

Highly Enantioselective Hetero-Diels–Alder Reaction of *trans*-1-Methoxy-2-methyl-3-trimethylsiloxybuta-1,3-diene with Aromatic and Aliphatic Aldehydes Catalyzed by 3-Substituted BINOL–Titanium Complex

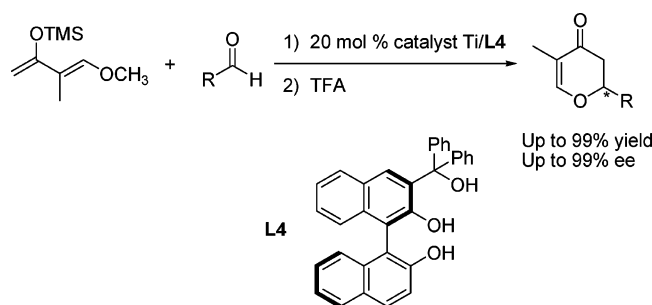
Xin-Bin Yang,^{†,§} Jie Feng,[†] Ji Zhang,[†] Na Wang,[†] Li Wang,[†] Jun-Liang Liu,[†] and Xiao-Qi Yu^{*,†,‡}

Department of Chemistry, Key Laboratory of Green Chemistry and Technology (Ministry of Education), Sichuan University, Chengdu, 610064, P. R. China, State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan 610041, P. R. China, and Rongchang Campus, Southwest University, Chongqing 402460, P. R. China

xqyu@tfol.com

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ABSTRACT



3-Diphenylhydroxymethyl-substituted BINOL–titanium complex prepared in situ was found to be a highly efficient catalyst for hetero-Diels–Alder reaction of diene 1 with both aromatic and aliphatic aldehydes to give 2,5-disubstituted dihydropyrene in up to 99% yield and 99% ee.

The catalytic asymmetric hetero-Diels–Alder (HDA) reaction of Danishefsky's diene with aldehydes provided a powerful approach for achieving optical active dihydropyrones, which was applied widely in the synthesis of carbohydrates and numerous natural compounds.^{1–16} Multi-substituted dihydropyrones could be obtained by the modification on different positions of substrate dienes or alde-

hydes.¹⁷ In 1983, Danishefsky and co-workers first reported the synthesis of chiral 2,5-disubstituted dihydropyrene by asymmetric HDA reaction between *trans*-1-methoxy-2-methyl-3-trimethylsiloxybuta-1,3-diene (diene 1) and benzaldehyde, in which moderate enantioselectivity was achieved.^{17a} More recently, Feng and co-workers reported much better

[†] Key Laboratory of Green Chemistry and Technology, Sichuan University.

[‡] West China Medical School, Sichuan University.

[§] Southwest University.

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results between diene **1** and aromatic aldehydes with the use of (*R*)-BINOL–Ti(OiPr)₄ complex.¹⁷ⁱ However, to the best of our knowledge, few catalytic systems could induce high enantioselectivity for aromatic and aliphatic aldehydes in the HDA reactions. Therefore, searching for universal catalysts for asymmetric HDA reactions between diene **1** and different kinds of aldehydes is of great importance.

Many modified BINOLs with different substituents on naphthalene rings were prepared and used as chiral ligands in asymmetric catalytic reactions.^{18–23} Herein, we wish to report that the titanium(IV) catalysts derived from 3-mono-substituted or 3,3'-disubstituted (*R*)-BINOLs could exhibit an enhanced catalytic activity for the asymmetric HDA reaction between diene **1** and aromatic or aliphatic aldehydes. For this purpose, ligands **L1**–**L4** were studied (Figure 1). We found that **L4** in combination with Ti(OiPr)₄ could

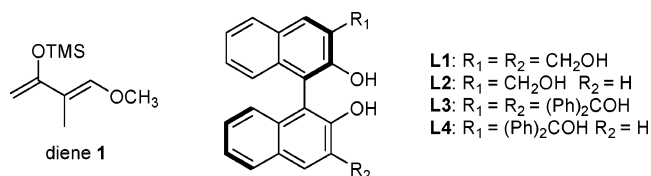


Figure 1. Structure of diene **1** and chiral ligands **L1**–**L4**.

catalyze the HDA reaction with excellent enantioselectivity, especially for aliphatic aldehydes.

Various ligands (Figure 1) were examined as catalysts for the HDA reaction between diene **1** and benzaldehyde. The reactions were carried out in the presence of (*R*)-BINOL derivatives **L1**–**L4** (20 mol %) and Ti(OiPr)₄ (20 mol %) in CH₂Cl₂ at 0 °C for 72 h. Interestingly, we found that the Ti(IV) complex of 3-diphenylhydroxymethyl-substituted BINOL ligand (**L4**) could give the desired product in the highest yield associated with the highest enantioselectivity. In contrast, the Ti(IV) complexes of **L1**–**L3** displayed poor catalytic activity. It could be considered that the monosubstituted diphenylhydroxymethyl group played an important role in the catalytic process.

