Pergamon

Tetrahedron Letters 42 (2001) 6573–6575

TETRAHEDRON
LETTERS

Highly enantioselective addition of diethylzinc to aldehydes catalyzed by a new chiral C_2-symmetric Ti–diol complex

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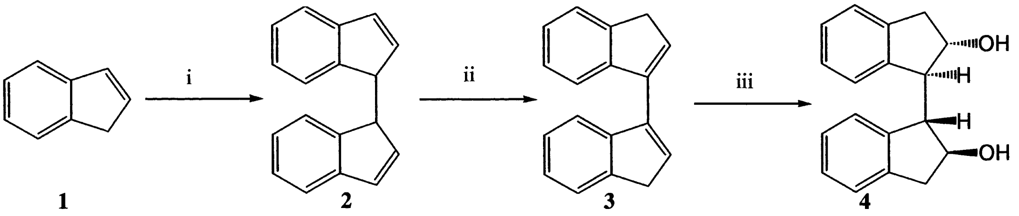
Received 9 April 2001; revised 9 July 2001; accepted 20 July 2001

Abstract—A novel C_2-symmetric chiral diol was synthesized and was found to catalyze the enantioselective addition of diethylzinc to aldehydes to afford optically active secondary alcohols with ee's up to 99%. © 2001 Elsevier Science Ltd. All rights reserved.

The catalytic enantioselective formation of C–C bonds is one of the most interesting and challenging areas of intense research. Enormous progress has been made in this area during the past decade.[1] Amongst the useful methods, the asymmetric addition of diethylzinc to aldehydes is demonstrated to be very convenient for the synthesis of optically active secondary alcohols and naturally occurring products.[2] A variety of chiral catalysts such as chiral β-amino alcohols,[3] β-aminothiols,[4] diamines,[5] Ti-complexes[6] and polymers tethered to chiral ligands[7] have been developed for this reaction with high enantioselectivity. However, the general applicability of these catalysts is still limited because most are good for only a certain type of aldehyde with only a few giving high enantioselectivity for a wide range of substrates.[8] Therefore, the search for new, well-designed catalysts is still an important pursuit.

On searching for a better catalyst based on the concept that a C_2-symmetry element often reduces the number of competing diastereomeric intermediates, we have synthesized (1*R*,1*R*′)-biindenyl-(2*S*,2*S*′) diol **4** (Scheme 1). The synthesis of our ligand was accomplished in high yield starting from commercially available 1-indene **1**. The coupling of **1** was achieved by using BuLi and dry $CuCl_2$ to give 1,1′-biindene **2** which rearranged in a solution of triethylamine (Et_3N) in pyridine to afford 3,3′-biindene **3** in 78% overall yield.[9] Asymmetric hydroboration of **3** using (+)-monoisopinocampheylborane [(+)-$IPCBH_2$][10] followed by oxidation with H_2O_2 gave the desired chiral diol **4** in 58% yield.[11] The key feature of the chiral diol is that it possesses two phenyl rings, which restrict its conformational flexibility. The four stereogenic carbon centers in the backbone dictate the orientation of the phenyl rings and the structure is



Scheme 1. *Reagents and conditions*: (i) (a) BuLi (1.4 equiv.), −30°C, (b) dry $CuCl_2$ (1 equiv.), −30°C, 50 min, 83% yield; (ii) triethylamine/pyridine (4 equiv.), rt, 5 min, 94% yield; (iii) (a) (+)-$IPCBH_2$ (2 equiv.), 0°C, 1 h, rt, 2 h, (b) 30% H_2O_2 (1.2 ml)/NaOH (1.2 ml, 3 M), rt, 30 min, 57% yield.

Keywords: C_2-symmetric diol; diethylzinc; asymmetric reaction.

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PII: S0040-4039(01)01335-1

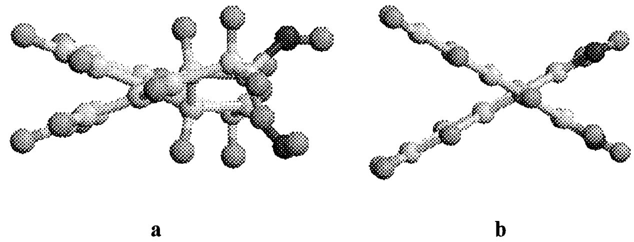
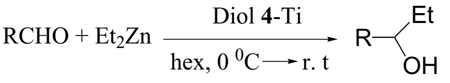


Figure 1. Computer-generated 3D structures of chiral diol **4** (**a**) and BINOL (**b**) (Alchemy 2000, Version 1).

similar to the axially dissymmetric BINOL according to molecular modeling (Fig. 1).

We first tested the effectiveness of this compound as a chiral ligand in the titanium complex-catalyzed enantioselective addition of diethylzinc to benzaldehyde. The result was very promising and the optically active 1-phenyl-1-propanol was obtained in 97% yield and 91% ee (Table 1, entry 1). This finding prompted us to evaluate the catalytic capability of the new catalyst with other aldehydes. The results showed that the chiral diol **4** was highly efficient (up to 99% ee) in this asymmetric reaction.

