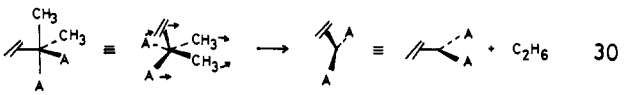
Table I. Extended-Hückel Parameters

	orbital	H_{ii}, eV	exponent[a]
Ni	4s	-9.17	2.10
	4p	-5.15	2.10
	3d	-13.49	5.75 (0.5798) + 2.30 (0.5782)
P	3s	-18.6	1.60
	3p	-14.0	1.60
C	2s	-21.4	1.625
	2p	-11.4	1.625
H	1s	-13.6	1.3
A	1s	-14.34	1.3

[a] The d function is a double-ζ type.

TBP **27** (**23a**), to which the molecule relaxes from the nearby cis entry point, **26** (**22a**). The axial site of a TBP is not suited to ethylene, and **28** (**23b**) as well as **29** (**23e**) are unstable structures. There appear to be notable steric repulsions with the equatorial ligands, coupled with better back-bonding when the ethylene rotates back to an equatorial site. Stabilities of the other structures not listed in **24**-**29** fall in between those of **27** and **28**. The cis-trans rearrangements are again high-energy processes and unlikely to occur.[18]

The exit channel for R-R elimination might well be **23a**. The activation energy for the pathway **30** of the model $Ni(CH_3)_2(H_2C{=}CH_2)A_2$ was calculated to be 0.9 eV. The barrier is close to the one obtained for the pathway **14** of $Ni(CH_3)_2A_3$ (see Figure 3). One might anticipate that the barrier would be much lowered when A, and thus phosphine, is replaced by ethylene, because the strong π-accepting nature of ethylene stabilizes the three-coordinate product substantially. Presence of a π acceptor should also aid the alkane elimination itself. However, the calculated result opposes this naive expectation. Perhaps the π-acceptor effect is masked by the concomitant strong σ-donor character of ethylene. It has been known for experiments that addition of olefins facilitates reductive elimination, but only when electronegative substituents are attached to them.[1a]



30

(18) It should be noted here that olefin insertion into M-R bonds, another ubiquitous reaction in organometallic chemistry, was found a difficult process for d^8 $PtXL_2(H_2C{=}CH_2)R$. Thorn, D. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079-2089.

Appendix

The parameters of the extended-Hückel calculations[19] are listed in Table I. A weighted H_{ij} formula was used for calculations. Exponents of Ni 3d orbitals were taken from the work of Richardson et al.,[20] while other exponents and the H_{ij} values are the same as those used previously.[21]

Geometrical assumptions included the following: C—H 1.09 Å, C=C 1.34 Å, P—H 1.42 Å, Ni—$C(CH_3)$ 2.02 Å, Ni—(ethylene midpoint), 2.00 Å, Ni—P 2.23 Å, CH_3 and PH_3 tetrahedral.

Registry No. *trans*-$Ni(CH_3)_2(PH_3)_2$, 93219-79-5; *cis*-$Ni(CH_3)_2(PH_3)_2$, 79218-07-8.

(19) (a) Hoffmann, R. *J. Chem. Phys.* **1963**, *39*, 1397-1412. (b) Hoffmann, R.; Lipscomb, W. N. *Ibid.* **1962**, *36*, 2179-2189.
(20) Richardson, J. W.; Powell, R. R.; Nieuwpoort, W. C. *J. Chem. Phys.* **1963**, *38*, 796-801.
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An Efficient Asymmetric Oxidation of Sulfides to Sulfoxides

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Abstract: The Sharpless reagent for asymmetric epoxidation was modified by addition of 1 mol equiv of H_2O to give a new homogeneous reagent ($Ti(O\text{-}i\text{-}Pr)_4$/diethyl tartrate/$H_2O$/$t$-BuOOH = 1:2:1:1). This reagent cleanly oxidizes prochiral functionalized sulfides into optically active sulfoxides. The observed ee mainly ranged between 75 and 90% for alkyl aryl sulfoxides and 50-71% for dialkyl sulfoxides. A strong temperature dependence on ee was also observed in the asymmetric oxidation of methyl *p*-tolyl sulfoxide.

Chiral sulfoxides are gaining considerable importance in synthesis as chiral synthons for the asymmetric C-C bond formation.[1-4] Up to now, the main asymmetric synthesis of chiral sulfoxides has been based on the separation of the intermediate diastereomeric menthyl sulfinates.[5-8] Asymmetric oxidation of prochiral sulfides is not a preparative method for chiral sulfoxides:only moderate to high enantiomeric excesses have been observed in some cases.[9-14] We wish to present a simple method

(1) Mikolajczyk, M.; Drabowicz, J. *Top. Stereochem.* **1982**, *13*, 333.
(2) Solladié, G. *Synthesis* **1981**, 185.
(3) Posner, H. G.; Mallamo, J. P.; Miura, K.; Hulle, M. "Asymmetric Reactions and Processes in Chemistry"; American Chemical Society: Washington, DC, 1982; ACS Symp. Ser.
(4) (a) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613. (b) Solladié, G.; Matloubi-Moghadam, F. *J. Org. Chem.* **1982**, *47*, 91.
(5) Andersen, K. K. *Tetrahedron Lett.* **1962**, 93.
(6) Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternary, A. L., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1958.
(7) In some specific cases[2,8] procedures allow for recovery of only one diastereomer in epimerizing conditions at sulfur, by taking advantage of the greater stability or insolubility of one diastereoisomer.
(8) Mioskowski, C.; Solladié, G. *Tetrahedron Lett.* **1980**, *36*, 227.
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(10) Oxidation by other chemical reagents (ee <10%): (a) Higuchi, T.; Pitman, I. H.; Gensch, K. H. *J. Am. Chem. Soc.* **1966**, *88*, 5676. (b) Furia, F. D.; Modena, G.; Curci, R. *Tetrahedron Lett.* **1976**, 4637. (c) Liu, K. T.; Tong, Y. C. *J. Chem. Res. (S)* **1979**, 276.

