Synthesis of new bifunctional BINOL derivatives

Yi-Li Zhang and Qing-Hua Fan*

Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, P. R. China

A series of new 3,3′-disubstituted BINOL derivatives have been synthesised. In a preliminary study, the asymmetric induction of these ligands was investigated in the addition of diethyl zinc to benzaldehyde in the absence of $Ti(O^{i}Pr)_4$. This showed different enantioselectivity and activity from those of the unsubstituted BINOL.

Keywords: BINOL, chiral ligand, synthesis, asymmetric

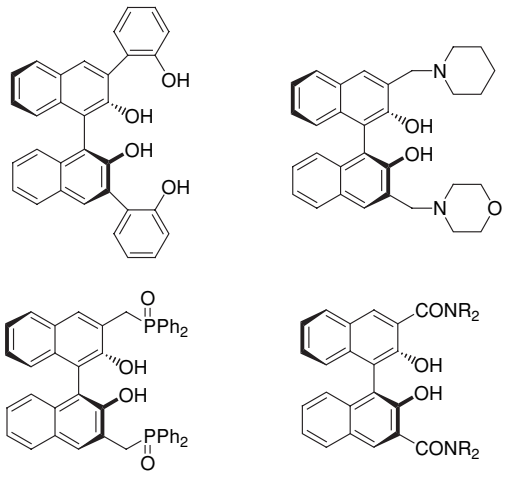
Homogeneous asymmetric catalysis is an important developments in modern chemistry.[1] Optically pure 1,1'-binaphthol (BINOL) and its derivatives are the most extensively studied chiral ligands. The C_2-symmetry and rigid structure of the naphthyl ring made BINOL a successful ligand across a wide area of asymmetric catalysis.[2] Substitution of BINOL may affect both the steric environment around the catalytically active centre and the electronic properties of the oxygen atoms. This can fine-tune the enantioselectivity and/or catalytic activity of the functionalised BINOL ligands. The 3,3'-postion are closer to the reactive centre than other positions on the backbone of BINOL, substituents here are expected to exert much more effect on the catalytic properties. Among the many reported examples of the 3,3'-disubstituted BINOL ligands, the bifunctional ones are more significant. Some representative examples are listed in Scheme 1.[3] As a result of the unique role of the diarylhydroxylmethyl group (the so-called "magic" group) as a structural unit in covalently bound chiral auxiliaries and in chiral ligands,[4] we report the synthesis of a new series of bifunctional BINOL derivatives (**1a**–**1e**, as shown in Scheme 2) bearing diarylhydroxylmethyl group located on the 3,3'-position of the binaphthyl backbone. Their application in the asymmetric addition of diethyl zinc to benzaldehyde in the absence of $Ti(O^{i}Pr)_4$ was also examined.

There are two methods for the preparation of chiral BINOL-type ligands:[2a] (a) through coupling reactions of substituted naphthol units; and (b) through regioselective modification of the binaphthol scaffold. Recently, Chan and co-workers reported the synthesis of **1a** via a catalytic asymmetric oxidative coupling of 2-naphthol. However, the much low enantioselectivity (<76% ee) prevents it being employed in asymmetric catalysis as a chiral ligand.[5] Therefore, we used the second method for the synthesis of **1a**–**1e** and the synthetic route is outlined in Scheme 3.

