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Catalytic Asymmetric Oxidation of Alkyl Aryl Sulfides Mediated by a Series of Chiral *N*-Alkyl-1,2-diphenylaminoethanol/ Titanium/Water Complexes

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ABSTRACT

A series of chiral *N*-alkyl-1,2-diphenylaminoethanol/titanium/water complexes were investigated as potential efficient catalyst for the enantioselective oxidation of alkyl aryl sulfides. The structure of the aminoethanols strongly influenced on the reactivity and enantioselectivity. Using (1*S*,2*S*)-*N*-methyl-1,2-diphenylaminoethanol (**6**) as ligand in oxidation of methyl phenyl sulfide, gave (*S*)-sulfoxide with moderate yield and ee.

Key Words: Aminoethanol; Titanium(IV) complexes; Chiral sulfoxide; Asymmetric catalysis.

Optically active sulfoxides have been extensively used as building blocks in the pharmaceutical industry and chiral auxiliaries in asymmetric synthesis.[1] In recent year, a lot of research have been carried out in enantioselective oxidation of readily available prochiral sulfides to sulfoxides.[2–10] Amongst the chiral ligands employed for the oxidation, (1*S*,2*S*)-1,2-diphenylethan-1,2-diol has been proved to be an effective one. But it was found to decompose both via pinacol-type transposition and via degradative oxidation when the reaction time was over 2 h, and so further extension of the reaction time could even give rise to a decrease of ee.[7] (1*S*,2*S*)-1,2-Diphenylaminoethanol, which has the same chiral carbon backbone and one different function group with (1*S*,2*S*)-1,2-diphenylethan-1,2-diol, and their derivatives as chiral ligands had been successfully employed in many asymmetric catalytic reactions.[11–13] We also have successfully used oxazolines which derivate from (1*R*,2*S*)-, (1*S*,2*S*)-1,2-diphenylaminoethanol in the enantioselective oxidation of sulfides.[14] These results further prompted us to investigate the catalytic efficiency of chiral 1,2-diphenylaminoethanols and their derivatives in the asymmetric oxidation of sulfides. Herein, we wish to report the results obtained in the asymmetric oxidation of alkyl aryl sulfides **1** to their sulfoxide **2** and sulfone **3** in the presence of catalytic amount of complexes formed in situ by reacting $Ti(O^iPr)_4$, *N*-alkyl-1,2-diphenylaminoethanols **4–11** and water (Sch. 1).

The results obtained from the enantioselective oxidation of methyl phenyl sulfide (used as test substrate) indicated that **6** was an efficient ligand (Table 1, Entry 3). Use of 5 mol% of **6**/$Ti(O^iPr)_4$/H_2O as catalyst in CCl_4 at 0°C and 2.0 equiv. of TBHP (70% in water) as oxidant resulted in sulfoxide in 50% yield with 50% ee (*S*). When the alkyl on *N*-atom was changed, the yields and enantioselectivities decreased sharply.

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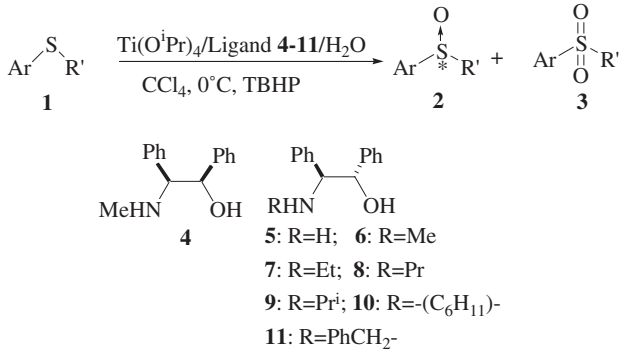

Scheme 1.