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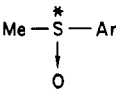
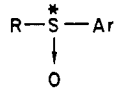
Table I. Asymmetric Oxidation of Aryl Methyl Sulfides into



	Ar	reaction conditions[a]	yield,[c] %	$[\alpha]^{20}_D$ (in acetone[g])	ee,[e] % (configuration)
1	*p*-tolyl	−20 °C, 4 h[b]	90	+132° (*c* 2)	91[d] (*R*)
2	phenyl	−20 °C, 5 h	80	+130° (*c* 1.7)	89[d] (*R*)
3	*p*-bromophenyl	−20 °C, 4 h	70	+77 (*c* 1.8)	80[d] (*R*)
4	*p*-chlorophenyl	−21 °C, 16 h	95	+97° (*c* 2)	78[d] (*R*)
5	*p*-(CO_2Me)Ph	−21 °C, 60 h	50	+260° (*c* 0.5)[h]	91
6	*o*-(CO_2Me)Ph	−17 °C, 7 h	50	+84° (*c* 0.4)[i]	60 (*R*)
7	2-naphthyl	−20 °C, 4 h	88	+127° (*c* 2)[h]	90
8	*p*-methoxyphenyl	−17 °C, 6.5 h	72[f]	+104° (*c* 2.8)	86
9	*p*-methoxyphenyl	−21 °C, 15 h	58[f]	−102[k] (*c* 2)[h]	86
10	*o*-methoxyphenyl	−17 °C, 6.5 h	70	+251° (*c* 0.4)	84
11	*p*-nitrophenyl	−20 °C, 60 h	63	+77° (*c* 2.8)	77
12	*p*-hydroxyphenyl	−21 °C, 20 h	90	+67° (*c* 1)	50
13	*p*-(CH_2OH)Ph	−21 °C, 48 h	71	+77° (*c* 1.2)[j]	76
14	2-pyridyl	−21 °C, 16 h	63	+48° (*c* 1.5)[j]	77
15	4-pyridyl	−21 °C, 16 h	51	+54° (*c* 3.8)[j]	not determined

[a] [Sulfide] = [reagent] = 10^{-1} M in CH_2Cl_2, under nitrogen atmosphere. Reagent: Ti(O-*i*-Pr)$_4$ + (*R*,*R*)-diethyl tartrate + H_2O + TBHP (1:2:1:1.1). [b] Conditions as in *a* but with 2.0 mol equiv of TBHP. [c] Isolated yields, reactions at the 5-mmol scale and expressed with respect to Ti(O-*i*-Pr)$_4$. The starting material accounts for the remainder; sulfone was not detected unless stated. [d] Measured by the specific rotation of isolated sulfoxides with use of the maximum specific rotations given in ref 6 and 26. [e] Measured by ^{1}H NMR (250 or 400 MHz) with Eu(hfmc)$_3$ or (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-1-phenylethylamine.[27] [f] In addition there is 15% sulfone. [g] unless stated. [h] $[\alpha]^{20}_D$ in $CHCl_3$. [i] $[\alpha]^{20}_D$ in $EtOH_{96}$. [j] $[\alpha]^{20}_D$ in MeOH. [k] Reaction as *a* but with (*S*,*S*)-diethyl tartrate.

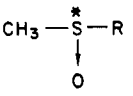
Table II. Effect of Alkyl Chain on the Asymmetric Oxidation of Alkyl Aryl Sulfides into



R	Ar	reaction conditions	yield, %	$[\alpha]^{20}_D$ (in acetone[e])	ee, % (configuration)
CH_3	*p*-tolyl	−20 °C, 4 h[a]	90	+132° (*c* 2)	90[c,d] (*R*)
CH_3CH_2	*p*-tolyl	−20 °C, 3 h[b]	71	+139.4° (*c* 1.3)	74[c] (*R*)
$CH_3(CH_2)_3$	*p*-tolyl	−20 °C, 3 h[b]	75	+38° (*c* 1.2)	20[c] (*R*)
$(CH_3)_2CH$	*p*-tolyl	−20 °C, 3 h[b]	56	+111° (*c* 2.6)	63[c] (*R*)
$C_6H_5CH_2$	*p*-tolyl	−20 °C, 12 h[b]	41	+17.5° (*c* 1)	7[c] (*R*)
CH_3	2-naphthyl	−20 °C, 4 h[a]	88	+120° (*c* 2)[f]	90[d]
$CH_3(CH_2)_2$	2-naphthyl	−21 °C, 12 h[a]	78	+39° (*c* 1)	24[d]

[a] As in footnote *a* in Table I. [b] As in footnote *b* in Table I. [c] Measured by the specific rotation of isolated sulfoxides with use of the maximum specific rotations given in ref 6. [d] Measured by NMR as in footnote *e* in Table I. [e] Unless stated. [f] $[\alpha]^{20}_D$ in $CHCl_3$.

Table III. Asymmetric Oxidation of Alkyl Methyl Sulfides into



R	reaction conditions[a]	yield, %	$[\alpha]^{20}_D$ (in acetone)	ee,[c] % (configuration)
$CH_3(CH_2)_7$	−21 °C, 64 h	77	−44° (*c* 0.5)	71
$C_6H_5(CH_2)_3$	−21 °C, 60 h	84	−29° (*c* 3.9)	50
cyclohexyl	−21 °C, 18 h	67	−44.3° (*c* 1.4)	54
tert-butyl	−21 °C, 22 h	72	−2.1° (*c* 1.5)	53 (*R*)
$C_6H_5CH_2$	−20 °C, 4 h	88	−33.6° (*c* 3)[b]	58 (*S*)
p-$OMeC_6H_4CH_2$	−20 °C, 15 h	40	−25.5° (*c* 1.3)	not determined
CH_3CH_2-$CH(CH_3)$	−21 °C, 24 h	93[d]	−12° (*c* 0.5)	42 and 38, respectively

[a] As noted in footnote *a* in Table I. [b] $[\alpha]^{20}_D$ in $EtOH_{96}$. [c] Measured by NMR as in footnote *e* in Table I. [d] Two diastereomers in the ratio 40:60.

for the direct oxidation of a variety of sulfides into optically active sulfoxides, with an ee often in the range of 80–90%. Initially, we tried to oxidize the sulfides by using the Sharpless reagent for asymmetric epoxidation of allylic alcohols[15] and we selected the methyl *p*-tolyl sulfide **1** as a model substrate. The standard Sharpless reagent[15,16] Ti(O-*i*-Pr)$_4$/(*R*,*R*)-diethyl tartrate (DET)/*t*-BuOOH (TBHP) (1:1:2 in CH_2Cl_2, −20 °C) leads to racemic methyl *p*-tolyl sulfoxide **2** (41%) and methyl *p*-tolyl sulfone (17%). However, we found that the combination Ti(O-

(11) Oxidation in the presence of bovin serum albumin (ee up to 81%): Sugimoto, T.; Kokubo, T.; Miyazaki, J.; Tanimoto, S.; Okano, M. *Bioorg. Chem.* **1981**, *10*, 311.