The HDA reaction conditions catalyzed by Ti/**L4** were optimized, and the results are listed in Table 1. The reaction carried out in toluene could give higher yield and ee than those in other solvents such as dichloromethane, THF, and diethyl ether (entries 1–4). The mole ratio 1:1 of metal/ligand afforded best catalytic results. Slight increase of the relative amount of **L4** resulted in dramatic decrease of ee

Table 1. HDA Reaction between Diene **1** and Benzaldehyde Catalyzed by Ti/**L4** under Various Conditions^a

entry	solvent	L4 :Ti(OiPr) ₄ (mol %)	T (°C)	yield (%) ^{a,b}	ee (%) ^c
1	CH ₂ Cl ₂	20:20	0	87	86
2	THF	20:20	0	94	86
3	Et ₂ O	20:20	0	87	45
4	toluene	20:20	0	98	94
5	toluene	22:20	0	99	45
6	toluene	24:20	0	90	28
7	toluene	30:20	0	81	–8
8	toluene	18:20	0	99	88
9	toluene	16:20	0	96	87
10	toluene	10:20	0	80	30
11	toluene	20:20	–20	88	81
12	toluene	20:20	25	99	84

^a Unless indicated, all reactions were carried out on a 0.20 mmol scale with **L4** and Ti(OiPr)₄ (20 mol %) in 2.0 mL of solvent at 0 °C for 72 h.
^b Isolated yields. ^c The ee values were determined by HPLC using chiralcel OJ column.

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(entries 4–7). On the other hand, lower enantioselectivities were also obtained in the reaction with less **L4** (entries 8–10). When reaction temperature decreased to $-20\text{ }^{\circ}\text{C}$, lower yield and enantioselectivity were obtained (entry 11). However, when the reaction was performed at $25\text{ }^{\circ}\text{C}$, the enantioselectivity was also affected (entry 12).

Inspired by the previous results, we applied various aromatic and aliphatic aldehydes to the HDA reaction catalyzed by **Ti/L4** under optimized conditions; the results are listed in Table 2. Excellent yields and ees were obtained for almost all of the tested substrates.

Table 2. HDA Reaction of Diene **1** with Various Aldehydes Catalyzed by **L4**/**Ti**(*OiPr*)₄

entry	aldehyde	product	yield (%) ^a	ee (%) ^b
1	benzaldehyde	3a	98	94
2	4-nitrobenzaldehyde	3b	91	99
3	3-nitrobenzaldehyde	3c	86	96
4	2-nitrobenzaldehyde	3d	94	92
5	4-chlorobenzaldehyde	3e	99	93
6	3-chlorobenzaldehyde	3f	99	95
7	2-chlorobenzaldehyde	3g	82	87
8	4-methylbenzaldehyde	3h	89	93
9	3-methylbenzaldehyde	3i	98	90
10	2-naphthbenzaldehyde	3j	99	93
11	4-cyanobenzaldehyde	3k	92	99
12	4-bromobenzaldehyde	3l	98	92
13	4-trifluoromethylbenzaldehyde	3m	98	88
14	2-furaldehyde	3n	98	86
15	propionaldehyde	3o	86	90
16	butyraldehyde	3p	91	99
17	isobutyraldehyde	3q	75	92
18	valeraldehyde	3r	94	92
19	heptaldehyde	3s	92	97
20	crotonaldehyde	3t	86	91

^a Isolated yields. ^b The ee values were determined by HPLC using chiralcel OJ or OD-H column (see Supporting Information for details).

For aromatic aldehydes (entries 1–14), ortho-substitution might lead to less enantioselectivity (entries 4 and 7). Benzaldehyde bearing an electro-withdrawing group in the para position exhibited the highest levels of enantioselectivity (entries 2 and 11). Interestingly and importantly, a variety of aliphatic aldehydes, including linear (entries 15, 16, 18, and 19), α -branched (entry 17), and α,β -unsaturated (entry 20) aldehydes, also gave good to excellent results (entries 15–20).

The linear relationship between the ees of chiral ligand **L4** and HDA product **3a** was investigated. It is obvious that the catalytic system showed both weak positive and strong negative nonlinear effects (Figure 2). We were interested to find that the absolute configuration of the product **3a** was switched when the ees of partially resolved **L4** were decreased to 30%. The results suggested that the active species of the HDA reaction might change with the decrease of ee of the chiral ligand.¹³