Table 1. Effect of ligand on the reactivity and enantioselectivity.[a]

Entry	Ligand	Time (h)	Yield[b] (%)	Ee[c] (%) (config.)[d]
1	4	23	50	15.3 (*R*)
2	5	36	26	5 (*S*)
3	6	45	50	50 (*S*)
4	7	41	47	3 (*S*)
5	8	65	44	4 (*S*)
6	9	63	40	2 (*S*)
7	10	64	33	2 (*S*)
8	11	50	34	2 (*S*)

[a]Reaction conditions: sulfide/ligand/Ti(O^{i}Pr)$_4$/H$_2$O = 1.0:0.1:0.05:1.0, reaction temperature = 0°C, CCl_4 was used as solvent, 2.0 equiv. of TBHP (70% in water) was used as oxidant.
[b]Isolated yield.
[c]Determined by HPLC on a Daicel Chiralcel OB column.
[d]The absolute configuration was assigned by comparison with literature values.[2a]

Even changed from methyl to ethyl, the enantioselectivity of the product varied from 50% ee to almost racemic. When use (1*S*,2*S*)-1,2-diphenylaminoethanol (**5**) as ligand, both the yield and enantiomeric excess of sulfoxide were very low (Table 1, Entry 2). This indicated that it was significant inferior to (1*S*,2*S*)-1,2-diphenylethan-1,2-diol in the same catalytic reaction procedure owing to the different electronic property and coordinate ability of the amino and hydroxy group. The configuration of C (1) influenced strongly on the enantioselectivity of sulfoxide. When

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aminoethanol **4** was used as chiral ligand, the sulfoxide was obtained in 50% yield with 15% ee (*R*). Analyzing the configuration of enantiomeric excess of sulfoxides and the structure of corresponding chiral aminoethanols **4** and **6**, we can conclude that the absolute configuration of enantiomeric excess of sulfoxides was determined by the stereogenic center of C (1) in aminoethanols.

In order to achieve good reactivity and high asymmetric induction, several reaction parameters had to be optimized. A series of solvents including CH_2Cl_2, DCE, C_7H_8, CCl_4, THF, Et_2O were screened. The best solvent was found to be CCl_4. The effect of temperature was also tested, the reactivity and enantioselectivity varied with the temperature from 0 to 20°C. The optimum reaction temperature was found to be 0°C. The effect of a molar ratio of **6** to $Ti(O^iPr)_4$ was examined (Table 2). When 2.0 equiv. of **6** were used per Ti, the best yields and enantioselectivities were obtained (Table 2, Entry 3). We also studied the influence of adding water when prepared the catalytic complex on the reaction. It was found that the enantioselectivity was not obviously influenced by it, but it causes the reactivity greatly increased. This may be the result of causing the catalyst to form the dimmer and to be activated.

The amount of catalyst also influenced the reactivity and the enantioselectivity (Table 3). Five mole percent catalyst was sufficient to achieve good enantioselectivity (Table 3, Entry 2). When the amount of

Table 2. Effect of molar ratio of **6** to $Ti(O^iPr)_4$ on the reactivity and enantioselectivity.[a]

		Yield[b] (%)		Enantioselectivity	
Entry	**6**/$Ti(O^iPr)_4$	Total yield	**2**	Chemo (**2**:**3**)	Ee[c] (%) (config.)[d]
1	1:1	59	49	83:17	11 (*S*)
2	1.2:1	60	51	85:15	21 (*S*)
3	2:1	77	67	87:13	52 (*S*)
4	2.2:1	53	46	86:14	49 (*S*)
5	3:1	56	51	91:9	54 (*S*)

[a]Reaction conditions: 5% catalyst amount, sulfide/H_2O = 1:1, reaction temperature = 0°C, reaction time = 72 h, CCl_4 as solvent was used, 4.0 equiv. of TBHP (70% in water) was used as oxidant.
[b]Isolated yield.
[c]Determined by HPLC on a Daicel Chiralcel OB column.
[d]The absolute configuration was assigned by comparison with literature values.[2a]

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Table 3. Effect of catalyst amount on the reactivity and enantioselectivity.[a]

