J. Chem. Sci. (2019) 131:64
https://doi.org/10.1007/s12039-019-1635-4

REGULAR ARTICLE

Catalytic asymmetric oxidation of sulfides to sulfoxides using (*R*)-6,6′-Diphenyl-BINOL as a chiral ligand

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MS received 8 February 2019; revised 26 April 2019; accepted 3 May 2019

Abstract. The chiral metal complex produced *in situ* from (*R*)-6,6′-Diphenyl-BINOL and Ti(O−*i*–Pr)$_4$ as a catalytic system for asymmetric sulfoxidation of aryl methyl and aryl benzyl sulfides in the presence of 70% aqueous TBHP as the oxidant has been investigated. The influence of variation of reagents mole ratios, temperature, solvent and oxidant was examined, and the optimized conditions were then used to oxidize a number of aryl methyl and aryl benzyl sulfides, producing sulfoxides in high enantiopurities (up to 90% ee) and good yields (up to 81%).

Keywords. (*R*)-6,6′-Diphenyl-BINOL; enantiopure sulfoxides; chiral ligand.

1. Introduction

Enantiopure sulfoxides have been widely used as chiral auxiliaries in a broad range of synthetic reactions like carbon-carbon[1,2] and carbon-oxygen[3] bond-forming reactions, cycloaddition reactions,[4–6] radical addition reactions[7,8] and in asymmetric catalysis.[9] Enantiopure sulfoxides have also found use in the pharmaceutical industry due to their important biological activity, for example, gastric acid proton pump inhibitor like Esomeprazole.[10] Other biologically active compounds containing the sulfinyl moiety include modafinil and sulindac, which have been used to treat narcolepsy and inflammation respectively.[11,12]

The most attractive method for the preparation of enantiopure sulfoxides is catalytic asymmetric sulfide oxidation.[13] The first synthetically useful systems for asymmetric oxidation of sulfides were reported in 1984 by Kagan[14,15] and Modena.[16] Both of these methods are based on the Sharpless asymmetric epoxidation.[17,18] These asymmetric sulfide oxidation methods represented the first practical and efficient methods for the catalytic asymmetric oxidation of sulfides.

1,1′-binaphthyl-2,2′-diol (BINOL) and related C_2-symmetric ligands possessing axial chirality have found a wide utility in asymmetric catalysis.[19] Since 1990, the enantiomeric atropoisomers of BINOL are widely used ligands for both stoichiometric and catalytic asymmetric reactions.[20] The introduction of substituents at 6,6′-positions of BINOL have a profound effect on the activity and enantioselectivity, as both electronic and steric properties[21–24] of the catalyst are influenced. *(S)*–6,6'-Diphenyl-BINOL was efficiently used as a chiral ligand in the lanthanoid- catalyzed epoxidation of chalcone.[25] These successful catalytic activities of 6,6'-Diphenyl-BINOL prompted us to investigate its activity as a chiral ligand in asymmetric oxidation of sulfides.

2. Experimental

2.1 *Materials and physical measurements*

(R)-BINOL, all the sulfides and all other reagents were procured from Sigma Aldrich, and used directly without additional treatment. Commercial grade solvents were used for

