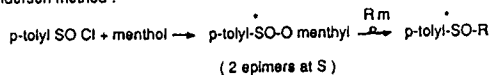
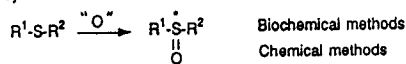


Methods

- 1°) Resolution of racemic sulfoxides
- 2°) Chemical transformation of a chiral sulfoxide (with stereochemical control at S)
- 3°) Andersen method:



- 4°) Asymmetric oxidation:



EXPERIMENTAL PROCEDURE

1°) PREPARATION OF THE REAGENT

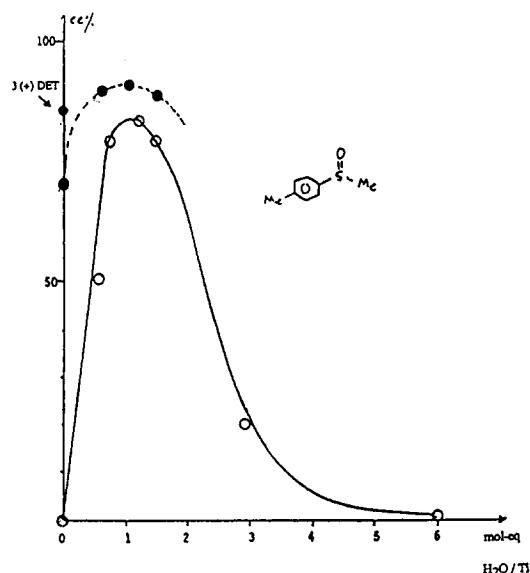
- $Ti(OiPr)_4 + (+)\text{-DET} (1:2) \xrightarrow{10^{-1}}$ in CH_2Cl_2
- H_2O is then introduced (after DET)
- $20^\circ C$ for 30 min

2°) OXIDATION

- Addition of sulfide
- Cooling at $-20^\circ C$
- Addition of 1.1 eq $t\text{-BuOOH}$
- Reaction time: a few hours.

References:

- Pitchen, P.; Dunach, E.; Deshmukh, M. N. and Kagan, H. B., *J. Am. Chem. Soc.*, 1984, **106**, 8188.
 Pitchen, P. and Kagan, H. B., *Tetrahedron Lett.*, 1984, **25**, 1049.
 Dunach, E. and Kagan, H. B., *New J. Chem* 1985, **9**, 1.
 Kagan, H. B.; Dunach, E.; Nemecek, C.; Pitchen, P.; Samuel, O. and Zhao, S. H., *Pure Appl. Chem.*, 1985, **57**, 1911.
 Nemecek, C., Dunach, E. and Kagan, H. B., *New J. Chem*, 1986, **10**, 761.
 Zhao, S.; Samuel, O. and Kagan, H. B., *C. R. Acad. Sci. Paris.*, 1987, **304**, II, 273.
 Zhao, S., Samuel, O. and Kagan, H. B., *Tetrahedron*, 1987, **43**, 5135.
 Kagan H. B., *Stereochemistry of Organic and Bioorganic Transformations, Proceedings of the Workshop Conference Hoechst, 17th 1986*; Bartmann, W., Sharpless, K. B., Eds.; VCH; Weinheim, Federal Republic of Germany, 1987; pp31-48.
 Samuel, O.; Ronan, B. and Kagan, H. B., *J. Organomet. Chem.*, 1989, **370**, 43.
 Zhao, S. H.; Samuel, O. and Kagan, H. B., *Organic Syntheses*, 1989, **68**, 49.
 For another Ti reagent see:
 Di Furia, F.; Modena, G. and Seraglia, R., *Synthesis*, 1984, 325.
 Bortolini, O.; Di Furia, F.; Modena, G. and Rossi, M., *Tetrahedron Lett.*, 1986, **27**, 6257.

