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Asymmetric Oxidation of a Dihydrothienopyrimidine

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KEYWORDS

Catalysis, DoE, asymmetric oxidation, sulfide oxidation, sulfoxide

ABSTRACT

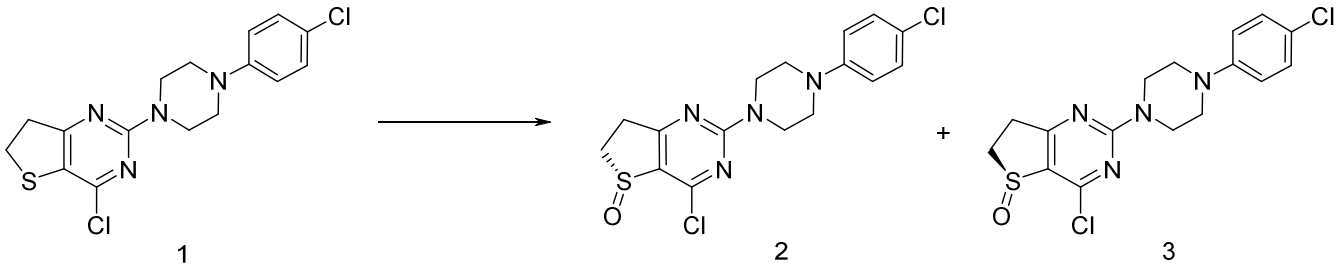
A robust catalytic asymmetric oxidation of prochiral sulfide **1** has been achieved by the use of a chiral titanium-hydrobenzoin complex. Reproducible reaction conditions were identified by screening reaction parameters and DOE optimization. The enantioselectivity was found to be mostly influenced by the amount of water and the time the catalyst was aged before addition of the sulfide.

INTRODUCTION

Asymmetric sulfoxides are present as key substructures in many compounds of medicinal and pharmaceutical importance. Thienopyrimidine oxides possess therapeutic activity that make them attractive targets for treatment of cardiovascular, sedative, respiratory and gastrointestinal disorders, inflammation, diseases of the peripheral or central nervous system, and cancers.[1] One of the contributors to the biological activity of these compounds is the presence of a sulfoxide group. The key challenge in preparing such compounds is usually associated with the enantioselective synthesis of the desired sulfoxide stereocenter. Despite the wide number of reported catalytic asymmetric methods,[2] relatively few catalytic processes are currently being applied in industry,[2l,3] presumably due to poor

reproducibility of the enantioselectivity associated with minor variations in reaction conditions. Kagan's group addressed reproducibility challenges in the enantioselectivity of their equimolar titanium-ethyl tartrate conditions by controlling the temperature and the preparation protocol of the chiral titanium complex.[2d] The highest degree of reproducibility was ensured by adding the titanium to the ligand, then holding the resulting complex for 2.5 min before adding water dropwise over 90 seconds. The latter operation time was found more crucial.

As part of our program towards developing a scalable synthesis of dihydropyrimidines bearing chiral sulfoxide groups, we became interested in the asymmetric oxidation of sulfide **1**.[1d] We report herein our findings to provide a robust asymmetric sulfoxidation of dihydrothienopyrimidine **1**.



Scheme 1. Asymmetric sulfide oxidation of dihydrothienopyrimidine **1**.

RESULTS AND DISCUSSION

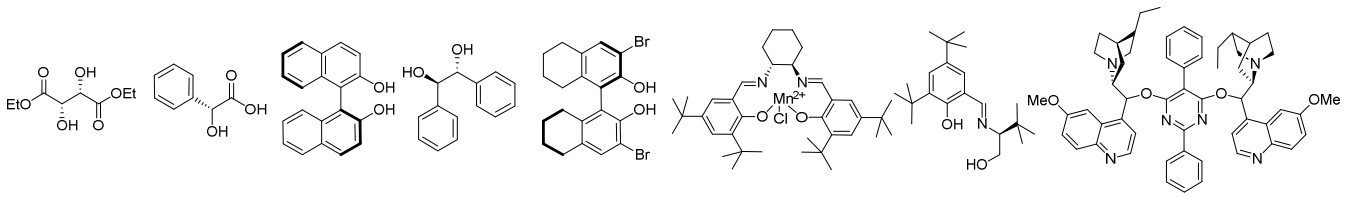
The asymmetric oxidation of sulfide **1** was first examined by surveying different protocols (Table 1).[4] We initially explored Kagan's type conditions using equimolar or catalytic amounts of titanium which afforded the sulfoxide with selectivities up to 73% ee and 2% over oxidation to the corresponding sulfone (entries 1-3).[2a,d,k] When using mandelic acid as ligand, very low enantioselectivy and high amounts of sulfone were obtained (entry 4).[2g] We then investigated Uemura's type conditions using BINOL-type ligands with little success (entries 5-6).[2e,5b] Best results were obtained using the methodology developed by Rosini and co-workers in the presence of titanium tetraisopropoxide (5 mol%), (*R*,*R*)-hydrobenzoin (10 mol%) and water (1 equiv) which gave 92% ee of **3** (entry 7).[5b] The main advantage of this catalytic protocol is the high induction of enantioselectivity in the formation of