(12) Oxidation using microorganisms (ee up to 99%): (a) Auret, B. J.; Boyd, D. R.; Henbest, H. B.; Koss, S. *J. Chem. Soc. C* **1968**, 2371. (b) Abushanab, E.; Reed, D.; Suzuki, F.; Sih, C. J. *Tetrahedron Lett.* **1977**, 3415.

(13) Methyl phenyl sulfide could be oxidized into sulfoxide (48% ee) by a monoperoxomolybdenum complex bearing two chiral phenylhydroxamato ligands (Sharpless, K. B.; Current, S., 1976, unpublished results).

(14) Electrochemical oxidation of cyclohexyl phenyl sulfide (54% ee) with platinum electrode modified by poly(L-valine): Komori, T.; Nonaka, J. *J. Am. Chem. Soc.* **1983**, *105*, 5690.

(15) (a) Sharpless, K. B.; Katsuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464. (c) Sharpless, K. B.; Hill, J. G.; Rossiter, B. E. *J. Org. Chem.* **1983**, *48*, 3607.

(16) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55*, 1823.

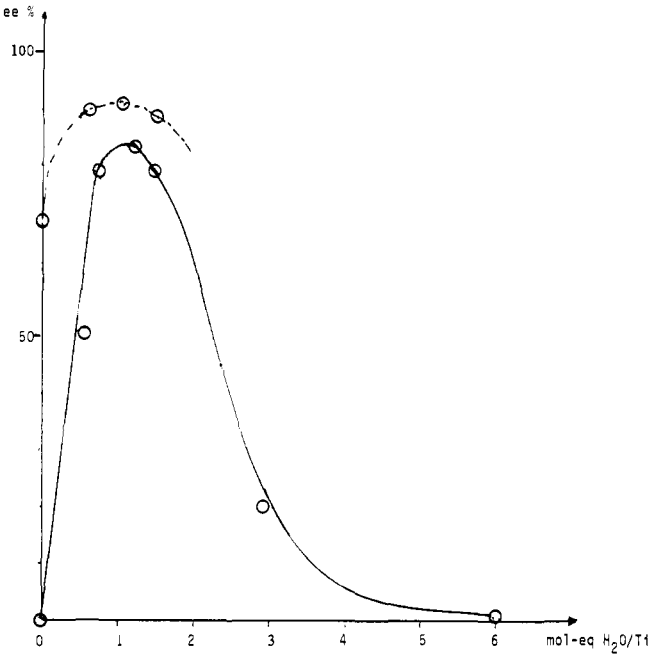


Figure 1. Influence of water in the asymmetric oxidation of methyl *p*-tolyl sulfide (experimental conditions of Table I, footnote *b*, −20 °C): DET/Ti(O-*i*-Pr)$_4$ = 1, curve A (—); DET/Ti(O-*i*-Pr)$_4$ = 2, curve B (- - -).

i-Pr)$_4$/(*R*,*R*)-DET/H_2O/TBHP (1:(1 or 2):1:2) dramatically changes the enantiomer composition, 84 or 90% ee respectively for **2**, at −20 °C. The chemical yield is satisfactory (90%), and sulfone formation is avoided.[17]

The experimental procedure is very simple, and the sulfoxide is isolated after hydrolysis and filtration (see Experimental Section). The method can be applied to the oxidation of many sulfides without sulfone formation, even with excess TBHP. Results are summarized in Tables I–III.

The reagent is prepared in dichloromethane at room temperature with the sequential addition of Ti(O-*i*-Pr)$_4$, diethyl tartrate, and water. It is crucial to add water at the end; a reverse order will lead to a precipitate (presumably TiO_2). Thus a perfectly soluble species is obtained; the yellow solution can then be used at the desired temperature. The same results (chemical yield and e.e.) are obtained with 1.1 or 2 mol equiv of TBHP.

Water Influence on the Stereoselective Oxidation

A systematic investigation of the effect of water content on the oxidation of methyl *p*-tolyl sulfide **1** at −20 °C shows an interesting phenomena for the combination Ti(O-*i*-Pr)$_4$/(*R*,*R*)-DET/H_2O/TBHP (1:1:*x*:2), where *x* was changed from 0 to 6. Curve A of Figure 1 reveals an optimum for *x* = 1 (84% ee). Racemic sulfoxide is obtained both for x = 0 and x = 6. The chemical yield is poor (29%) in this last case, and there is some precipitation of titanium dioxide. In all the other experiments chemical yield remains good and sulfone formation (17%) was only observed in anhydrous conditions (x = 0).

Another set of experiments is indicated in Figure 1 (curve B): it involves a reagent containing 2 mol equiv of diethyl tartrate per Ti(O-*i*-Pr)$_4$. Without water this system is quite efficient (formation of sulfoxide **2** with 70% ee), addition of water also gives here a strong increase in the optical yield (up to 90% ee). In anhdyrous conditions 3 mol equiv of diethyl tartrate per Ti(O-*i*-Pr)$_4$ leads to 82% ee for asymmetric oxidation of **1**. Since it gives the best results for the stereoselective oxidation of methyl *p*-tolyl sulfide, the combination Ti(O-*i*-Pr)$_4$/(*R*,*R*)-DET/H_2O. (1:2:1) was used all through our work. Most of the time 1.1 mol equiv of TBHP allows to get satisfactory yields. In conclusion, a useful reagent for the selective asymmetric sulfide–sulfoxide oxidation has been obtained by introduction of a controlled amount of water.