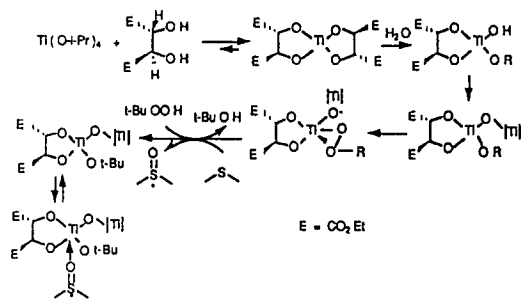


Influence of water in the asymmetric oxidation of methyl p-tolyl sulfide by $t\text{-BuOOH}$ at $-20^\circ C$. $DET / Ti(Oi-Pr)_4 = 1$: curve (---), $DET / Ti(Oi-Pr)_4 = 2$: curve (---).

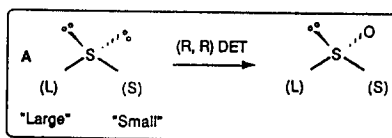
Asymmetric oxidation of aryl alkyl sulfides by $t\text{-BuOOH}$ and the reagent $(Ti(OiPr)_4)/(+)\text{-DET}/H_2O = 1:2:1^a$

Entry	Ar	R	Isolated yield (%)	ee(%) ^b
1	p-Tolyl	Methyl	90	89
2	p-Tolyl	Ethyl	71	74
3	p-Tolyl	n-Butyl	75	25
4	p-Tolyl	CH_2CO_2Me	81	64
5	p-Anisyl	Methyl	70	74
6	o-Anisyl	Methyl	58	86
7	1-Naphthyl	Methyl	98	89
8	2-Naphthyl	Methyl	88	90
9	2-Naphthyl	n-Propyl	78	24
10	Phenyl	Cyclopropyl	73	95
11	Phenyl	CH_2Cl	60	47
12	2-Pyridyl	Methyl	63	77

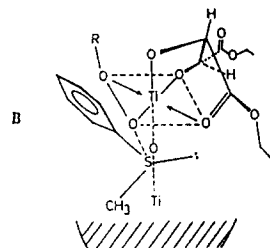
- a: Reaction performed at 5 mmol scale. (Sulfide)=(reagent)= $2 \cdot 10^{-1} M$ in CH_2Cl_2 at $-20^\circ C$.
- b: Measured by 1H NMR with $Eu(hfc)_3$ or (R)-(3,5-dinitrobenzoyl)-1-phenylethylamine. All sulfoxides have (R) configuration.



Tentative mechanism for asymmetric oxidation of sulfides with water-modified Ti reagent.



L = Ar S = alkyl
L = t-Bu S = n-alkyl
L = C≡C S = Me



SOME LIMITATIONS OF ASYMMETRIC OXIDATIONS WITH Ti / ROOH

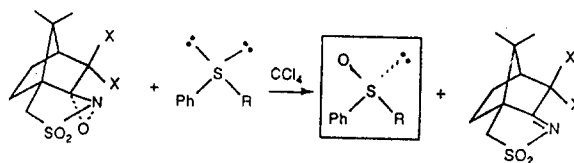
High ee (up to 95 %) only for aryl methyl sulfoxides

Low catalytic efficiency.

No chances to get high ee's for R¹-S(=O)-R² if R¹ very similar to R² (eg C₆ versus C₈).

No oxidation of diaryl sulfoxides.