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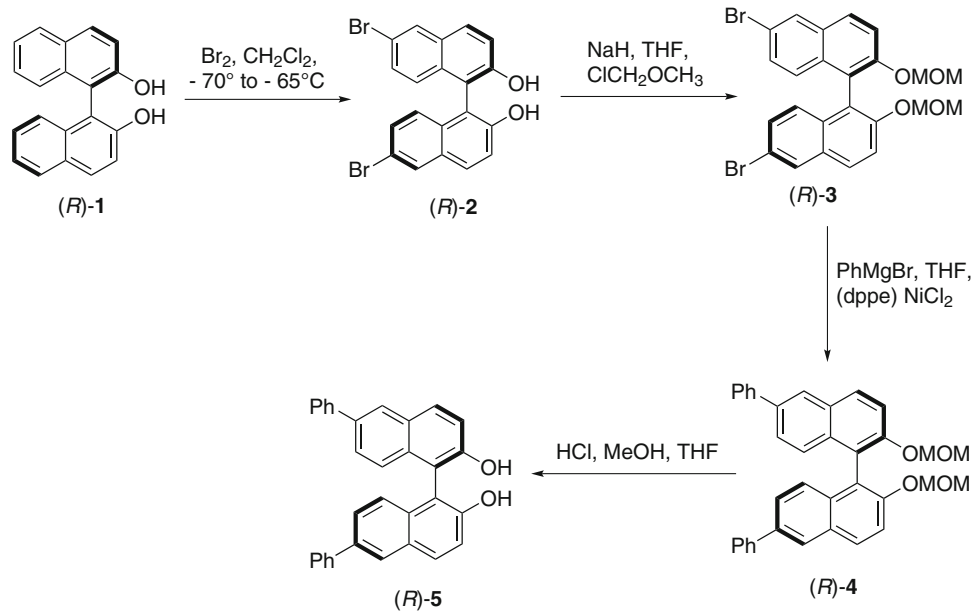
Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12039-019-1635-4) contains supplementary material, which is available to authorized users.

Published online: 19 July 2019

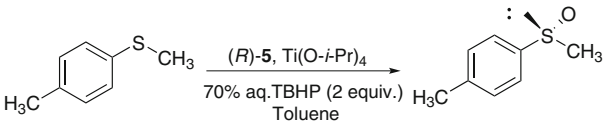


Scheme 1. Synthesis of (*R*)-6,6′-Diphenyl-BINOL.

reaction and purification. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were obtained as solutions in deuterium substituted reagent on Bruker 500 MHz AVANCE III HD, Software-Topspin 3.5. Chemical shifts are reported in parts per million (ppm, δ). Melting points were recorded on Buchi M-560 melting point apparatus. Specific optical rotations were measured on Rudolph Research Analytical, Autopol V plus instrument. The elemental analyses were performed on a Yanaco CHN FOER MT-3 element analyzer. The ee values of the purified products were determined by HPLC on a chiral stationary phase using Chiralcel OB-H, OD-H columns with n-hexane/*i*-PrOH mixture as an eluent. Absolute configurations were assigned by comparison of the sign of the specific optical rotations with literature data.

2.2 *Typical procedure for the catalytic oxidation of sulfides*

To a solution of (*R*)-6,6′-Diphenyl-BINOL (0.31 g, 0.70 mmol) in toluene (10 mL) were added Ti(O-*i*-Pr)$_4$ (0.1 mL, 0.35 mmol), water (0.13 mL, 7 mmol) and stirred for 60 min at room temperature. To the resulting homogeneous solution was added methyl *p*-tolyl sulfide (2.0 g, 14.0 mmol), and the mixture was stirred at room temperature for 60 min. The solution was then cooled to 0–5 °C, 70% aqueous TBHP solution (4.1 mL, 28 mmol) was added slowly. The mixture was stirred at 0–5 °C for another 60 min and at room temperature for another 19 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to obtain the crude product. This was further purified by column chromatography (ethyl acetate, cyclohexane 1:1) to get 1.8 g (81% yield) of (*R*)-methyl-*p*-tolyl sulfoxide (**1a**). $[\alpha]_D^{20} = +129°$ (c = 2 in acetone); lit: $[\alpha]_D = +132$ (c = 2.0 in acetone) for (*R*), 91% *ee*;[141] ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.67 (s, 3H), 7.30 (d, J = 7.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 43.9, 123.5, 123.5, 130.0, 130.0, 141.5, 142.3; HPLC: t_R (*R*) = 14.2 min (major isomer), t_R (*S*) = 9.1 min (minor isomer) (Chiralcel OB-H column, n-Hexane/*i*-PrOH = 50 : 50, flow rate = 0.8 mL/min, wavelength = 254 nm).