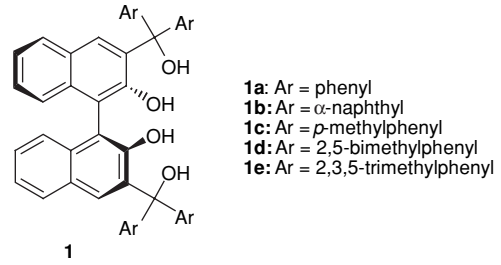
As shown in Scheme 3, the commercially available (S)-BINOL was used as starting material. First, the hydroxyl group of BINOL was protected with the methoxyl methyl (MOM) group.[6] The resulting protected (*S*)-**3** was then lithiated with *n*-BuLi followed by carboxylation with CO_2 to give (*S*)-**4**.[7] The obtained diacid **4** was further esterified with CH_3I to give the key intermediate diester (*S*)-**5**. Finally, the resulting diester was refluxed with the aryl Grignard reagents (10 equiv) in THF to afford the bifunctional BINOL ligands (**1a**–**1e**) in moderate to high yields. The Grignard reagents also acted as deprotecting reagent. These ligands were further purified by flash column chromatography and were characterised by ^1H NMR and HRMS. All results are consistent with the compounds synthesised.

With these BINOL-type ligands in hand, we tested their catalytic efficiency by choosing the asymmetric addition of diethylzinc to benzaldehyde as the model reaction. Chiral diols such as BINOL[2] and TADDOL[8] as catalysts were found to be highly effective in this kind of reaction. However, in most diol cases $Ti(O^{i}Pr)_4$ has been used to form titanate catalysts to obtain high yields and ees.[9,10] Without the use of Ti(iv)-coordination the diols themselves often show lower catalytic activity and selectivity due to the aggregation of the zinc complexes.[11] Unlike unsubstituted BINOL, the bifunctional BINOL ligands (**1a**–**1e**) have two steric bulk substituents as well as two coordinating hydroxyl groups at the 3,3'-position of the binaphthyl backbone. As expected, these ligands showed very different catalytic properties from that of BINOL in the asymmetric addition of diethylzinc to benzaldehyde. The preliminary results were listed in Table 1. All ligands gave higher yield and enantioselectivity than BINOL. A high ee (up to 74%) was obtained with ligand **1b**. This is much higher than that of BINOL (5% ee). Most interestingly, the aryl groups in the substituents affected not only the enantioselectivity but also the configuration of the product. Ligands **1a** and **1b** gave the product with opposite configuration as compared with ligands **1c** to **1e** as well as BINOL.

In conclusion, a new series of 3,3'-disubstituted BINOL ligands have been synthesised and applied to the asymmetric addition of diethyl zinc to benzaldehyde. These ligands showed very different catalytic activity and enantioselectivity

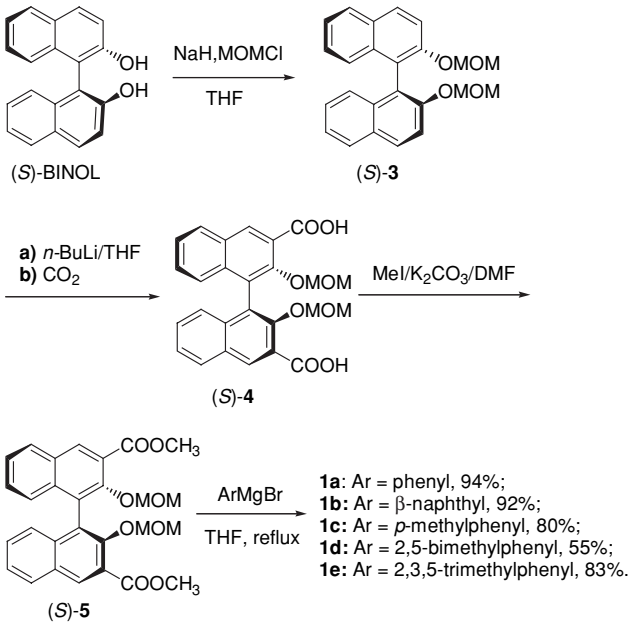


Scheme 1



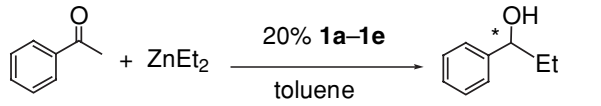
Scheme 2

* Correspondent. E-mail: fanqh@iccas.ac.cn



Scheme 3

Table 1 Asymmetric addition of diethylzinc to benzaldehyde catalysed by bifunctional BINOL ligands in the absence of $Ti(O^{i}Pr)_4$[a]