(17) Preliminary account: Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, 1049.

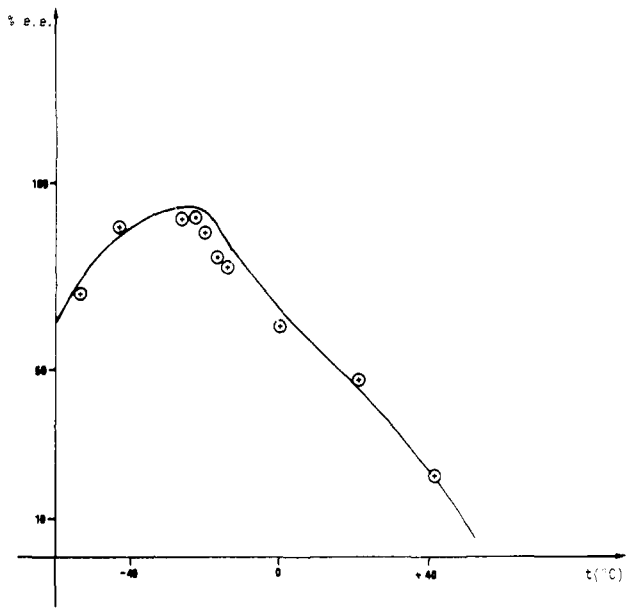


Figure 2. Influence of temperature in the asymmetric oxidation of methyl *p*-tolyl sulfide by reagent Ti(O-*i*-Pr)$_4$/(+)-DET/H_2O/*t*-BuOOH = 1:2:1:2.

Asymmetric Oxidation of Sulfides

Our new reagent (1:2:1:1.1 stoichiometry) was used to oxidize many sulfides in 5-mmol scale at −20 °C under the conditions described in the experimental section. It was observed that the series aryl methyl sulfoxide (Table I) give predominantly ee in the range 80–90%. The highest ee's (~90%) were observed for the oxidation of several sulfides (entries 1, 2, 5, 7). A methoxy group in ortho or para position gives the same e.e. (entries 8 and 10). However a CO_2Me function in the ortho position leads to a strong decrease in the enantiomeric excess by respect to the para substitution (entries 5 and 6). The optically active 2-pyridyl and 4-pyridyl methyl sulfoxides (entries 14 and 15) could not be compared because we failed to measure the ee of methyl 4-pyridyl sulfoxide. In the series alkyl aryl sulfide (Table II) the optimum ee is obtained when alkyl = Me. The decrease in ee is especially strong for a *n*-butyl or a benzyl substituent while an isopropyl group gives a better result (63% ee in the case of isopropyl *p*-tolyl sulfoxide). We have studied some dialkyl sulfides (Table III). Appreciable enantiomeric excesses were observed, the best one being 71% for methyl octyl sulfoxide. It is interesting to see that *tert*-butyl methyl sulfoxide was formed with a lower optical purity (53% ee). These results show the usefulness of our method since it is not easy to obtain highly optically active dialkyl sulfoxides by standard methods. It is interesting to see that the reagent allows the clean oxidation of many types of functionalized sulfides: phenolic OH, CO_2Me, CH_2OH, nitro, and pyridyl groups do not interfere in the reaction. Ester group functions (entries 5 and 6 of Table I) can be used and no transesterification was observed in the corresponding sulfoxides. Either enantiomer of sulfoxides can be obtained by the choice of the absolute configuration of diethyl tartrate (see in Table I the case of *p*-methoxyphenyl methyl sulfoxide, entries 8 and 9). The scale up of the reactions allows easily the preparation of large quantities of chiral sulfoxides. The use of diisopropyl tartrate as ligand does not change the results obtained with DET.

Influence of Temperature

The oxidation of methyl *p*-tolyl sulfide by the reagent Ti(O-*i*-Pr)$_4$/(*R*,*R*)-DET/H_2O/TBHP (1:2:1:2) between −54 °C and +41 °C was undertaken to study the temperature dependence on ee. Unexpectedly, it showed an optimum of ee around −21 °C (Figure 2). Such behavior is indicative of a change of mechanism

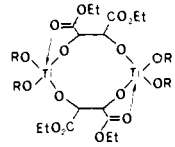


Figure 3. Sharpless reagent for epoxidation of allylic alcohols:[16] Ti(O-*i*-Pr)$_4$ + tartrate (1:1).

and was sometimes observed in asymmetric synthesis.

There is a good linear correlation[18] between ln {(1 + ee)/(1 − ee)} and $1/T$, between +41 °C and −20 °C, in support for a preferential mechanism. It is surprising to see a change of enantioselectivity around −22 °C. We will come back to this point after the discussion of the structure of the species responsible for the stereoselective oxidation.

Structure of the Modified Reagent

The structure of the Sharpless reagent Ti(O-*i*-Pr)$_4$/DET/TBHP (1:1:2) is not yet completely known. It has been assumed[16] that it is a dimer with alcohol exchanges giving two tartrate units acting as bridges between the two metal centers (Figure 3). An infrared spectrum in dichloromethane in the region 1800–1600 cm^{-1} shows two ester bands (1735 cm^{-1} free; 1635 cm^{-1} chelated).[16] We found that in the presence of 2 equiv of DET per Ti(O-*i*-Pr)$_4$ the infrared absorptions of the complex are at 1745 and 1675 cm^{-1}. This last species is not active for the asymmetric epoxidation of allylic alcohols[15] but allows efficient asymmetric oxidation of sulfides. After the controlled addition of 1 equiv of water to Ti(O-*i*-Pr)$_4$ + DET (1:1), the initial two-band system (1735, 1635 cm^{-1}) is immediately transformed into a new one (1745, 1675 cm^{-1}), almost superimposable on the one obtained with 2 equiv of DET vs. Ti(O-*i*-Pr)$_4$. It appears that similar species have been obtained and, indeed, the two reagents (Ti/DET, 1:2 and Ti/DET/H_2O, 1:1:1) are stereoselective in asymmetric oxidation of methyl *p*-tolyl sulfide. Our assays show that the combination Ti(O-*i*-Pr)$_4$/DET/H_2O (1:2:1) gives the highest ee (see Figure 1).