Scheme 2. Asymmetric oxidation of methyl *p*-tolyl sulfide.

3. Results and Discussion

3.1 *Synthesis of (R)–6,6′–Diphenyl–BINOL*

(*R*)-6,6′-Diphenyl-BINOL was synthesized as shown in Scheme 1 by following the sequence of reactions reported in the literature.[25]

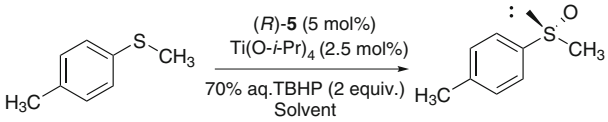
In the first step (*R*)-BINOL was reacted with Br_2 at −70° to −65 °C in dichloromethane to get (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol (*R*)**-2**, which was treated, without further purification, with chloromethyl methyl ether in the presence of sodium hydride in THF at room temperature to obtain (*R*)-bis(methoxymethyl) ether (*R*)**-3**. Treatment of (*R*)**-3** with phenyl magnesium bromide in the presence of a catalytic amount of (dppe) $NiCl_2$ in THF furnished the corresponding (*R*)-6,6′-diphenyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (*R*)**-4**. Demethoxymethylation of (*R*)**-4** afforded the desired (*R*)-6,6′-diphenyl-1,1′-bi-2-naphthol (R)**-5**.

Table 1. Asymmetric oxidation of methyl *p*-tolyl sulfide with different mole ratios of (*R*)-**5** and Ti(O-*i*-Pr)$_4$ under reaction conditions[a].

Entry	(*R*)-**5**-Ti(O-*i*-Pr)$_4$ (mol/mol)	(*R*)-**5** (mol%)	Time[b]	Yield[c] (%)	e.e.[d] (%)(config.)[e]
1	1:0.5	5	19 h	81	90 (*R*)
2	1:0.5	10	18 h	81	80 (*R*)
3	1:0.5	20	19 h	80	82 (*R*)
4	1:1	5	17 h	82	72 (*R*)
5[f]	1:0.5	5	19 h	79	62 (*R*)
6[g]	1:0.5	5	18 h	75	75 (*R*)

[a]Reaction conditions: Methyl *p*-tolyl sulfide (1 mmol), (*R*)-6,6′-Diphenyl-BINOL (5 mol%) except for entries 2 and 3, Ti(O-*i*-Pr)$_4$ (2.5 mol%) except for entries 2, 3 and 4, 70% aq. TBHP (2 equiv), water (0.5 equiv), toluene at room temperature except for entry 5 & 6. [b]Monitored using TLC until all the sulfide was found consumed. [c]Isolated yield after column chromatography of the crude product. [d]Determined by HPLC analysis on a Chiralcel OB-H column. [e]Absolute configuration was determined by the comparison of the sign of the specific rotation with that of reported in the literature.[14] [f]Reaction was performed at 0–5 °C. [g]Reaction was performed at 50–55 °C.

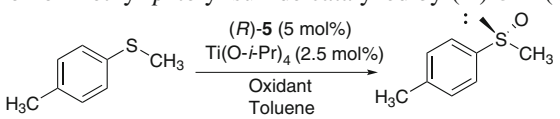
Table 2. Asymmetric oxidation of methyl *p*-tolyl sulfide catalyzed by (*R*)-**5**-Ti(O-*i*-Pr)$_4$ in different solvents[a].