the sulfoxides with negligible kinetic resolution due to over oxidation to sulfone.[5b] Evaluation of other catalytic protocols based on metals like Mn, V, Fe or W resulted in lower yields and enantioselectivities.

Table 1. Initial screening for the oxidation of **1**

Entry	MX (equiv)	Ligand (equiv)	Additives (equiv)	Peroxide (equiv)	Solvent	T (°C)	time	Isolated yield	% Sulfone	ee * (%)
1	Ti(*i*-PrO)$_4$ (1)	*(S,S)*-DET (2)	H_2O (1)	CHP (2)	CH_2Cl_2	-20	24 h	99%	2	-73
2	Ti(*i*-PrO)$_4$ (1)	*(S,S)*-DET (4)	-	CHP (2)	CH_2Cl_2	-20	24 h	99%	2	-31
3	Ti(*i*-PrO)$_4$ (0.3)	*(S,S)*-DET (0.6)	H_2O (0.1) *i*-Pr_2NEt (0.3)	CHP (1)	toluene	35	24 h	90%	7	-1
4	Ti(*i*-PrO)$_4$ (0.4)	(*S*)-mandelic acid (0.6)	MS	CHP (1)	CH_2Cl_2	23	5 h	99%	11	15
5	Ti(*i*-PrO)$_4$ (0.1)	*(S)*- BINOL (0.2)	H_2O (2)	aq *t*-BuOOH (2)	$CHCl_3$	0	48 h	71%	nd	-51
6	Ti(*i*-PrO)$_4$ (0.1)	*(R)*-dibromo-BINOL (0.2)	H_2O (2)	CHP (2)	toluene	23	5 h	99%	14	-6
7	Ti(*i*-PrO)$_4$ (0.05)	*(R,R)*-hydrobenzoin (0.1)	H_2O (1)	aq. *t*-BuOOH (2)	toluene	0	48 h	90%	2	-92
8	*(R,R)*-Jacobsen cat. (0.02)		-	aq. H_2O_2 (6)	CH_3CN	23	15 h	11%	nd	5
9	$VO(acac)_2$ (0.02)	Schiff base (0.04)	-	aq. H_2O_2 (1.1)	CH_2Cl_2	23	43 h	82%	2	35
10	$Fe(acac)_3$ (0.02)	Schiff base (0.04)	*p*-Anisic acid (0.01)	aq. H_2O_2 (1.2)	CH_2Cl_2	23	15 h	55%	nd	7
11	WO_3 (0.05)	$(DHQN)_2$-PYR (0.1)	-	aq. H_2O_2 (1.05)	THF	23	24 h	78%	3	-59

Abbreviations: MS (molecular sieves), CHP (cumene hydroperoxide), THF (tetrahydrofuran), nd (not detected). *ee was determined by HPLC. Positive values of ee indicate that enantiomer **2** was obtained as major isomer, while negative values indicate the opposite enantiomer **3** was obtained as major.



Analysis of the product enantioselectivity at different enantiopurities of ligand revealed a negative non-linear effect similar to Kagan's catalytic system using a tartrate as ligand[6] and opposite to Uemura's catalytic system using BINOL.[7] The asymmetric depletion highlighted the importance of using ligand of high enantiopurity to ensure high values of ee in the product (Figure 1).