In conclusion, the presence of a band of the chelated ester at 1675 cm^{-1} seems well correlated with a high enantioselectivity of the reagent. In all cases further introduction of methyl *p*-tolyl sulfide does not change the IR spectra while addition of the corresponding sulfoxide **2** slightly displaces the band of the chelated ester (ν(CO)).

The effect of 1 mol equiv of water and 1 (or more) mol equiv of diethyl tartrate, clearly seen by infrared and by the change in ee, is also easily detected by a strong increase with time of the optical activity of the reaction medium (because of high specific rotation of methyl *p*-tolyl sulfoxide). Experiments were devised at 20 °C in a polarimeter cell. Figure 4a shows the variation or rotation with progressive addition of (*R*,*R*)-diethyl tartrate to Ti(O-*i*-Pr)$_4$. An immediate change occurs after each addition, with a stabilization of the rotation after addition of almost 3 equiv of DET. Formation of complexes occurring by isopropyl alcohol displacement seems total at this stage, indicative of a 1:3 complex or a 1:2 complex where the equilibrium is shifted by the excess of DET. The oxidation of methyl *p*-tolyl sulfide could be easily followed at 20 °C in a polarimeter cell. The evolution of the optical activity for the oxidation of methyl *p*-tolyl sulfide is described in Figure 4b, for the reagents Ti(O-*i*-Pr)$_4$/(+)DET/*t*-BuOOH (1:1:2) and Ti(O-*i*-Pr)$_4$/(+)DET/H_2O/*t*-BuOOH (1:1:1:2). Addition of the sulfide to the reagent does not change the optical activity. The addition of *t*-BuOOH develops a strong positive rotation for the water modified reagent, which is indicative of the formation of (*R*)-methyl *p*-tolyl sulfoxide.

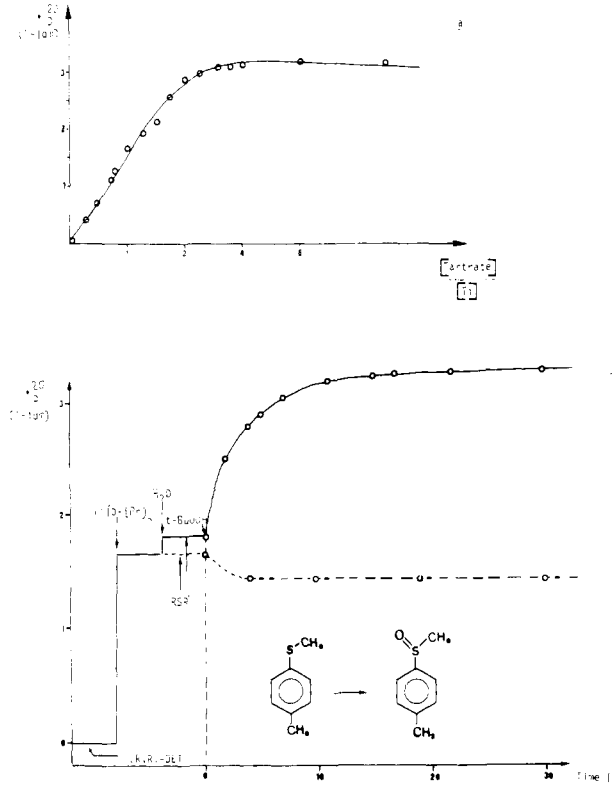
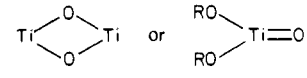


Figure 4. (a) Variation in optical activity by addition of (*R*,*R*)-diethyl tartrate to Ti(O-*i*-Pr)$_4$ in CH_2Cl_2 ([Ti] = 10^{-1} M). (b) Variation of optical activity during oxidation of **1** ((—) 1 mol equiv of H_2O; (- - -) anhydrous conditions). A part from temperature, the experimental conditions are those of Table I, footnote *b*.

From the forgoing discussion it can be concluded that the classical Sharpless reagent (Ti/DET = 1:1) is transformed into a new species by controlled addition of water. It is unlikely that the water molecule acts as ligand since it is well-known that titanium alcoholates are hydrolyzed stepwise ultimately leading to titanium dioxide.[20] The first steps of the process are the formation of Ti–OH and then T–O–Ti bonds. One working hypothesis on the effect of water is that the addition of 1 equiv of water into the Sharpless reagent of Figure 3 hydrolyzes a Ti–O–*i*-Pr bond with further formation of a μ-oxo bridge between two dimers (Ti–O–Ti). In order to make full use of the water which is introduced it is likely that several μ-oxo bridges are established leading to a polymeric active species. We do not favor unusual complexes of the type



because of rareness of literature data on such complexes.[21] In the oxidant reagent the *tert*-butyl peroxide could substitute one alkoxy ligand and stay as a dihapto ligand since it was recently established that a vanadium peroxo complex had a dihapto structure.[22]

The structure of the reagent with the stoichiometry 1:1:1 (Ti/DET/H_2O) seems close to the one with the stoichiometry 1:2:0, on the basis of the infrared spectra. A common feature of these two reagents is the high OH/Ti ratio compared to the stoichiometry necessary for the epoxidation of allylic alcohols (2OH/Ti). For oxidation of sulfides, no vacant exchangeable site

(18) A least-squares fit gives a correlation coefficient of 0.979 and the following equation: ln (1 + ee)/(1 − ee) = $1142/T - 3.47$. By making the usual and oversimplified assumption[19] that (1 + ee)/(1 − ee) approximates the ratio k_R/k_S of the rate constants of two competitive reactions (leading respectively to (*R*) and (*S*) enantiomers), the equation allows the calculations of differences in activation parameters. $\Delta\Delta H^{\ddagger}_{R/S}$ = −5.2 kcal mol^{-1}, $\Delta\Delta S^{\ddagger}_{R/S}$ = −16.0 cal mol^{-1} deg^{-1}. The preferred pathway which is under enthalpic control is characterized by a much lower activation entropy, indicative of a highly organized transition state.

(19) Izumi, Y.; Tai, A. "Stereo-differentiating Reactions"; Academic Press: New York, 1977; p 183.

(20) Bradley, D. C.; Mehrotra, R. C.; Gaur, D. P. "Metal alkoxides"; Academic Press, London, New York, 1978.