Entry	Solvent	Time[b]	Yield[c] (%)	e.e.[d] (%)(config.)[e]
1.	Toluene	19 h	81	90 (*R*)
2.	CCl_4	17 h	80	83 (*R*)
3.	$CHCl_3$	18 h	75	79 (*R*)
4.	CH_2Cl_2	18 h	63	59 (*R*)
5.	Ethyl acetate	20 h	67	55 (*R*)
6.	Acetonitrile	19 h	65	61 (*R*)

[a]Reaction conditions: Methyl *p*-tolyl sulfide (1 mmol), (*R*)-6,6′-Diphenyl-BINOL (5 mol%), Ti(O-*i*-Pr)$_4$ (2.5 mol%), 70% aq. TBHP (2 equiv), water (0.5 equiv), solvent and room temperature. [b]Monitored using TLC until all the sulfide was found to be consumed. [c]Isolated yield after column chromatography of the crude product. [d]Determined by HPLC analysis on a Chiralcel OB-H column. [e]Absolute configuration was determined by comparison of the sign of the specific rotation with that reported in the literature.[14]

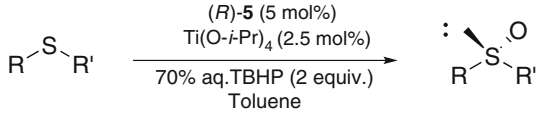
Table 3. Asymmetric oxidation of methyl *p*-tolyl sulfide catalyzed by (*R*)-**5**-Ti(O-*i*-Pr)$_4$ using different oxidants[a].



Entry	Oxidant	Time[b]	Yield[c] (%)	e.e.[d] (%)(config.)[e]
1.	70% aq. TBHP (2 eq.)	19 h	81	90 (*R*)
2.	70% aq. TBHP (4 eq.)	15 h	65	77 (*R*)
3.	70% aq. TBHP (3 eq.)	15 h	80	82 (*R*)
4.	CHP	20 h	60	0
5.	30% aq. H_2O_2	18 h	65	54 (*R*)

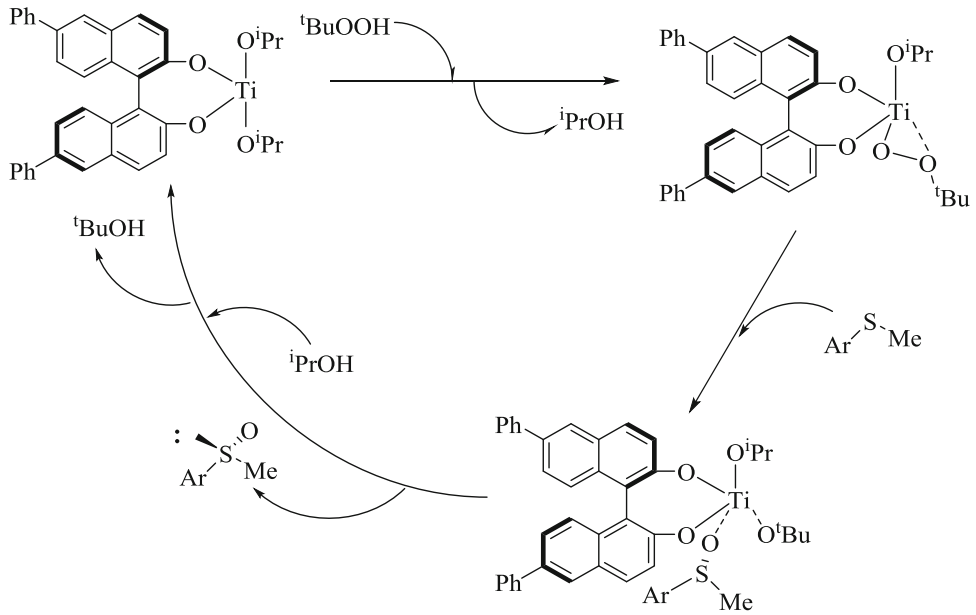
[a]Reaction conditions: Methyl *p*-tolyl sulfide (1 mmol), (*R*)-6,6′-Diphenyl-BINOL (5 mol%), Ti(O-*i*-Pr)$_4$ (2.5 mol%), Oxidant, water (0.5 equiv), toluene at room temperature. [b]Monitored using TLC until all the sulfide was found consumed. [c]Isolated yield after column chromatography of the crude product. [d]Determined by HPLC analysis on a Chiralcel OB-H column. [e]Absolute configuration was determined by the comparison of the sign of the specific rotation with that reported in the literature.[14]