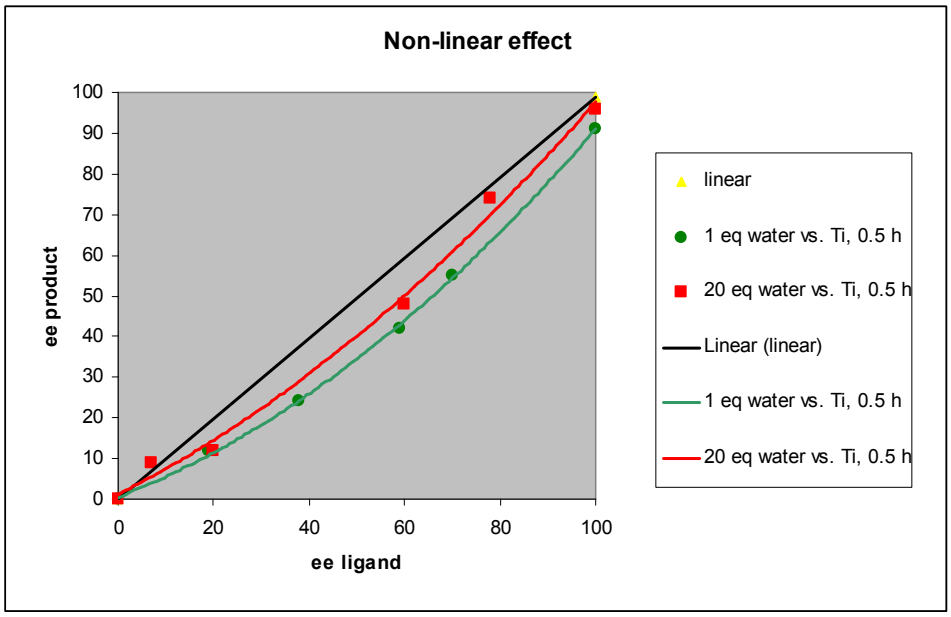


Figure 1. Non-linear effect in the asymmetric oxidation of **1** at two different concentrations of water.

Further optimization of the reaction conditions was performed by screening alternative ligands, additives, oxidants, solvents and temperatures. Evaluation of other commercially available ligands such as (*S*,*S*)-1,2-di(1-naphthyl)-1,2-ethanediol and (*S*,*S*)-1-(1-naphthyl)-2-(2-naphthyl)-1,2-ethanediol afforded lower selectivities of 43 and 28% ee, respectively. Addition of *i*-Pr_2NEt,[21] N-methylmorpholine or 1,4-dimethylpiperazine to the Ti/hydrobenzoin/water catalytic system caused loss of reactivity and enantioselectivity. *tert*-Butyl hydroperoxide in water or decane proved to be a superior oxidant to hydrogen or cumene hydroperoxide. Solvents such as fluorobenzene or dichloromethane provided lower enantiomeric excesses of sulfoxide. When the catalyst was prepared at 0-25 °C before adding the water, the enantioselectivity of the oxidation was consistently about 90% ee, however, when the catalyst was prepared at 45 °C before water addition, the selectivity decreased to 68% ee. In addition, when the peroxide was dosed to the reaction mixture at 0-25 °C, there was no effect on the enantioselectivity. Finally, comparable results were obtained when the reaction was carried out under anaerobic or aerobic conditions.

Following Kagan's reproducibility studies on ethyl tartrate as ligand,[2d] we evaluated the slow addition of the water during the catalyst preparation with hydrobenzoin and found no significant impact on the variability of the enantioselectivity. However, we identified two critical factors to insure reproducibility of high enantioselectivity: first was stirring due to the heterogeneous nature of the reaction media at moderately concentrated reaction (0.5 M); and secondly, the time the catalyst was hold before addition of the sulfide. The optimized procedure is as follows: titanium and water were added sequentially dropwise to a solution of ligand in toluene at 20-25 °C, followed by the sulfide; the resulting suspension was stirred for 15 min before cooling to 0 °C and the peroxide was added.

Further screening of the key factors affecting the Ti/hydrobenzoin/water catalytic system, i.e. catalyst load, amount of water at the catalyst preparation stage, and the time the catalyst was hold before addition of the sulfide, - was performed using statistical design of experiments (DoE)[8] to develop a robust process and to maximize the enantiomeric excess of the reaction. The procedure studied for optimization was the following: titanium(IV) isopropoxide (5-20 mol%) was added to (*S*,*S*)-hydrobenzoin (10-40 mol%) in toluene at 23 °C followed by water (0-1.5 equiv). After stirring for certain time (0.5-2 h), the sulfide (1.0 equiv) was added, and the reaction mixture was cooled to 0 °C over 30 min before addition of *tert*-butyl hydroperoxide (2 equiv).