(21) Monomeric titanyl complexes are known in some cases; see, for example: Fournari, P.; Guilard, R.; Fontessi, M.; Latour, J. M.; Marchon, J. C. *J. Organomet. Chem.* **1976**, *110*, 205 and references quoted therein.

(22) Mimoun, A.; Chaumette, P.; Mignard, M.; Saussine, L. *Nouv. J. Chim.* **1983**, *7*, 467.

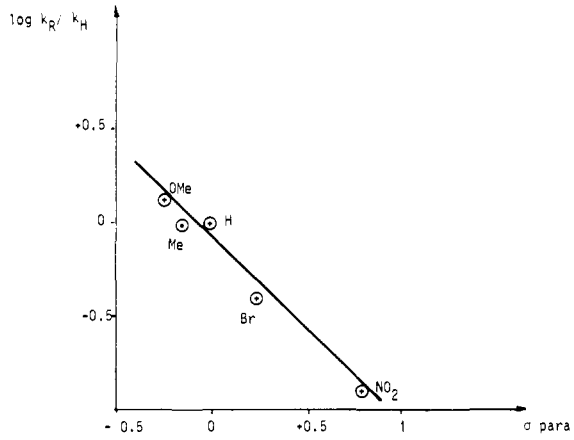


Figure 5. Hammett plot for the oxidation of p-R-$C_6H_4SCH_3$ by the water-modified reagent (−20 °C, ρ = −1.02).

on titanium is necessary. More work is necessary to come closer to the structure of the modified reagents. Several attempts were made to use other chiral ligands than DET. When 2 equiv of (−)-menthol were used, $[\alpha]^{20}_D$ of the solution (1 dm) of menthol goes from −1.27° to −2.45° after addition of Ti(O-*i*-Pr)$_4$. The reagent Ti(O-*i*-Pr)$_4$/menthol/H_2O/TBHP (1:2:1:2) oxidized **1** at −20 °C in 95% yield, to give (*R*)-**2** almost racemic (ee 0.6%).

The use of a chiral ester monoalcohol like (*S*)-ethyl lactate led to similar results: the reagent (1:2:1:2) gave only 1.3% ee in (*R*)-**2**. The replacement of the ester functions of DET by amides ((*R*,*R*)-tetramethyltartramide) gives a complex with Ti(O-*i*-Pr)$_4$: the $[\alpha]^{20}_D$ (l = 1 dm) goes from −1.02° to +2.70°). The oxidation of **1** with the reagent 1:1:1:2 is chemically and stereoselectively not very satisfactory: (*S*)-**2** is obtained in 60% yield after 72 h at +5 °C with 1.6% ee.

Mechanism of the Reaction

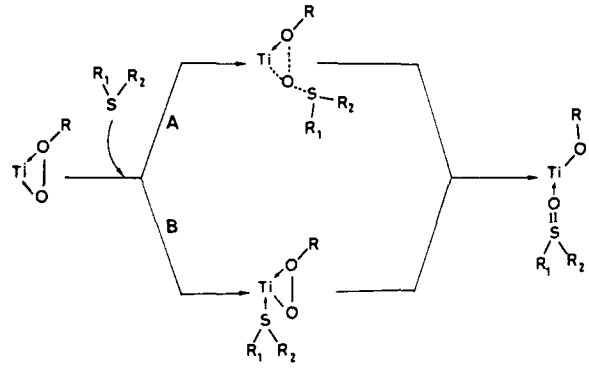
Competitive experiments between methyl phenyl sulfide and various para-substituted derivatives were carried out. A Hammett correlation log (k_R/k_H) = $\rho\sigma$ was obtained (Figure 5) with a negative ρ value (−1.02). This value is indicative of an electrophilic attack on sulfur and is close to the ρ values obtained in the sulfide oxidation by H_2O_2 or benzoyl peroxide (−1.17 and −1.30).[23]

In order to accommodate these data two mechanisms could be considered (Scheme I): external attack on the sulfur by the chiral titanium hydroperoxide (path A) or coordination of sulfur to titanium prior to the oxidation (path B). In both cases it is not necessary to have a site on titanium with an exchangeable alkoxy group, as was the case for the epoxidation of allylic alcohols.[15] Distinction between paths A and B could not be experimentally established since there was no modification detected on the infrared absorptions or the optical rotation of the reagent after sulfide addition (vide supra). These experiments do not eliminate path B involving coordination of the sulfide as the slow step followed by a fast intermolecular oxidation.

Coordination of sulfides to Ti(IV) (path B) is not an unlikely process, and various titanium complexes with sulfide ligands have been identified.[24,25] On the other side the negative ρ value, close to the one observed for oxidation by H_2O_2 or benzoyl peroxide where external attack is the only process, favors path A. It can be also accommodated by path B if the coordination is the rate-determinng step (although no ρ values are available in literature for comparison).

It is interesting to note that asymmetric induction occurs in path B at the coordination stage (the sulfur atom becomes chiral) while in path A the oxidation directly creates the asymmetry at

Scheme I. Tentative Mechanisms for the Oxidation of Sulfides by *t*-BuOOH and Titanium Complexes



sulfur. The temperature effect could be tentatively interpreted by a change of mechanism, path A being predominant above −20 °C and path B being competitive at lower temperaures (or vice versa).

It appears that there is a good correlation between the steric bulkiness of groups in the families of sulfides and the absolute configuration and ee. It is then possible to use the model of Scheme II to predict the results of many asymmetric oxidations of sulfides when (+)-DET is the chiral ligand. This model is consistant with the decrease in optical yield in the family Ar-*S*-alkyl ($CH_3 > CH_2CH_3 > CH_2CH_2CH_2CH_3$) where (*R*)-sulfoxides are obtained. It is also in agreement with the formation of (*R*)-aryl methyl sulfoxides where Ar stands for many types of aromatic rings. It seems very likely that the aryl alkyl sulfoxides obtained in Tables I and II, for which absolute configurations were unknown, can be assigned to the (*R*) configuration on the basis of the model of Scheme II.