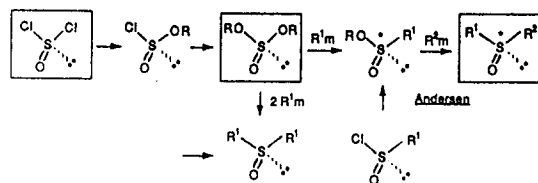
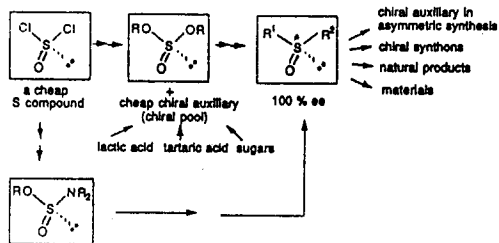
Asymmetric oxidation of sulfides by chiral oxaziridines



R = Me X = H 26 % ee
X = Cl 95 % ee

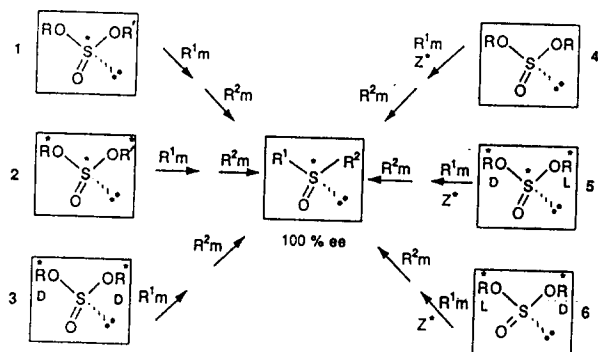
R = Cyclopropyl X = H 23 % ee
X = Cl 92 % ee

THE CONVERSION OF SULFITES TO CHIRAL SULFOXIDES IS IT POSSIBLE? IS IT A CONVENIENT AND GENERAL METHOD?

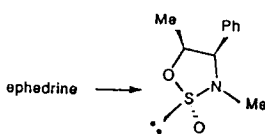


F. A. Davis et al.

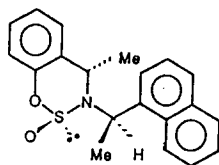
J. Am. Chem. Soc. 1989, 111, 5964.



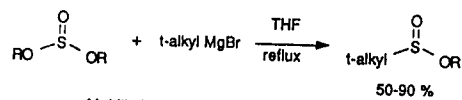
1, 2 : different leaving groups
 3 : diastereotopic leaving groups
 4-6 : enantiotopic leaving groups



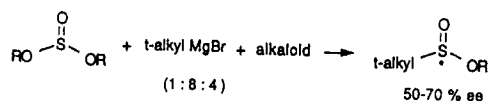
F. Wudl and T. B. K. Lu, *J. Am. Chem. Soc.*, 1979, 95, 6355.



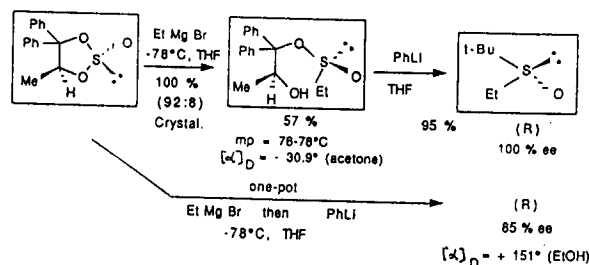
K. Hiroi, S. Sato, R. Kitayama, *Chem. Letters*, 1980, 1595.



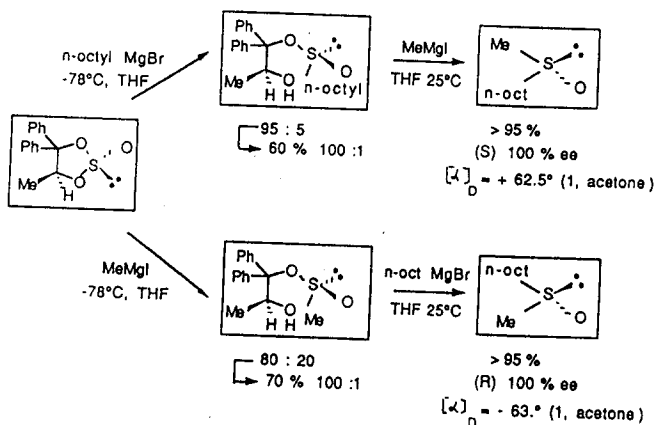
M. Mikolaczyk, J. Drabowicz
Synthesis, 1974, 124.



