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Nonlinear effects as 'indicators' in the tuning of asymmetric catalysts

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Abstract

Nonlinear effects (NLEs) have been used as a new tool to characterize the various modifications of a chiral titanium complex used in stoichiometric or catalytic mode in asymmetric sulfoxidation by cumyl hydroperoxide. Spectacular changes from (+)- to (−)-NLEs were observed for minor modifications of the experimental conditions.

1. Introduction

Nonlinear effects (NLEs) have been discovered for various classes of reactions,[1–8] both in catalytic and stoichiometric reactions (with respect to the chiral auxiliary). It is a good indication that diastereomeric species are involved directly in the catalytic cycle or in the reaction scheme, or remain as dormant and unreactive species. The presence of a (+)-NLE (amplification) may have some practical consequences. A nonlinear effect may be a useful piece of information to discuss mechanistic details of a reaction, as exemplified in the case of the catalyzed asymmetric addition of diethylzinc to benzaldehyde.[9] A change of experimental conditions may also perturb the size and sign of a nonlinear effect. This has been recently shown by Feringa et al. who found that addition of anthraquinone reversed the NLE in the catalytic enantioselective allylic oxidation of cyclohexene using copper proline complexes and *t*-butyl hydroperoxide.[10] Kobayashi et al. also described important perturbations of NLE in Diels–Alder reactions catalyzed by lanthanide triflates after introduction of achiral additives or after change of the lanthanide ion.[11]

We wish to report here the use of the nonlinear effect as an 'indicator' for the comparison of closely related chiral catalysts or chiral mediators. This approach will be illustrated in the specific case of asymmetric sulfoxidation.

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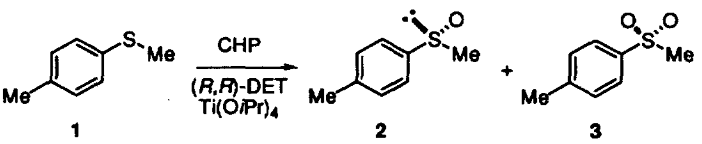


Fig. 1.

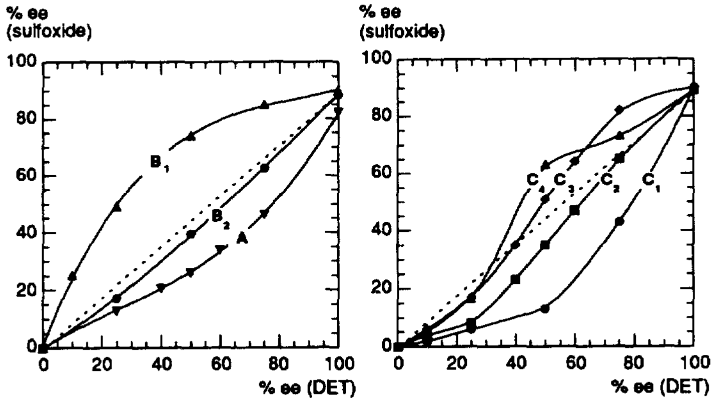
2. Results and discussion

We have developed the enantioselective oxidation of sulfides by hydroperoxides in the presence of titanium complexes derived from the Sharpless reagent. We initially prepared the combination Ti(O-*i*Pr)$_4$:(*R*,*R*)-diethyl tartrate (DET):H$_2$O=1:2:1 which gave enantiomeric excesses of up to 90% in *p*-tolyl methyl sulfide **1** oxidation with *t*-butyl hydroperoxide as oxidant.[12] Modena et al. independently prepared a reagent of stoichiometry Ti(O-*i*Pr)$_4$:(*R*,*R*)-DET=1:4 providing sulfoxide **2** in 88% ee.[13] Careful control of the generation of our titanium complex allowed >99% ee to be reached with cumene hydroperoxide (CHP) as oxidant.[14] We also studied a combination of Ti(O-*i*Pr)$_4$:(*R*,*R*)-DET:*i*PrOH=1:4:4 giving 90% ee in (*R*)-**2** (CHP as oxidant). This latter combination in the presence of 4 Å molecular sieves recently allowed a catalyst (10% mol equiv.) to be set up giving up to 95% ee in (*R*)-**2**.[15,16] A wide diversity of titanium species[17] with different behaviors are obviously generated by minor modifications of the experimental conditions. We investigated some of the above sulfoxidations using DET of various ees (Fig. 1).