The modification of the experimental procedure in order to set up a catalytic system faces the problem of the inhibition effect of sulfoxides, which are known to be good ligands for titanium alcoholates.[20] The reagent Ti(O-*i*-Pr)$_4$/DET/H_2O/TBHP (1:2:1:2) at room temperature for 1 h does not visibly oxidize sulfide **1** when 1 equiv of sulfoxide **2** was previously added. A catalytic assay using 0.25 equiv of the titanium reagent (with 1.1 equiv of TBHP) showed a very slow oxidation of methylphenyl sulfide: after 1 week at −21 °C a 65% yield of sulfoxide was isolated, thus representing a turnover of 2.6 for the titanium species. However, the optical yield of methyl phenyl sulfoxide lowered to 53% (instead of the expected 90%), suggesting the competition of an achiral oxidation mechanism. It was also shown that TBHP, in the absence of titanium alkoxides, can oxidize sulfides at a slow rate at −20 °C. Comparative assays at −20 °C establish that our titanium reagent Ti(O-*i*-Pr)$_4$/DET/H_2O (1:2:1) accelerates the TBHP oxidation rate of methyl phenyl sulfide by a factor of 150.

Conclusion

It is interesting to see that prochiral sulfides which are not able to chelate on titanium lead to very high enantioselectivities. The oxidation system that we describe is a significant improvement compared to the previous chiral reagents for sulfide oxidation. It allows the clean oxidation of many types of aryl alkyl sulfides into the corresponding sulfoxides with ee in the range 80–90% in a predictable manner. It applies also to the asymmetric oxidation of dialkyl sulfides. The method seems promising and flexible enough to obtain directly functionalized chiral sulfoxides useful in various synthetic schemes,[1-4] and to prepare new chiral synthons. We are currently investigating this field as well as the extension of the method to the asymmetric oxidation of other heteroatoms.

Experimental Section

Apparatus. ^1H NMR spectra were recorded on Perkin-Elmer Model R 32 90 MHz, Brucker 400 MHz, and Cameca 200 MHz spectrometers. IR spectra were obtained by using a Perkin-Elmer 237 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

(23) (a) Modena, G.; Maioli, L. *Gazz. Chim. Ital.* **1957**, 87, 1306. (b) Pryor, W. A.; Hendrickson, W. H., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 7114.
(24) Bortolini, O.; Di Furia, F.; Modena, G. *J. Mol. Catal.* **1983**, *16*, 61. Bortolini, O.; Campello, C.; Di Furia, F.; Modena, G. *J. Mol. Catal.* **1982**, *14*, 63.
(25) Fowles, G. W. A.; Rice, D. A.; Wilkins, J. D. *J. Chem. Soc. A*, **1971**, 1920.

Scheme II. Model for the Prediction of Absolute Configuration of Sulfoxides in Asymmetric Oxidation of Sulfides

Chemicals. CH_2Cl_2 was purified by treatment with basic alumina, distilled over calcium hydride, and stored under nitrogen. TBHP solutions in CH_2Cl_2 were prepared according to ref 15 and stored over molecular sieves under nitrogen. TBHP solution in toluene was prepared according to ref 15c. Silica gel (Merck, Kieselgel 60) was used for column chromatography. (+)- and (−)-diethyl tartrate ((+)- or (−)-DET) was purchased from the Aldrich Co. Ti(O-*i*-Pr)$_4$ and Eu(hfc)$_3$ were obtained from Fluka. These reagents were used as such, and both were stored under anhydrous conditions. Sulfides were prepared according to the literature by alkylation of the corresponding thiols.

Asymmetric Oxidation. The procedure for sulfide oxidation is exemplified in the case of methyl *p*-tolyl sulfide. Ti(O-*i*-Pr)$_4$ (1.49 mL, 5 mmol) and (*R*,*R*)-DET (1.71 mL, 10 mmol) are dissolved at room temperature in 50 mL of CH_2Cl_2 under nitrogen. H_2O (5 mmol) is introduced through a spectrum via a microsyrynge. Stirring is maintained until the yellow solution becomes homogeneous (15–20 min) and sulfide (0.7 g, 5 mmol) is added. The solution is cooled to −20 °C or at the desired reaction temperature, and 5.5 mmol of a TBHP solution in CH_2Cl_2 (≃2 M) or toluene (≃3.6 M) are then introduced. After reaction, water (10 mol equiv) is added dropwise by a microsyringe to the solution at −20 °C. A strong stirring was maintained for 1 h at −20 °C and for one additional hour at room temperature. The white gel is filtered (a small amount of alumina added to the solution helps the filtration) and thoroughly washed with CH_2Cl_2. The filtrate is kept in the presence of NaOH (5%) and brine for 1 h and then separated. The organic phase is dried over Na_2SO_4 and concentrated to give the crude product, which does not contain sulfone. Chromatography (AcOEt, cyclohexane 1:1) on silica gel gives 0.70 g (90%) of methyl *p*-tolyl sulfoxide: $[\alpha]^{20}_D$ +131° (*c* 2, acetone) (lit.[6] data for enantiomerically pure (*R*)-sample: $[\alpha]^{20}_D$ +145.5° (acetone)). Enantiomeric excess was calculated to be 90% ee and confirmed by ^{1}H NMR (400 MHz) with a new chiral shift reagent.[27] The present procedure is an improvement of the one that was previously reported.[17]

For benzylic sulfoxides or sulfoxides bearing ester functions a modification of the workup is necessary. After the filtration the solution was washed only with brine. The experiments of Figure 3 were performed with use of 2 equiv of TBHP with respect to Ti(O-*i*-Pr)$_4$.

All the sulfoxides were isolated and characterized by the usual spectral methods. The careful drying of the sulfoxides is necessary before the measurement of optical rotation. The ee measurements were performed on freshly obtained samples. It is known that some sulfoxides can racemize slowly with time (e.g., for benzylic sulfoxides). We observed in the specific case of the methyl *p*-nitrophenyl sulfoxide a slow racemization with time. The oxidation on 40-mmol scale was done with 8.12 g of *p*-bromophenyl methyl sulfide at −21 °C for 24 h, following the same conditions as described above. The corresponding sulfoxide (6.66 g) was obtained in 76% yield and 80% optical purity.