J. Drabowicz, S. Legedz, M. Mikolaczyk
Tetrahedron, 1988, 44, 5243.

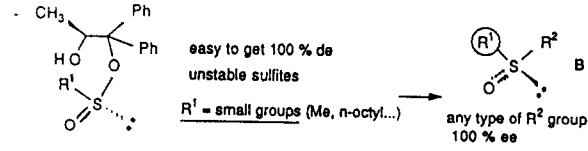
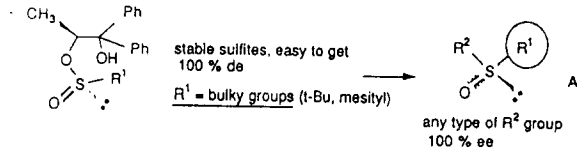


Rebierre, F.; Kagan, H.B.; *Tetrahedron Lett.*, 1989, 30, 3659.

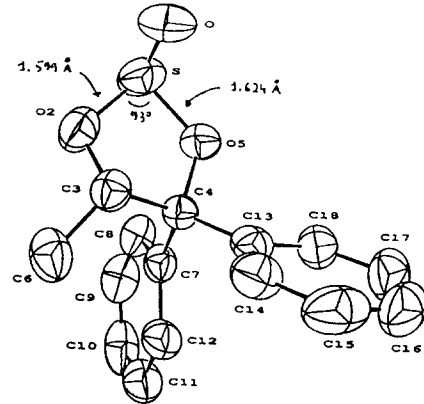


SOME PRACTICAL ASPECTS

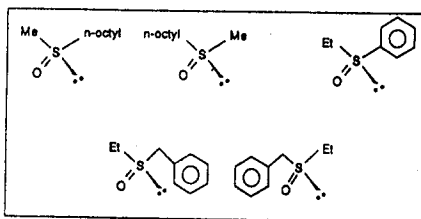
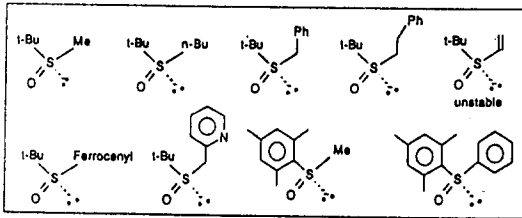
- All isolated sulfonates are crystalline compounds



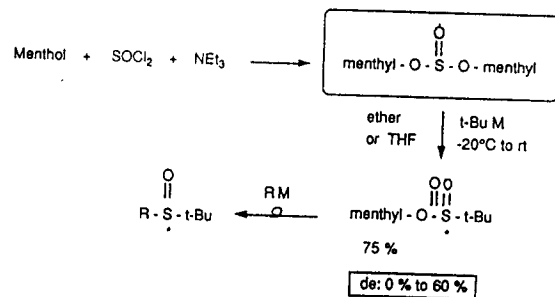
- To get enantiomer of A : permutation in introduction of R^1 and R^2 if R^1 is also a bulky, if R^1 is large and R^2 small the same enantiomer is recovered.
- To get enantiomer of B : permutation in introduction of R^1 and R^2 if both substituents are small.
- How to get enantiomer of A when one group is large and the other small ?
 Use of (R)-isobutyl lactate recently commercialized (Fluka) ! It gives the (R) cyclic sulfite.