When compared with BINOL, we were pleased to observe that the diol **4** exhibits even higher enantioselective induction (entries 2, 3 and 7), especially for 3-chlorobenzaldehyde and 3-nitrobenzaldehyde where the ee values were much superior to BINOL.[6] 4-Methoxybenzaldehyde and 4-*N*,*N*′-dimethylbenzaldehyde gave only low ee's of 53 and 44%, respectively (entries 6 and 9). It was reported that electronic properties have a remarkable effect on the enantioselectivity of this reaction and substituents bearing electron-withdrawing groups in the *para*-position of the aryl aldehydes afford higher enantioselectivity than those with electron-donating groups.[12] The fact that the two aldehydes containing electron-donating groups (Hammett constants $p=-0.83$ for $-N(CH_3)_2$, $p=-0.27$ for –OMe) gave low enantioselectivity is consistent with the previous observations. Although the origin of the electronic influences on the enantioselectivity still remains unclear, it is quite clear that substituents bearing electron-withdrawing or electron-donating groups exhibit different reactivity and enantioselectivity. A further investigation of the chiral diol is underway in this laboratory.



Scheme 2.

Typical experimental procedure: To a solution of the diol (7 mg, 0.026 mmol) was added $Ti(O^iPr)_4$ (60 μl) under an argon atmosphere (Scheme 2). After stirring at room temperature for 0.5 h, a solution of Et_2Zn (0.38 ml of a 1 mmol/ml Et_2Zn solution in hexane, 0.38 mmol) was added. The resulting mixture was stirred for another 0.5 h and then cooled to 0°C. Benzaldehyde (15 μl, 0.13 mmol) was added and the solution was stirred until the color faded, indicating the completion of the reaction. HCl (5%, 3 ml) was added at 0°C to quench the reaction and the aqueous layer was extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give an oil, which was purified by column chromatography to afford the optically active secondary alcohol.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 29972016), The Hong Kong Polytechnic University ASD Fund, and the Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of the Ministry of Education of China for financial support.

Table 1. The enantioselective addition of diethylzinc to aldehydes catalyzed by Ti–diol complex **4**

Entry	Aldehyde[a]	Time, temp.	Yield (%)[b]	ee (%)[c,d]
1	Benzaldehyde	0°C, 3 h; rt, 7 h	97	91 (92)
2	3-Chlorobenzaldehyde	0°C, 3 h; rt, 12 h	88	99 (88)
3	4-Chlorobenzaldehyde	0°C, 3 h; rt, 7 h	91	97 (88)
4	2-Methoxybenzaldehyde	0°C, 3 h; rt, 8 h	94	94
5	3-Methoxybenzaldehyde	0°C, 3 h; rt, 12 h	91	96
6	4-Methoxybenzaldehyde	0°C, 3 h; rt, 7 h	95	53 (79)
7	3-Nitrobenzaldehyde	0°C, 3 h; rt, 48 h	81	99 (70)
8	2,4-Dimethoxybenzaldehyde	0°C, 3 h; rt, 24 h	93	82
9	4-*N*,*N*′-Dimethylbenzaldehyde	0°C, 3 h; rt, 24 h	91	44
10	3,4-Dimethoxybenzaldehyde	0°C, 3 h; rt, 15 h	96	95
11	Piperonal	0°C, 3 h; rt, 48 h	87	88
12	1-Bromo-2-naphthal	0°C, 3 h; rt, 8 h	99	74
13	(*E*)-Cinnamaldehyde	0°C, 3 h; rt, 7 h	98	86

[a] Aldehydes:Et_2Zn:diol = 1:3:0.2.

[b] Isolated yields.

[c] Determined using a Daicel chiracel OD column.

[d] Data in the brackets are from experiments using *S*-BINOL as chiral ligand in the same reaction (Ref. 6a).

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11. Synthesis of **3** was according to Ref. 9. The procedure for the asymmetric preparation of chiral diol **4** is as follows: Under an argon atmosphere at −20°C, 0.72 g (3.13 mmol) of **3** in 2 ml dry THF was slowly added dropwise to a solution of 10 mmol (+)-IpcBH$_2$ (0.63 mmol/ml, 6.3 mmol) in THF. The mixture was stirred under these conditions for 4 h, then warmed to room temperature and the stirring continued overnight. The reaction was then cooled to −20°C and 0.5 ml MeOH was added dropwise, and the mixture was returned to room temperature. Aqueous NaOH 1.2 ml (3 mmol/ml) and 1.2 ml 30% H_2O_2 were introduced successively to the flask and the mixture was stirred for another 2 h at 55°C to ensure complete reaction had occurred. The reaction mixture was cooled to room temperature. The usual work-up, followed by purification of the residue by column chromatography (petroleum ether:ethyl acetate, 1:2), afforded the product, which was then recrystallized repeatedly from hexane to give ligand **4** as needle-like crystals (0.47 g, 47% yield). The absolute configuration was assigned according to the known asymmetric hydroboration of trisubstituted olefins by (+)-IpcBH$_2$.[10] Chiral diol **4**: R_f = 0.41 (hexane:EtOAc, 1:2); mp 116°C; ^{1}H NMR (CDCl$_3$): δ 1.91 (m, 2H), 2.88 (dd, 2H, ABX system, J_{AB} = 16.2 Hz, J_{AX} = 5.4 Hz), 3.21 (dd, 2H, J_{BX} = 6.6 Hz), 3.62 (m, 2H), 4.54 (m, 2H), 6.66–7.27 (m, 8H); IR: 3355, 2919, 1460, 1065, 1026, 734 cm^{-1}. Anal. found for $C_{18}H_{18}O_2$: C, 80.87; H, 6.95; O, 12.18. Calcd: C, 81.17; H, 6.81; O, 12.02%.
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