Acknowledgment. We thank CNRS for its financial support. Two of us (P.P. and M.N.D.) acknowledge DGRST and IFP fellowships, respectively. We thank Professor K. B. Sharpless for useful discussions and communication of unpublished data.

Registry No. 1, 623-13-2; (*R*)-**2**, 1519-39-7; $C_6H_5SCH_3$, 100-68-5; (*R*)-$C_6H_5S(O)CH_3$, 4850-71-9; *p*-$BrC_6H_4SCH_3$, 104-95-0; (*R*)-*p*-$BrC_6H_4S(O)CH_3$, 28227-62-5; *p*-$ClC_6H_4SCH_3$, 123-09-1; (*R*)-*p*-$ClC_6H_4S(O)CH_3$, 28227-63-6; *p*-$(MeO_2C)C_6H_4SCH_3$, 3795-79-7; (*R*)-*p*-$(MeO_2C)C_6H_4S(O)CH_3$, 93303-91-4; *o*-$(MeO_2C)C_6H_4SCH_3$, 3704-28-7; (*R*)-*o*-$(MeO_2C)C_6H_4S(O)CH_3$, 4850-73-1; *p*-$MeOC_6H_4SCH_3$, 1879-16-9; (*R*)-*p*-$MeOC_6H_4S(O)CH_3$, 93381-75-0; (*S*)-*p*-$MeOC_6H_4S(O)CH_3$, 93381-76-1; *o*-$MeOC_6H_4SCH_3$, 2388-73-0; (*R*)-*o*-$MeOC_6H_4S(O)CH_3$, 84413-74-1; *p*-$O_2NC_6H_4SCH_3$, 701-57-5; (*R*)-*p*-$O_2NC_6H_4S(O)CH_3$, 93222-06-1; *p*-$HOC_6H_4SCH_3$, 1073-72-9; (*R*)-*p*-$HOC_6H_4S(O)CH_3$, 93183-65-4; *p*-$(HOCH_2)C_6H_4SCH_3$, 3446-90-0; (*R*)-*p*-$(HOCH_2)C_6H_4S(O)CH_3$, 93183-64-3; *p*-$CH_3C_6H_4SCH_2CH_3$, 622-63-9; (*R*)-*p*-$CH_3C_6H_4S(O)CH_2CH_3$, 1519-40-0; *p*-$CH_3C_6H_4S(CH_2)_3CH_3$, 21784-96-3; (*R*)-*p*-$CH_3C_6H_4S(O)(CH_2)_3CH_3$, 20288-49-7; *p*-$CH_3C_6H_4SCH(CH_3)_2$, 14905-81-8; (*R*)-*p*-$CH_3C_6H_4S(O)CH(CH_3)_2$, 1517-74-4; *p*-$CH_3C_6H_4SCH_2C_6H_5$, 5023-60-9; (*R*)-*p*-$CH_3C_6H_4S(O)CH_2C_6H_5$, 4820-07-9; $CH_3(CH_2)_7SCH_3$, 3698-95-1; (−)-$CH_3(CH_2)_7S(O)CH_3$, 93183-63-2; $C_6H_5(CH_2)_3SCH_3$, 87231-07-0; (−)-$C_6H_5(CH_2)_3S(O)CH_3$, 93183-67-6; $(CH_3)_3CSCH_3$, 6163-64-0; (*R*)-$(CH_3)_3CS(O)CH_3$, 20580-80-7; $C_6H_5CH_2SCH_3$, 766-92-7; (*S*)-$C_6H_5CH_2S(O)CH_3$, 14090-81-4; *p*-$MeOC_6H_4CH_2SCH_3$, 5925-86-0; (−)-*p*-$MeOC_6H_4CH_2S(O)CH_3$, 93303-92-5; (±)-$CH_3CH_2CH(CH_3)SCH_3$, 64693-06-7; $CH_3CH_2CH(CH_3)S(O)CH_3$ (isomer 1), 93527-27-6; $CH_3CH_2CH(CH_3)S(O)CH_3$ (isomer 2), 93527-28-7; 2-(methylthio)-naphthalene, 7433-79-6; (*R*)-2-(methylsulfinyl)naphthalene, 18690-03-4; 2-(methylthio)pyridine, 18438-38-5; (*R*)-2-(methylsulfinyl)pyridine, 93183-62-1; 4-(methylthio)pyridine, 22581-72-2; (*R*)-2-(methylsulfinyl)pyridine, 93381-77-2; 2-(propylthio)naphthalene, 75052-54-9; (*R*)-2-(propylsulfinyl)naphthalene, 93381-78-3; (methylthio)cyclohexane, 7133-37-1; (−)-(methylsulfinyl)cyclohexane, 93183-66-5.

(26) Cooke, R. S.; Hammond, G. S. *J. Am. Chem. Soc.* **1970**, *92*, 2739.
(27) Deshmukh, M.; Dunach, E.; Jugé S.; Kagan, H. B. *Tetrahedron Lett.* **1984**, 3467.
(28) **Note Added in Proof**: A paper recently appeared (Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis*, **1984**, 325) which describes asymmetric oxidation of four aryl alkyl sulfides (ee from 14% till 88%) by *t*-BuOOH and Ti(O-*i*-Pr)$_4$/(DET) (1:4).
The structure of the Sharpless reagent has just been established by X-ray cristallography. This analogue has a structure similar to that shown in Figure 3 where each tartramide acts as a bidentate diolate to a titanium and there is a double bridging between the two titaniums through the tartramide alkoxy groups (K. B. Sharpless, private communication).

Acutiphycin and 20,21-Didehydroacutiphycin, New Antineoplastic Agents from the Cyanophyte *Oscillatoria acutissima*

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Received February 13, 1984

Abstract: The lipophilic extract of the freshwater blue-green alga *Oscillatoria acutissima* contains two novel macrolides, acutiphycin (**1**) and 20,21-didehydroacutiphycin (**2**), which exhibit cytotoxicity and antineoplastic activity. The structures and absolute stereochemistries of **1** and **2** have been determined by spectral studies and chemical degradation.

Blue-green algae, in particular those belonging to the Oscillatoriaceae, are potential sources of new antineoplastic agents.[1] The crude extract of *Oscillatoria acutissima*, for example, shows cytotoxicity against KB and NIH/3T3 cells and significant an-

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