We call **A**, **B**, **C** the following cases (oxidation of **1** into sulfoxide **2** by CHP):

A: 1 mol equiv. Ti(O-*i*Pr)$_4$:(*R*,*R*)-DET=1:4
B: Ti(O-*i*Pr)$_4$:(*R*,*R*)-DET:*i*PrOH=1:4:4
C: Ti(O-*i*Pr)$_4$:(*R*,*R*)-DET:*i*PrOH:MS 4 Å=1:4:4:1

Titanium complexes **A** (Modena reagent),[13] **B** and **C** were prepared at 16°C in CH$_2$Cl$_2$ and the reactions were performed at −25°C in the presence of 2 equiv. of CHP. These three systems were studied at the 2 mmol scale and were compared as closely as possible (same batches of Ti(O-*i*Pr)$_4$, DET, CHP and MS 4 Å and much care in the oxidation procedure).[18] In the above experiments (*R*,*R*)-DET (100% ee) gave 85–90% ee for stoichiometric reactions **A** and **B** and for the catalytic reaction **C**. However some dramatic differences between the three systems could be seen by investigating the reaction on the full range of ees of diethyl tartrate (Scheme 1, data in Tables 1 and 2).



Scheme 1.

Reagent **A** gave rise to a negative NLE quite similar to the NLE produced by our initial water-modified reagent.[3] Reagent **B** (1 mol equiv., **B$_1$**) is characterized by a positive NLE, while its use in the catalytic

Table 1
Oxidation of sulfide **1** in the absence of molecular sieves (Scheme 1)

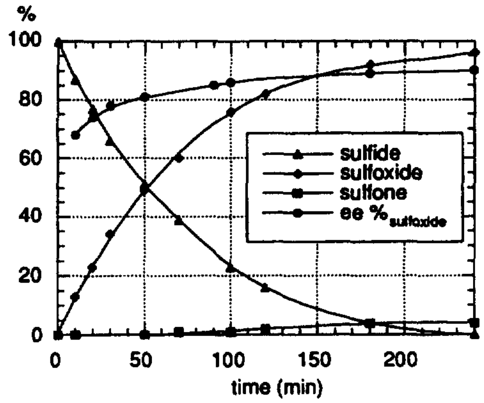
DET ee %	Sulfoxide **2** ee% (*R*) 100% cat. (**A**)	 100% cat. (**B**$_1$)	 10% cat. (**B**$_2$)
0	0	0	0
10	-	25	-
25	13	49	17
40	21	-	-
50	26	74	39
60	34	-	-
75	46	85	63
100	82	90	89

Table 2
Oxidation of sulfide **1** in the presence of molecular sieves (Scheme 1)

DET ee %	10% cat. ee % (**C**$_1$)	70% cat. ee % (**C**$_2$)	90% cat. ee % (**C**$_3$)	100% cat. ee % (**C**$_4$)
0	0	0	0	0
10	2	4	6	25
25	6	8	17	49
40	-	23	35	-
50	13	35	51	74
60	-	47	64	-
75	43	65	82	85
100	90	89	90	90

mode (10% mol equiv., **B**$_2$) leads to a disappearance of NLE (Scheme 1). The catalyst **B**$_2$ in the presence of molecular sieves gave rise to a (−)-NLE (**C**$_1$, Scheme 1). A second set of experiments in the presence of molecular sieves was performed in which the amount of the titanium combination was modified from 10% mol equiv. to 1 mol equiv. (at a fixed concentration, 7×10^{-2} M, of sulfide **1**). For a Ti/**1** ratio of between 1 and 10 the ee of sulfoxide **2** remains close to 90%, while there is a strong influence on the NLE (Scheme 1). A 70% mol equiv. of combination **C**, case **C**$_2$, gave a weak (−)-NLE while with 90% and 100% mol equiv., cases **C**$_3$ and **C**$_4$, the NLE curve crosses the straight line. Here, DET of low ee provides a (−)-NLE while DET of ee >40% gives a (+)-NLE. Such two-shape curves are quite rare.[19] This surprising inversion of the sign of the nonlinear effect with the amount of the chiral titanium complex may have several origins. The most likely is the influence of the concentration of the complex.

In order to gain some information on the mechanism of the reaction, the catalytic sulfoxidation **C**$_1$ (DET: 100% ee) was followed as a function of the reaction time (Scheme 2, data in Table 3). Surprisingly the ee of sulfoxide **2** increases during the course of the reaction (from 68% ee at 13% conversion) to 90% ee at 90% conversion. It is not a kinetic resolution since the amount of the corresponding sulfone remains very low (5% at 90% conversion), furthermore we checked that racemic sulfoxide **2** gives no kinetic resolution in the presence of catalyst **C**$_1$. The most likely explanation is an evolution of the catalyst structure during the first half of the reaction.[20,21] Since the ee of the product is conversion-dependent it is necessary to check that the NLE curves of Scheme 1 involve similar conversions in order to make comparisons. Hopefully all the reactions provided almost the full conversion of the sulfide **1**, whatever the ee of DET.