We utilized DOE program MODDE 8.0[9] and applied a 2 level full factorial design with one center point, and complemented it with additional experiments for reproducibility evaluation. Therefore, on the basis of nine parallel runs, plus four runs for reproducibility using 1.5 equivalents of water and 0.5 h for catalyst preparation, it was possible to analyze the data by analysis of variance.[10] In all cases, complete conversions with 88-97% yield were obtained and 64-97% ee were observed.[11] The summary plot showed high goodness of fit, high goodness of prediction, high model validity and high reproducibility. Analysis of the factor coefficient plot indicated that the enantiomeric excess would mostly be maximized by minimizing the holding time of the catalyst before addition of the sulfide, and minimizing the amount of water added during catalyst formation (Figure 2). Analysis of the response contour plot

revealed two possible operational areas for maximum enantioselectivities: using 0-0.6 equivalents of water at short catalyst preparation times, or using less than 0.1 equivalents of water for preparation of the catalyst during 1.2-2 h. The reproducibility runs using 1.5 equivalents of water and stirring the catalyst for 0.5 h before sulfide addition provided 88-95% yield and 89-93% ee.

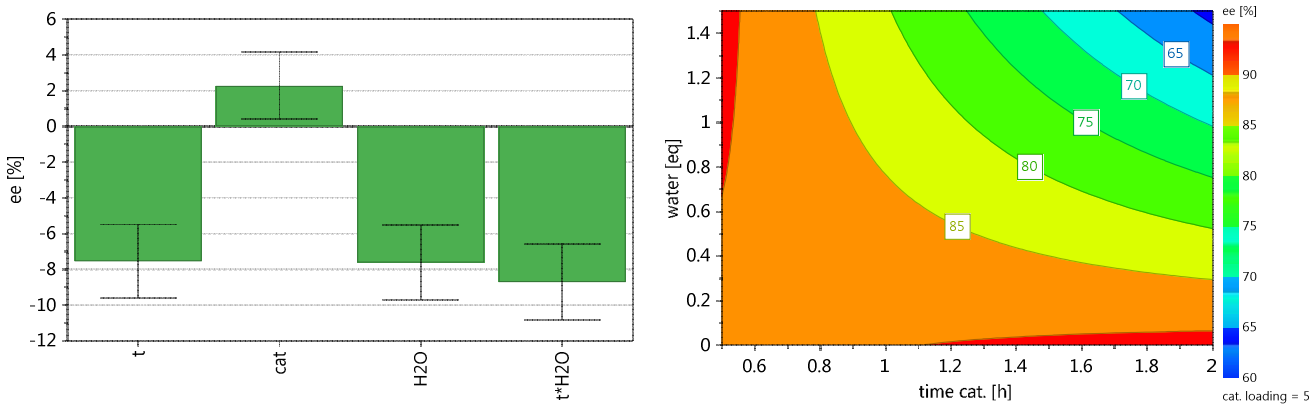


Figure 2. Factor coefficient plot and response contour plot at 5 mol% catalyst load.

Verification experiment on 5 g scale using 5 mol% catalyst, 1 equivalent of water and stirring the catalyst mixture for 30 min before addition of sulfide allowed isolation of 88% of sulfoxide with 89% ee. Catalyst loading was briefly evaluated at this point, being reduced to 2.5 mol% with no impact on yield or enantioselectivity.

In order to further minimize the time between preparation of the catalyst and addition of sulfide, we evaluated the formation of catalyst in the presence of sulfide. Adding the titanium and the water to a mixture of sulfide and ligand in toluene, cooling to 0 °C over 30 min and adding the peroxide afforded the sulfoxide in 90% ee.

The above investigations resulted in the development of the following reproducible more robust procedure: Titanium and water were added sequentially to a slurry of ligand and sulfide in toluene at 20-25 °C; the mixture was cooled to 0 °C over 1 h, and the peroxide was added; the reaction mixture was stirred at 0 °C. The last protocol was also examined at lower concentration of **1** of 0.25 M instead 0.5 M which increased solubility of the sulfide affording a quasi-homogenous reaction without affecting the

enantioselectivity. Finally, the catalyst load was reduced to 2.5 mol% without impacting the conversion or the enantiomeric excess of the product.

In conclusion, a reproducible robust procedure for the asymmetric sulfoxidation of dihydrothienopyrimidine **1** was developed by identifying new oxidation conditions and optimizing the process parameters. We utilized DoE to address irreproducibility issues on the asymmetric oxidation of sulfides using titanium-hydrobenzoin complex which constitutes the first report on catalytic asymmetric sulfoxidation. Maximum enantioselectivities were obtained at short catalyst preparation times or at low amounts of water, achieving optimal results when preparing the catalyst in the presence of the sulfide.