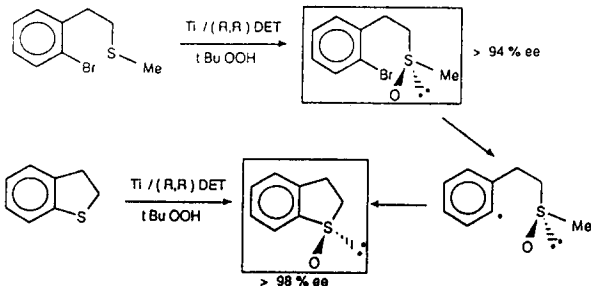


Some ep sulfonides prepared from (S) sulfite

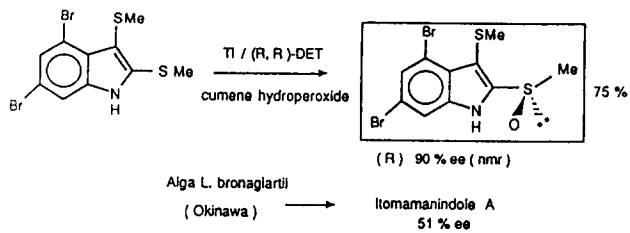


R^1 is on the left, R^2 is on the right, on the drawing





Beckwith and Boate, *J.C.S. Chem. Commun.* 1986, 189.

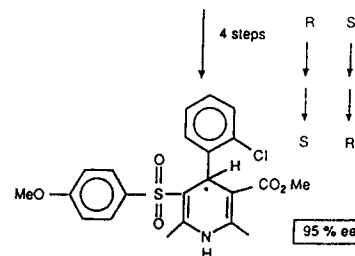
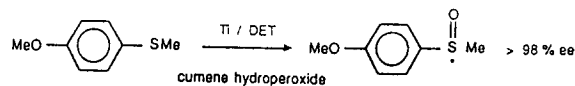


Alga *L. bronagiaritii*
(Okinawa)

Itomamanindole A
51% ee

J. Tanaka, T. Higo, G. Bernardinelli, C. W. Jefford
Tetrahedron Lett. 1988 29 6091

(R,R)-DET → (R)
(S,S)-DET → (S)

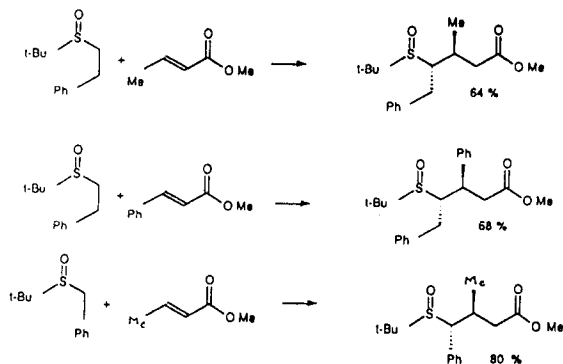


Cardiovascular drug

R. Davis, J. R. Pfister et al, (Syntex)
J. Am. Chem. Soc. 1988 110, 7873.

STEREoselective CONJUGATE ADDITIONS OF SULFOXIDE STABILIZED CARBANIONS TO α,β -UNSATURATED ESTERS

M. Casey et al.
Tetrahedron Lett. 1988 29, 5821.
Tetrahedron Lett. 1989 30, 6919.



CONCLUSION

ASYMMETRIC OXIDATION

- 1*) Many cases with 90-95% ee, especially for Ar-S-CH₃
- 2*) Alkyl-S-CH₃: ee < 80%
- 3*) Cumene hydroperoxide: best peroxide. reaction can be catalytic in Ti complex (0.2 to 0.5 eq.)
- 4*) Easy scale-up. Cheap chiral auxiliary. Can give access to both enantiomers.
- 5*) Limitations: inertness of diaryl sulfides.
sulfides with chelating groups: unpredictable results.

CHIRAL CYCLIC SULFITES

- 1*) Easy preparation of chiral sulfite.
- 2*) Good method to get t-Bu-S-R (R = alkyl or aryl).
- 3*) Promising for preparation of alkyl-S-R.
- 4*) Predictable absolute configuration.
- 5*) Limitations: Till now no reaction with enolates. Necessity to increase de (sulfinate) in order to get a one-pot procedure avoiding the purification stage. Instability of some sulfonates.

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