Scheme 2. Catalytic sulfoxidation of **1** (C_1, DET 100% ee)

3. Conclusion

In conclusion, we established that the nonlinear effects may provide an extremely sensitive tool to trace the modifications of a chiral catalyst, acting as a 'finger print', while the variation of the ee of the product for an enantiopure chiral auxiliary may be less informative.[22] This approach should also apply to other systems giving NLE.[23]

Table 3
Oxidation of sulfide **1** (Scheme 2) as a function of reaction time

Time (min)	Sulfide **1** (%)	Sulfoxide **2** (%)	Sulfone **3** (%)	ee % of **2**
0	100	0	0	-
10	87	13	0	68
20	77	23	0	74
30	66	34	0	78
50	51	49	0	81
70	39	60	1	-
90	-	-	-	85
100	23	76	1	86
120	16	82	2	-
180	4	92	4	89
240	0	96	4	90

4. Experimental

Measurements of ees were made by HPLC analysis on a Spectroseries P100 pump module with a Spectroseries UV100 detector and a Daicel Chiralcel OD-H column. Determinations for kinetics were made on a Fisons CG8000 series gas chromatograph with a DB1 30 m column.

4.1. General procedure for catalytic oxidation of sulfide 1

All the operations were performed under argon. The Schlenk and stirrer bar were dried in the oven and then capped with a septum and cooled under vacuum. The cold Schlenk was flushed with argon. CH_2Cl_2 was distilled from calcium hydride and stored over activated molecular sieves under argon. Molecular sieves (pellets 4 Å) were purchased from Prolabo and activated at 200°C under reduced pressure (0.01 mmHg) for 48 hours. The diethyl tartrate as well as titanium tetraisopropoxide was distilled over a Vigreux column before use. The commercially available cumene hydroperoxide (80% in cumene alcohol) was purchased from Aldrich and used without purification. The active free peroxide was determined by iodometric titration.

A solution of 50 µl of (*R*,*R*)-DET (0.3 mmol) in 1 ml of CH_2Cl_2 at 16°C was added to a Schlenk containing 5% weight equivalent (with respect to the sulfide) of 4 Å molecular sieves. This solution was stirred for 2.5 min and 22 µl of $Ti(O\text{-}i\mathrm{Pr})_4$ (0.07 mmol) was added slowly. The resulting mixture was stirred for 10 min at 16°C and 22 µl of 2-propanol (0.3 mmol) was added slowly. Stirring was maintained for 10 min followed by cooling in a freezer (−22°C) without stirring for an additional 20 min. The reaction was allowed to take place after rapid addition of 100 mg of sulfide **1** (0.7 mmol) in 9 ml of CH_2Cl_2 and pre-cooled (−22°C) CHP (1.4 mmol), with storage of the flask in the fridge (−22°C) without stirring. After 16 h the mixture was poured into a solution of 1 g of ferrous sulfate heptahydrate (3.6 mmol) and 300 mg of citric acid (1.4 mmol) in 15 ml of water, 1 ml of 1,4-dioxan, 20 ml of ether, and was stirred for 15 min. The aqueous phase was extracted with ether (3×15 ml). The combined organic phases were stirred vigorously with 15 ml of 2 M aqueous NaOH for 1 h. The aqueous solution was then extracted with ether (3×15 ml). The combined organic solutions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Flash chromatography on silica gel (eluent: ethyl acetate) of the crude product first afforded unreacted sulfide, sulfone, cumyl alcohol then pure sulfoxide. The fractions of sulfoxide **2** were mixed before ee measurement (chiral HPLC) to avoid ee enrichment.[18]

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21. Asymmetric autoinduction (modification of the catalyst by the product) may be operating here (see, Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.*, **1989**, *111*, 7265; Bolm, C.; Bienewald, H.; Seger, A. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 1657). However, addition of either enantiomer of **2** at the beginning of the reaction did not improve the enantioselectivity.
22. We are currently investigating the various equilibria between monomeric and dimeric titanium complexes involved in the asymmetric oxidation. The concentration effect on NLEs may be quantitatively correlated with the distribution of titanium complexes. Ti(O-*i*Pr)$_4$ has been found to be devoid of catalytic activity in sulfoxidation and cannot be responsible for a (−)-NLE.
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