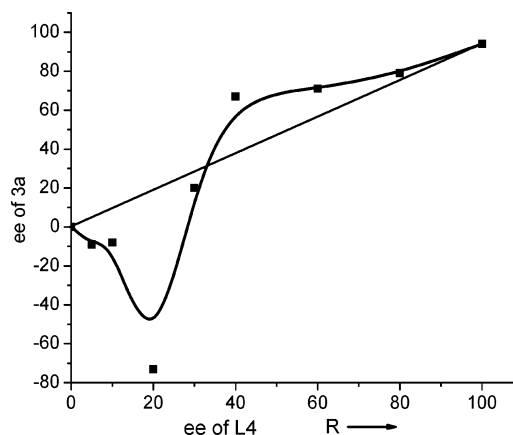
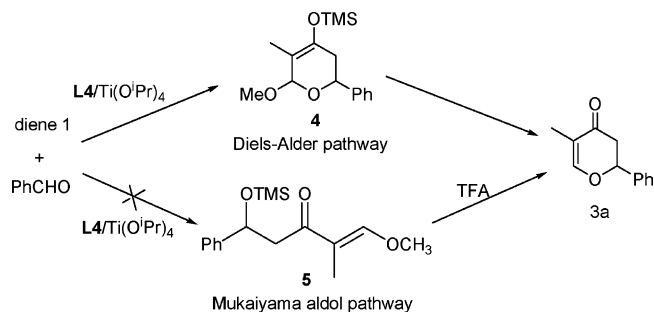


Figure 2. Relationship between ee values of **L4** and HDA product **3a**.

Mukaiyama aldol pathway and traditional Diels–Alder pathway were generally taken into account for Lewis acid catalyzed HDA reactions.^{2b,17h,24,25} A Mukaiyama aldol pathway was reported for the HDA reaction of diene **1** with benzaldehyde by the use of (*R*)-BINOL–**Ti**(*OiPr*)₄ catalyst.¹⁷ⁱ To survey the possible pathway of **L4**/**Ti**(*OiPr*)₄ catalyst, the reaction between diene **1** and benzaldehyde was performed under optimized conditions. The reaction was quenched by the addition of saturated NaHCO₃ before treatment with TFA. Only one new product could be detected by TLC. The product was isolated using silica gel column. This isolated intermediate was confirmed as **3a** by NMR. The result was the same with that after treatment with TFA. The fact indicated that mechanism of the HDA reaction was proposed as a traditional Diels–Alder pathway (Scheme 1).

Scheme 1. Possible Pathways for the HDA Reaction between Diene **1** and Benzaldehyde



The alkyl hydroxyl of **L4** was methylated to give **L5** (Figure 3), and the catalytic activity of **L5** was also investigated. Experimental results showed that comparing with the HDA reaction between diene **1** and benzaldehyde catalyzed by **Ti/L4**, **Ti/L5** displayed poor catalytic activity. This result demonstrated that the alkyl hydroxyl of **L4** was essential for the catalytic activity toward HDA reaction. NMR study was performed for further insight into the

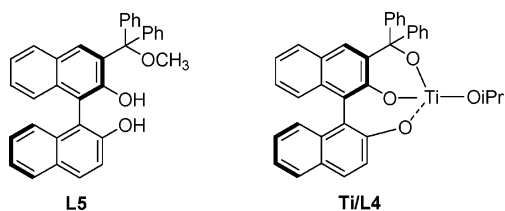


Figure 3. Chiral ligand **L5** and the complex of Ti/**L4**.

importance of alkyl hydroxyl of **L4** in the HDA reaction. The interaction between **L4** and $\text{Ti}(\text{OiPr})_4$ in CDCl_3 was monitored by ^{13}C NMR. As shown in Figure 4, the original singlet at $\delta = 82.92$ ppm (Figure 4A) for the carbon atom bearing the alkyl hydroxyl of **L4** shifted to 90.35 ppm (Figure 4B) after the addition of $\text{Ti}(\text{OiPr})_4$. The ^{13}C NMR data supported this hypothesis that Ti(IV) could coordinated to the hydroxyl on 3-substituent of **L4** (Figure 3).

In summary, we demonstrated that **L4** displayed high enantioselectivity in the asymmetric HDA reaction of diene **1** with both aromatic and aliphatic aldehydes. Comparing to the catalytic results by using Ti/**L1**–**L3** and **L5**, we could conclude that the 3-diphenylhydroxymethyl group appended to the BINOL ligand is critical for increase of catalytic activity, and the ^{13}C NMR provides evidence that this moiety binds to the Ti center to form a tridentate ligand. On the basis of the observed unusual nonlinear effect, it could be

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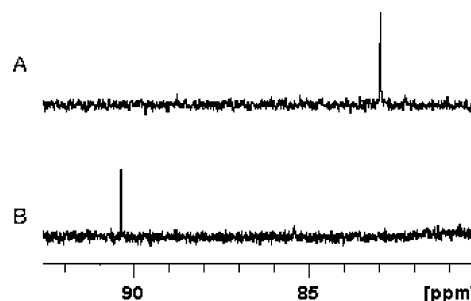


Figure 4. ^{13}C NMR spectrum of the carbon atom bearing the alkyl hydroxyl of **L4** (A) and **L4**/ $\text{Ti}(\text{OiPr})_4$ (B). See Supporting Information for detailed spectrum.

deduced that there might be a variety of aggregated catalyst species involved in the catalytic system. A traditional Diels–Alder pathway was also proposed by the analyses of reaction intermediate.

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Supporting Information Available: Experimental details and characterization data, including ^1H and ^{13}C NMR and HPLC. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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