Entry	Catalyst amount (%)	Yield[b] (%)		Enantioselectivity	
		Total yield	**2**	Chemo (**2**:**3**)	Ee[c] (%) (config.)[d]
1	2.5	43	43	100:0	23 (*S*)
2	5	77	67	87:13	52 (*S*)
3	10	57	47	82:18	50 (*S*)
4	20	70	60	87:13	51 (*S*)

[a]Reaction conditions: ligand **6**/Ti(O^iPr)$_4$ = 2:1, sulfide/H_2O = 1:1, reaction temperature = 0°C, reaction time = 72 h, CCl_4 as solvent was used, 4.0 equiv. of TBHP (70% in water) was used oxidant.
[b]Isolated yield.
[c]Determined by HPLC on a Daicel Chiralcel OB column.
[d]The absolute configuration was assigned by comparison with literature values.[2a]

Table 4. Effect of oxidant on the reactivity and enantioselectivity.[a]

Entry	Oxidant	Time (h)	Yield[b] (%)		Enantioselectivity	
			Total yield	**2**	Chemo (**2**:**3**)	Ee[c] (%) (config.)[d]
1	TBHP (1.5 equiv.)	48	26	26	100:0	45 (*S*)
2	TBHP (2.0 equiv.)	72	51	43	84:16	51 (*S*)
3	TBHP (2.0 equiv.)[e]	50	33	27	82:18	36 (*S*)
4	TBHP (3.0 equiv.)	72	72	59	82:18	56 (*S*)
5	TBHP (4.0 equiv.)	72	77	67	87:13	52 (*S*)
6	CHP (2.0 equiv.)	72	55	49	89:11	26 (*S*)

[a]Reaction conditions: sulfide/ligand **6**/Ti(O^iPr)$_4$/H_2O = 1.0:0.1:0.05:1.0, reaction temperature = 0°C, CCl_4 as solvent was used, TBHP (70% in water) was used as oxidant.
[b]Isolated yield.
[c]Determined by HPLC on a Daicel Chiralcel OB column.
[d]The absolute configuration was assigned by comparison with literature values.[2a,e]
[e]TBHP (5-6 M in decane) was used as oxidant.

catalyst was decreased to 2.5 mol%, the enantiomeric excess was only 23% (Table 3, Entry 1).

We also investigated the influence of oxidant on this reaction (Table 4). The best results were obtained when 3.0 equiv. of TBHP (70% in water) was used as oxidants (Table 4, Entry 4). TBHP (5–6 M in decane) was

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Table 5. The asymmetric oxidation of sulfides (ArSR).[a]

			Yield[b] (%)		Enantioselectivity	
Entry	Ar	R'	Total yield	**2**	Chemo (**2**:**3**)	Ee[c] (%) (config.)[d]
1	Ph	Me	72	59	82:18	56 (*S*)
2	*p*-MeC_6H_4	Me	73	65	89:11	39 (*S*)
3	*p*-BrC_6H_4	Me	60	55	92:8	42 (*S*)
4	Ph	Et	46	42	91:9	34 (*S*)

[a]Conditions: sulfide/ligand **6**/$Ti(O^iPr)_4/H_2O = 1.0:0.1:0.05:1.0$, reaction temperature = 0°C, reaction time = 72 h, CCl_4 as solvent was used, 4.0 equiv. of TBHP (70% in water) was used as oxidant.
[b]Isolated yield.
[c]Determined by HPLC on a Daicel Chiralcel OB column.
[d]The absolute configuration was assigned by comparison with literature values.[2a]

obviously inferior to TBHP (70% in water) (Table 4, Entries 2 and 3). When using cumene hydroperoxide (CHP) as oxidant, only 26% ee of sulfoxide was obtained (Table 4, Entry 6).

To further explore the potential of this catalyst system, we examined oxidation of other sulfides under the optimized condition; these results are summarized in Table 5. In all cases, the enantiomeric excess of the products was moderate (34 to 56% ee) and (*S*)-configuration sulfoxides were obtained. Depending on the structural features of the substrates, the chemical yields varied from 42 to 65%.

