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CATALYTIC ASYMMETRIC INDUCTION IN OXIDATION REACTIONS.
THE SYNTHESIS OF OPTICALLY ACTIVE EPOXIDES.

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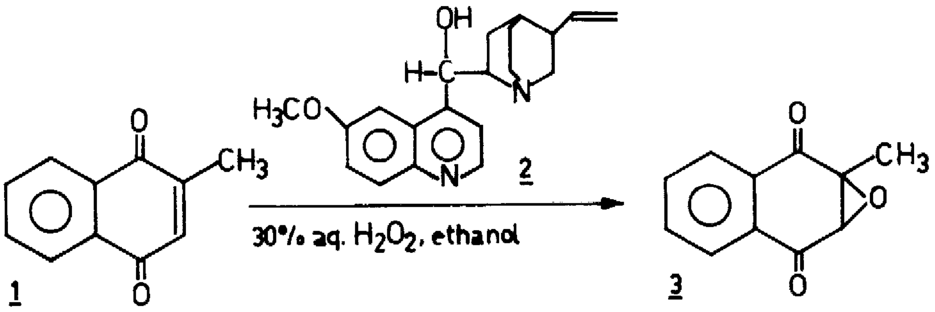
The epoxide function plays an important role in metabolic processes.[1] It is surprising therefore that the synthesis of optically active epoxides leaves much to be desired.[2,3]

We wish to report that the base-catalyzed hydrogen peroxide[4] or t-butyl hydroperoxide[5] mediated epoxidation of electron-poor olefins is subject to catalytic asymmetric induction.

Using quaternary ammonium salts derived from alkaloids[6] under phase-transfer conditions[7] we have synthesized a number of optically active epoxides starting from chalcones, a quinone and similar electron-poor olefins. Chemical yields are excellent in all cases, while the enantiomeric excess, as determined in one case, amounted to 25%.[8] No attempts have yet been made to optimize the enantioselectivity of this reaction.

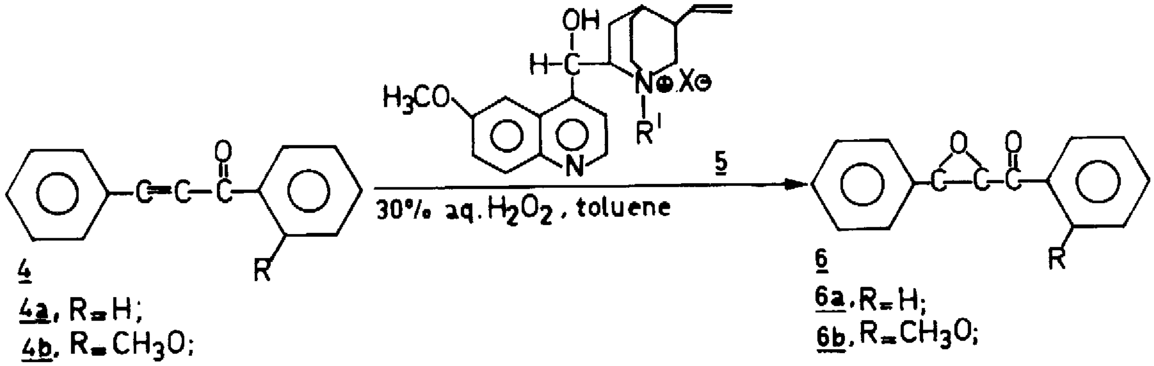
Initial experiments performed with quinine (2) as the catalyst in a mixture of 30% aq. H_2O_2 and ethanol showed that quinone 1[9] gave the corresponding epoxide 3 in 90% chemical yield. However, asymmetric induction was minimal and the results erratic.



