	97.0
1f	(*R*)-**3e**	**L11**/Ti/**L11** (0.1)	24	> 99	91.6
1f	(*R*)-**3f**	**L11**/Ti/**L12** (0.01)	42	42	91.8
1g	(*R*)-**3g**	**L11**/Ti/**L11** (0.1)	48	97	92.2
1g	(*R*)-**3g**	**L11**/Ti/**L12** (0.1)	48	94	96.3

[a] Absolute configurations were assigned by comparing the optical rotations with literature values. [b] Yields of isolated products. [c] Enantiomeric excesses were determined by GC (Cyclodex B column) or HPLC (Chiral OJ column). [d] Absolute configuration was not determined.

In conclusion, we have first demonstrated that the enantioselective carbonyl-ene reaction of glyoxylate ester with a variety of olefins can be carried out under nearly solvent-free conditions with the catalysis of 6,6′-I_2- or 6,6′-$(CF_3)_2$-binol-Ti at very low catalyst loadings (up to 0.01 mol %), affording the corresponding α-hydroxy esters in high yields and excellent enantioselectivities. The transformation of product **3a** into a new type of functionalized γ-butyrolactone **4a** was also achieved by stereoselective iodolactonization in excellent yield.

Experimental Section

General procedure for the quasi solvent-free enantioselective carbonyl ene reaction of ethyl glyoxylate with α-methylstyrene. To a solution of **L11** (27 mg, 0.05 mmol) and **L12** (21 mg, 0.05 mmol) in

toluene (1 mL) was added 0.5 M $Ti(OiPr)_4$ in CH_2Cl_2 (100 μL, 0.05 mmol), and the mixture was stirred for 2 h at room temperature. The mixture was cooled to 0 °C, and then α-methylstyrene (**1a**) (12.5 mL, 0.1 mol) and ethyl glyoxylate (**2**) (15 mL, 0.2 mol) were added. After stirring for 48 h at 0 °C, the reaction mixture was directly submitted to flash column separation on silica gel with EtOAc/hexane (1:4) as eluent to give (*R*)-**3a** (22 g, >99% yield with 95% *ee*). The enantiomeric excess of the product was determined by HPLC on a Chiralcel OJ column; eluent: hexane/2-propanol (97:3); flow rate: 0.7 mL min^{-1}; UV detection at $\lambda = 254$ nm; t_R((*S*)-**3a**) = 23.3 min (minor), t_R((*R*)-**3a**) = 30.7 min (major).

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Keywords: asymmetric catalysis · carbonyl-ene reaction · ligand effects · titanium

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[10] The absolute configuration of **4a** was determined by X-ray diffraction analysis, see the Supporting Information. CCDC-216977 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