Entry	Ligand	Ee/%[b]	Yield/%[b]	Config.
1	**1a**	19	48	*R*
2	**1b**	74	99	*R*
3	**1c**	24	50	*S*
4	**1d**	32	94	*S*
5	**1e**	12	93	*S*
6[c]	BINOL	5	19	*S*

[a]Reactions were carried out in toluene under the reaction conditions: **1** : benzaldehyde : $ZnEt_2$ = 0.2 : 1 : 3 (molar ratio), 1 ml toluene, 0 °C, 12 h. [b]Determined by chiral GC analysis. [c]Data obtained from Ref. 12.

to that of unsubstituted BINOL. Further work on applications of these new ligands in other asymmetric reactions is being carried out in our laboratory.

Experimental

General experimental details:

Unless otherwise noted, all experiments were carried out under an inert atmosphere of dry nitrogen by using standard Schlenk-type techniques. ^{1}H NMR spectra were recorded on a Bruker Model Avance DMX 300 Spectrometer (^{1}H 300 MHz). Chemical shift (δ) are given in ppm and are referenced to residual solvent peaks. ESI mass spectra were obtained on a BIFLEX instrument. High-resolution mass spectra were recorded on a GCT or an APEX_spectrometer. Optical rotations were measured on an AA-10R automatic polarimeter in the solvent indicated. Melting points were uncorrected. All enantiomeric excess values were obtained from GC analysis with a Chrompack 7502 chiral column. All solvents were dried using standard, published methods and were distilled under a nitrogen atmosphere before use. All other chemicals were used as received from Aldrich or Acros without further purification.

General procedure for the synthesis of **1** (**1a**–**1e**):

A solution of (*S*)-**4** (1 equiv) in THF was added to the freshly prepared ArMgBr (10 equiv) in THF at 0 °C. The reaction mixtures were allowed to warm to rt and then refluxed for 4 h. The reaction was quenched by dropwise addition of saturated NH_4Cl solution. After removal of most of the organic solvent, the residue was partitioned between H_2O and ethyl acetate. Organic layer was collected, washed by brine, dried over anhydrous Na_2SO_4, and concentrated to give crude product as yellow syrup. It was further purified by column chromatography (silica gel, petroleum/ ethyl acetate = 10/1, v/v).

4a: Light yellow powder (94% yield). M.p. 176–179 °C; $[\alpha]_D^{20}$ = –113° (*c* 1.05, THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (s, 2H, OH), 6.48 (s, 2H, OH), 7.00–7.55 (m, 30H, Ar–*H*); ESI-MS *m/z*: found 649.4 $[M\text{-}H]^-$; calcd for $C_{46}H_{34}O_4$ 650.2457 [M].

4b: Light yellow powder (92% yield). M.p. 195–197 °C (decomposition); $[\alpha]_D^{20}$ = –121° (*c* 1.11, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31–5.53 (m, 2H, OH), 7.18–8.68 (m, 38H, Ar–*H*); ESI-MS *m/z*: found 849.4 $[M\text{-}1]^-$; HRMS (FT-ICRMS) *m/z*: found 833.3047 $[M\text{-}17]^+$; calcd for $C_{62}H_{42}O_4$ 850.3083 [M].

4c: Light yellow powder (80% yield). M.p. 196–200 °C (decomposition); $[\alpha]_D^{20}$ = –101° (*c* 1.09, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H, CH_3), 2.30 (s, 6H, CH_3), 4.51 (s, 2H, OH), 6.63 (s, 2H, OH), 6.99–8.27 (m, 26H, Ar–*H*); ESI-MS *m/z*: found 705.4 $[M\text{-}1]^-$; HRMS (FT-ICRMS) *m/z*: found 689.3040 $[M\text{-}17]^+$; calcd for $C_{50}H_{42}O_4$ 706.3083 [M].