In conclusion, we have probed the possibility of using chiral *N*-alkyl-1,2-diphenylaminoethanols/titanium/water complexes as catalyst in the enantioselective oxidation of sulfides. The relationship between the structure of chiral ligands and the absolute configuration of sulfoxides were demonstrated. Further efforts to improve the catalytic efficiency of the reaction protocol are in progress.

EXPERIMENTAL

Melting points were determined on a Southend SS25PH appartus and were uncorrected. ^1H NMR spectra were recorded with a Bruker-300 spectrometer. IR spectra were recorded with a Nicolet 560 spectrophotometer. Optical rotations were measured using a Perkin–Elmer 341 digital polarimeter, in a cell of path length 10 cm and are given in units of 10^{-1} deg cm^2 g^{-1}. Chiral HPLC analyses were performed on a Beckman-

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110B chromatographic system with a Beckman 168 UV detector (254 nm). OB and OD column was purchased from Daicel Chemical Industries, Ltd. Elemental analyses were recorded on a Carlo Erba-1106 instrument. (1*R*,2*S*) and (1*S*,2*S*)-1, 2-diphenylaminoethanols were prepared by reported method.[15] (1*R*,2*S*)-*N*-methyl-1,2-diphenylaminoethanol **4** was prepared according to Lit.[16] The aminoalcohols **6–11** were prepared according to literature procedures.[17]

General Procedure for the Asymmetric Oxidation of Sulfides

To a suspension of chiral *N*-alkyl-1,2-diphenylaminoethanol (0.05 mmol) in CCl_4 (2.5 mL) was added $Ti(O^iPr)_4$ (0.025 mmol) by means of a syringe. This mixture was stirred at r.t. for 2 h and the solvent was removed under reduced pressure, and then CCl_4 (2.5 mL) and water (9 μL) were added. The mixture was stirred at r.t. for 1 h, the sulfide (0.50 mmol) was introduced by means of a syringe and the mixture was cooled to 0°C. After 0.5 h, TBHP (70% in water) was added by means of a syringe, and the mixture was stirred at 0°C for 72 h. The reaction mixture was directly purified by flash chromatograph (2:1 petroleum ether–ethyl acetate).

Methyl phenyl sulfoxide. δ_H (300 MHz; $CDCl_3$; Me_4Si): 2.72 (s, 3H, CH_3), 7.57 (m, 5H, Ar). ν_{max} (mull)/cm^{-1}: 1477, 1443, 1415, 1089, 1036. (*S*) 56% ee. $[\alpha]_D^{25}$ −34.4 (c 1.64, CH_3COCH_3).

***p*-Methylphenyl methylsulfoxide.** δ_H (300 MHz; $CDCl_3$; Me_4Si): 2.42 (s, 3H, $PhCH_3$), 2.71 (s, 3H, $SOCH_3$), 7.33 (d, 2H, $J = 7.98$ Hz, Ar), 7.54 (d, 2H, $J = 7.89$ Hz, Ar). ν_{max} (mull)/cm^{-1}: 1493, 1421, 1088, 1048. (*S*) 39% ee. $[\alpha]_D^{27}$ −10.4 (c 1.84, CH_3COCH_3).

***p*-Bromophenyl methylsulfoxide.** δ_H (300 MHz; $CDCl_3$; Me_4Si): 2.72 (s, 3H, CH_3), 7.60 (m, 4H, Ar). ν_{max} (mull)/cm^{-1}: 1469, 1417, 1387, 1084, 1043, 1008, 516. (*S*) 42% ee. $[\alpha]_D^{27}$ −19.5 (c 0.60, CH_3COCH_3).

Ethyl phenyl sulfoxide. δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.20 (t, 3H, $J = 7.4$ Hz, CH_3CH_2), 2.80 (m, 2H, CH_3CH_2), 7.60 (m, 5H, Ar). ν_{max} (mull)/cm^{-1}: 1443, 1086, 1044, 1021. (*S*) 34% ee. $[\alpha]_D^{27}$ −30.9 (c 1.0, CH_3COCH_3).

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