Table 4. Asymmetric oxidation of sulfides with (*R*)-**5**-Ti(O-*i*-Pr)$_4$ under reaction conditions[a]



Entry	R	*R′*	Time[b]	Yield[c] (%)	e.e.[d] (%)(config.)[e]
1.	*p*-Tolyl	Methyl	19 h	81	90 (*R*)
2.	Phenyl	Methyl	18 h	77	84 (*R*)
3.	4-Methoxy phenyl	Methyl	20 h	79	87 (*R*)
4.	4-Bromo phenyl	Methyl	17 h	72	77 (*R*)
5.	4-Nitro phenyl	Methyl	19 h	65	70 (*R*)
6.	Phenyl	Benzyl	19 h	76	82 (*R*)

[a]Reaction conditions: Sulfide (1 mmol), (*R*)-6,6′-Diphenyl-BINOL, Ti(O-*i*-Pr)$_4$ (2.5 mol%), 70% aq. TBHP (2 equiv), water (0.5 equiv), toluene and room temperature. [b]Monitored using TLC until all sulfide was found to be consumed. [c]Isolated yield after column chromatography of the crude reaction mixture. [d]For entries 1 to 5, determined by HPLC analysis on Chiralcel OB-H column, for entry 6 by using Chiralcel OD-H column. [e]Absolute configuration was determined by the comparison of the sign of the specific rotation with that reported in the literature.[14,26]



Scheme 3. Possible pathway of the reaction.

We have explored the catalytic activity of (*R*)-6,6′-Diphenyl-BINOL in combination with Ti(O-*i*-Pr)$_4$ for the asymmetric oxidation of sulfides. In the preliminary phase of optimization, methyl *p*-tolyl sulfide was chosen as a standard substrate (Scheme 2). Initial experiments (Table 1) were performed with different mole ratios of (*R*)-6,6′-Diphenyl-BINOL and Ti(O-*i*-Pr)$_4$. Mole ratios of (*R*)-6,6′-Diphenyl-BINOL were varied from 5 to 20 mol% and mole ratios of Ti(O-*i*-Pr)$_4$ were varied from 2.5 to 10 mol%. It was observed that with an increase in mole ratios of (*R*)-6,6′-Diphenyl-BINOL and Ti(O-*i*-Pr)$_4$, there was no increase in the ee values.

To study the effect of solvents on the oxidation of methyl *p*-tolyl sulfide, the reaction was carried out in different solvents like toluene, CCl_4, $CHCl_3$, CH_2Cl_2, ethyl acetate and acetonitrile following the same protocol (Table 2). In the case of acetonitrile, ethyl acetate and CH_2Cl_2 low yields and low ee were observed. Among toluene, CCl_4 and $CHCl_3$, with toluene high ee and good yield were observed. Hence, based on the results, toluene was found to be the most efficient reaction medium.

To examine the effect of oxidant on the oxidation of methyl *p*-tolyl sulfide, experiments were performed with different oxidants. Experiments were carried out with CHP, 70% aqueous TBHP and 30% aqueous H_2O_2 as oxidizing agents (Table 3). When CHP was used as the oxidant, the reaction proceeded very slowly and

gave the racemic sulfoxide. When 30% of aqueous H_2O_2 was used as the oxidant, the reaction went to completion, but produced low yields of the product with low ees. When 70% aqueous TBHP was used as the oxidant, the reaction proceeded to completion, and good yields and ees of the products were obtained. To optimize the mole ratios of 70% aqueous TBHP, experiments were performed using 2 to 4-mole equivalents of 70% aqueous TBHP. When 4-mole equivalents of 70% aqueous TBHP were used, more sulfone formation was observed with low conversion. With 2 and 3 mole equivalents of 70% aq. TBHP, similar yields and ees were observed.