4d: Light yellow powder (55% yield). M.p. 211–213 °C (decomposition). $[\alpha]_D^{20}$ = –103.5° (*c* 1.70, THF). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05–2.34 (m, 24H, CH_3), 4.38–4.60 (m, 2H, OH), 6.66–7.58 (m, 22H, Ar–*H*). ESI-MS *m/z*: found 761.4 $[M\text{-}1]^{-1}$; HRMS (FT-ICRMS) *m/z*: found 745.3669 $[M\text{-}17]^+$; calcd for $C_{54}H_{50}O_4$ 762.3709 [M].

4e: Light yellow powder (83% yield). M.p. 239–240 °C. $[\alpha]_D^{20}$ = –85.7° (*c* 1.75, THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05–2.29 (m, 36H, CH_3), 4.34–4.57 (m, 2H, OH), 6.60–7.65 (m, 18H, Ar–*H*). (ESI–MS) *m/z*: found 817.5 $[M\text{-}1]^{-1}$; HRMS (FT-ICRMS) *m/z*: found 801.4296 $[M\text{-}17]^+$; calcd for $C_{58}H_{58}O_4$ 818.4335 [M].

We are grateful to the National Natural Science Foundation of China and Chinese Academy of Sciences.

Received 23 June 2005; accepted 25 July 2005
Paper 05/3325

References

1 (a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis,* Wiley: New York, 1994; (b) I. Ojima, *Catalytic Asymmetric Synthesis,* 2nd edn.; Wiley: New York, 2000; (c) G.Q. Lin, Y.M. Li, A.S.C. Chan, *Principles and Applications of Asymmetric Synthesis,* Wiley: New York, 2001.
2 (a) Y. Chen, S. Yekta, A.K. Yudin, *Chem. Rev.*, 2003**, 103**, 3155; (b) L. Pu, *Chem. Rev.*, 1998, **98**, 2405; (c) J.M. Brunel, *Chem. Rev.*, 2005, **105** , 857.
3 (a) H. Kitajima, K. Ito, Y. Aoki, T. Katsuki, *Bull. Chem. Soc. Jpn* 1997, **70**, 207; (b) K. Ishihara, H. Kurihara, M. Matsumoto, H. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 6920; (c) Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.*, 1999, **121**, 2641; (d) Y.C. Qin, L. Liu, L. Pu, *Org. Lett.*, 2005, **7**, 2381.
4 M. Braun, *Angew. Chem. Int. Ed. Engl.*, 1996, **35**, 519.
5 (a) S.W. Hon, C.H. Li, J.H. Kuo, N.B. Barhate, Y.H. Liu, Y. Wang, C.T. Chen, *Org. Lett.*, 2001, **3**, 869; (b) N.B. Barhate, C.T. Chen, *Org. Lett.*, 2002, **3**, 2529.
6 G.H. Liu, W.J. Tang, Q.H. Fan, *Tetrahedron*, 2003, **59**, 8603.
7 G.H. Liu, Q.H. Fan, X.Q. Yang, X.M. Chen, *ARKIVOC*, 2003, (ii), 123.
8 D. Seebach, A.K. Beck, A. Heckel, *Angew. Chem. Int. Ed.*, 2001, **40**, 92.
9 F.Y. Zhang, C.W. Yip, R. Cao, A.S.C. Chan, *Tetrahedron: Asymmetry*, 1997, **8**, 585.
10 J. Balsells, T.J. Davis, P. Carroll, P.J. Walsh, *J. Am. Chem. Soc.*, 2002, **124**, 10336.
11 W.S. Huang, Q.S. Hu, L. Pu, *J. Org. Chem.*, 1999**, 64**, 7940.
12 Q.H. Fan, G.H. Liu, X.M. Chen, G.J. Deng, A.S.C. Chan, *Tetrahedron: Asymmetry*, 2001, **12**, 1559.