EXPERIMENTAL SECTION

Reagents were used as purchased without further purification. NMR spectra were recorded on a Bruker 400 MHz spectrometer. The chemical shift data are reported as δ (ppm) downfield from tetramethylsilane which is used as an internal standard; coupling constants (*J*) are reported in Hertz, and refer to apparent peak multiplicities. HPLC analysis was performed on an Agilent 1100 series using an Agilent XDB-C18 column; flow rate 2 mL/min; with a UV detection at 215 nm; mobile phase from 48% to 97% acetonitrile in water (0.1% $HClO_4$) in 1.3 min, then hold to 97% for 1.2 min. Enantioselectivities were measured on an Agilent 1100 series using a chiralpak AD-H column; flow rate 1 mL/min; with a UV detection at 220 nm; mobile phase 20% isopropanol in heptane for 10 min.

Procedure A

To a mechanically stirred solution of (*S*,*S*)-hydrobenzoin (292 mg, 1.36 mmol) in toluene (50 mL) in a 100 mL flask at 20 °C was added Ti(*i*-PrO)$_4$ (0.20 mL, 0.68 mmol). After 2-3 min, water (0.25 mL, 13.61 mmol) was added dropwise over 1 min. The mixture was stirred at 20 °C for 30 min before sulfide **1** (5.00 g, 90.6 wt% purity, 13.61 mmol) was added. After stirring for 15 min, the slurry was cooled to 0 °C over 20 min and 70% aqueous *tert*-butyl hydroperoxide (3.77 mL, 27.23 mmol) was added. After 23 h, the reaction mixture was quenched with 5% Na_2SO_3 (20 mL) and extracted with dichloromethane (50 mL). The combined organic layers were washed with water (20 mL), dried

($MgSO_4$) and concentrated. 5.57 g of sulfoxide **2** was obtained as yelow solid; 88% yield by NMR, 89% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.16 (m, 2H), 6.90-6.80 (m, 2H), 4.20-3.90 (m, 1H), 3.90-3.75 (m, 1H), 3.30-3.00 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 162.5, 160.7, 149.8, 129.4, 125.7, 123.9, 118.2, 49.6, 46.5, 44.7, 44.4, 33.7; LCMS (ESI) for $C_{16}H_{17}Cl_2N_4OS$ $(M+H)^+$: calcd. 383.1, obsvd. 383.0.

Procedure B

To a mechanically stirred suspension of sulfide (1.0 g, 2.72 mmol) and (*S*,*S*)-hydrobenzoin (58 mg, 0.27 mmol) in toluene (10 mL) at 20 °C was added Ti(*i*-PrO)$_4$ (40 µL, 0.14 mmol) followed by water (49 µL, 2.72 mmol). The mixture was cooled to 0 °C over 1 h before 70% aqueous *tert*-butyl hydroperoxide (0.75 mL, 5.45 mmol) was added. After 20 h, the reaction mixture was quenched with 5% Na_2SO_3 and extracted with dichloromethane. The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated. 95% conversion and 90% ee was obtained.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure for DoE studies and copies of ^{1}H and ^{13}C NMR spectra for compound **2**.

AUTHOR INFORMATION

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(4) Configuration of the sulfide center was initially assigned by comparison with literature (see ref. 5a), and confirmed by chemical correlation with an advanced compound which absolute configuration was determined by X-Ray analysis

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(9) MODDE is a registered trademark of Umetrics.

(10) Model validity and reproducibility were confirmed by complementing the model with data from two previous experiments.

(11) Experimental data included in the Supporting Information.

TOC/Abstract Graphic

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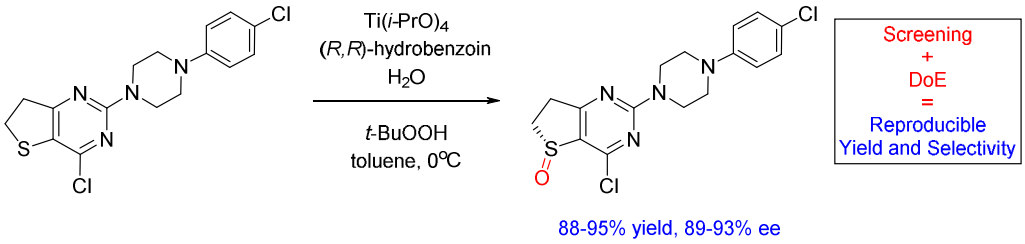

88-95% yield, 89-93% ee