On the ground of the optimization studies, 2.5 mol% Ti(O-*i*-Pr)$_4$ and 5 mol% (*R*)-6,6′-Diphenyl-BINOL with 2 equiv. 70% aq. TBHP, 0.5 equiv. water in toluene at room temperature were the best reaction conditions for the asymmetric oxidation of prochiral methyl *p*-tolyl sulfide to (*R*)-methyl *p*-tolyl sulfoxide.

In order to evaluate the scope and efficiency of optimized reaction conditions in the enantioselective oxidation of aromatic sulfides, oxidations of different sulfides ware studied under the optimized reaction conditions. The results are summarized in Table 4.

As shown in Table 4, high enantioselectivity is observed for the oxidation of the prochiral sulfides with electron-donating groups (CH_3, OCH_3, etc.) in the *para* position compared to electron-withdrawing groups (Br, NO_2, etc.) in the *para* position. Electron-withdrawing groups slightly affected the efficiency of the transformation, decreasing the enantioselectivity. The oxidation of phenyl benzyl sulfide (entry No. 6) proceeded with good enantioselectivity and yield.

The possible pathway (Scheme 3) of the reaction involves the coordination of (*R*)-6,6′-Diphenyl-BINOL to Ti(O-*i*-Pr)$_4$, thereby controling the orientation of the hydroperoxides to form an appropriate asymmetric environment for sulfoxidation.

4. Conclusions

In conclusion, the chiral metal complex derived from (*R*)-6,6′-Diphenyl-BINOL and Ti(O-*i*-Pr)$_4$ was successfully applied in the catalytic asymmetric oxidation of various prochiral sulfides. Under the optimized conditions, up to 90% ee was obtained for methyl *p*-tolyl sulfoxide with (*R*)-6,6′-Diphenyl-BINOL-Ti(O-*i*-Pr)$_4$ catalytic system at room temperature. An important feature of this catalytic system is that the chiral ligand can be recovered after column chromatography and can be recrystallized and reused.

Supplementary Information (SI)

Full experimental details, ^{1}H and ^{13}C NMR spectra for all the intermediates [(*R*)-**2** to (*R*)-**5**] & sulfoxides (**1a–1f**) are available at www.ias.ac.in/chemsci.

Acknowledgements

The authors are thankful to the M/S Lupin Limited and the authorities of Manipal Academy of Higher Education for the research program. We also acknowledge the valuable guidance, support and suggestions from Dr. P. R. Upadhyay, Dr. Milind Sindkhedkar and Dr. Vijaya Desai.

References

1. Solladie G 1983 In *Asymmetric Synthesis* Vol. 2 James D Morrison (Ed.) (Florida: Academic Press) p. 157
2. Sklute G, Amsallem D, Shabli A, Varghese J P and Marek I 2003 Four-component reactions for a new diastereoselective synthesis of chiral quaternary centers *J. Am. Chem. Soc.* **125** 11776
3. Carreno M C, Garcia R J L, Martin A M, Pedregal C, Rodriguez J H, Rubio A, Sanchez J and Solladie G 1990 Stereoselective reductions of 2-keto sulfoxides with hydrides *J. Org. Chem.* **55** 2120
4. Ruano J L G and De la P B C 1999 Asymmetric [4+2] cycloadditions mediated by sulfoxides *Top. Curr. Chem.* **204** 1
5. Lee A W M and Chan W H 1997 Chiral acetylenic sulfoxides and related compounds in organic synthesis *Top. Curr. Chem.* **190** 103
6. Arai Y and Koizumi T 1993 Chiral sulfinylethenes as efficient dienophiles for asymmetric diels-alder reactions *Sulfur Rep.* **15** 41
7. Renaud P and Gerster M 1998 Use of lewis acids in free radical reactions *Angew. Chem. Int. Ed.* **37** 2562
8. Toru T, Watanabe Y, Mase N, Tsusaka M, Hayakawa T and Ueno Y 1996 Diastereofacial control in the radical addition to chiral α-sulfinyl enones *Pure Appl. Chem.* **68** 711
9. Fernandez I, Valdivia V, Leal M P and Khiar N 2007 C_2-symmetric bissulfoxides as organocatalysts in the allylation of benzoyl hydrazones: spacer and concentration effects *Org. Lett.* **9** 2215
10. Cotton H, Elebring T, Larsson M, Li L, Sorensen H and von Unge S 2000 Asymmetric synthesis of esomeprazole *Tetrahedron: Asymm.* **11** 3819
11. Wojaczynska E and Wojaczynski J 2010 Enantioselective synthesis of sulfoxides: 2000–2009 *Chem. Rev.* **110** 4303
12. Bryliakov K P and Talsi E P 2008 Transition metal catalyzed asymmetric oxidation of sulfides *Curr. Org. Chem.* **12** 386
13. Plitt P, Pritzkow H, Oeser T and Kraemer R 2005 Biphenyl derived oxovanadium (IV) and copper (II) salen-type complexes—structure and redox tuning *J. Inorg. Biochem.* **99** 1230
14. Pitchen P, Dunach E, Deshmukh M N and Kagan H B 1984 An efficient asymmetric oxidation of sulfides to sulfoxides *J. Am. Chem. Soc.* **106** 8188

15. Pitchen P and Kagan H B 1984 An efficient asymmetric oxidation of sulfides to sulfoxides *Tetrahedron Lett.* **25** 1049
16. Furia F, Modena G and Seraglia R 1984 Synthesis of chiral sulfoxides by metal-catalyzed oxidation with *t*-Butyl hydroperoxide *Synthesis* 325
17. Sharpless K B and Katsuki T 1980 The first practical method for asymmetric epoxidation *J. Am. Chem. Soc.* **102** 5974
18. Rossiter B E, Katsuki T and Sharpless K B 1981 Asymmetric epoxidation provides shortest routes to four chiral epoxy alcohols which are key intermediates in syntheses of methymycin, erythromycin, leukotriene C-1, and disparlure *J. Am. Chem. Soc.* **103** 464
19. Brunel J M 2005 BINOL: a versatile chiral reagent *Chem. Rev.* **105** 857
20. Chen Y, Yekta S and Yudin A K 2003 Modified BINOL ligands in asymmetric catalysis *Chem. Rev.* **103** 3155
21. Sasai H, Tokunaga T, Watanabe S, Suzuki T, Itoh N and Shibasaki M 1995 Efficient diastereoselective and enantioselective nitroaldol reactions from prochiral starting materials: utilization of La-Li-6,6'-disubstituted BINOL complexes as asymmetric catalysts *J. Org. Chem.* **60** 7388
22. Terada M, Motoyama Y and Mikami K 1994 Diastereoselective and enantioselective glyoxylate-ene reaction catalyzed by new class of binaphthol-derived titanium complex *Tetrahedron Lett.* **36** 6693
23. Qian C T, Huang T S, Zhu C J and Sun J 1998 Synthesis of 3,3′-, 6,6′- and 3,3′,6,6′-substituted binaphthols and their application in the asymmetric hydrophosphonylation of aldehydes—an obvious effect of substituents of BINOL on the enantioselectivity *J. Chem. Soc., Perkin Trans. **1*** 2097
24. Qian C T, Zhu C J and Huang T S 1998 Enantioselective trimethylsilylcyanation of aldehydes catalyzed by chiral lanthanoid alkoxides *J. Chem. Soc., Perkin Trans. **1*** 2131
25. Chen R, Qian C and Vries J G 2001 Asymmetric epoxidation of α, β-unsaturated ketones catalyzed by chiral ytterbium complexes *Tetrahedron Lett.* **42** 6919
26. G E O'Mahony, A Ford and A R Maguire 2012 Copper-catalyzed asymmetric oxidation of sulfides *J. Org. Chem.* **77** 3288