We then turned to phase-transfer conditions using the quinine-salt 5 ($R^1 = C_6H_5CH_2$). Under conditions described in detail below for the chalcone 4a, the quinone 1 gave the corresponding epoxide 3 in high yield. Although this epoxide had an initial specific rotation of zero at 578 mμ its $|\alpha|^{RT}_{436}$ was -12° (c = 1.2, acetone).[10] Several recrystallizations from alcohol furnished epoxide 3 with $|\alpha|^{RT}_{578}$ 0°, $|\alpha|^{RT}_{546}$ 0°, and $|\alpha|^{RT}_{436}$ -142° (c=1, acetone). This compound gave satisfactory ORD and CD spectra.

Attempts to epoxidise chalcone 4a (R=H) under the influence of quinine (2) were disappointing. However, chalcones (4) and related compounds could be transformed in excellent chemical yields into optically active epoxides, using quaternary salts derived from quinine (e.g. 5. $R^1 = C_6H_5CH_2$) as chiral phase-transfer catalysts in the two phase system toluene/water.

Thus when a solution of 20.4 g of chalcone 4a (R=H) in 125 ml of toluene was vigorously stirred for 24 hrs at room temperature with a solution of 7.5 g NaOH in 90 ml of 30% aq. H_2O_2 and 750 mg of the salt 5 ($R^1 = C_6H_5CH_2$), the yellow colour of 4a (R=H) had disappeared completely Work-up of the reaction mixture and elution of the crude product on silicagel/CH_2Cl_2 (in order to remove the catalyst)[10] gave 21.8 g (99%) of the optically active epoxide 6a (R=H) as a white solid.[11]



4
4a, R=H;
4b, R=CH₃O;

6
6a, R=H;
6b, R=CH₃O;

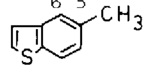
Compound 6a (R=H) has $|\alpha|^{RT}_{578}$ -51° (c=2.3, CH_2Cl_2) and exhibited satisfactory ORD and CD spectra. Attempts to determine the enantiomeric excess of 6a (R=H) are still in progress.

In order to determine the enantiomeric excess of 6b ($R = CH_3O$) this compound was prepared as described for 6a (R=H). Using the optically active PMR shift reagent $Eu(TFC)_3$ on 6b distinct differences were observed for the proton absorptions of the enantiomers of the epoxide. Peak ratios determined on crude material (prior to possible enantiomeric enrichment by crystallization) showed the presence of an enantiomeric excess of 25%, an accurate measure of the extent of asymmetric induction.[12] From a comparable experiment on crystallized, chemically pure material it was concluded that optically pure 6b has $|\alpha|^{RT}_{578}$ - 169°, $|\alpha|^{RT}_{546}$ - 206°, $|\alpha|^{RT}_{436}$ - 559° (c=1, CH_2Cl_2).

When we applied the quaternary salt derived from quinidine and $C_6H_5CH_2Cl$ (instead of 5) in the conversion 4a → 6a the epoxide 6a was formed again in high chemical yield. In this case, however, the (+) enantiomer was formed in excess, $|\alpha|^{RT}_{578}$ + 49° (c=4.3, CH_2Cl_2).

Furthermore we have successfully used t-butyl hydroperoxide as the oxygen source instead of aq. H_2O_2, leaving the remaining conditions for the conversion 4a → 6a (R=H) unchanged (5, $R^1 = C_6H_5CH_2$ as the catalyst); instead of a negative rotation we now found for 6a $|\alpha|^{RT}_{578}$ + 24°. Several other electron-poor olefins could be converted into the corresponding optically active epoxides by the phase-transfer procedure (see Table).

Table: Conversion of alkenes into epoxides.

Alkene	Conditions	$\lvert\alpha\rvert^{RT}$ of epoxide*
1	5, H_2O_2	-12° 436 mμ
1	5, t-C_4H_9OOH (-5°C)	- 8° "
$C_6H_5\overset{O}{\overset{\Vert}{C}}-CH=CH-C_6H_5$	5, H_2O_2	-51° 578 mμ
"	5, t-C_4H_9OOH	+24° "
"	Quinidine-$C_6H_5CH_2Cl$ salt, H_2O_2	+49° "
o-$CH_3O-C_6H_4-\overset{O}{\overset{\Vert}{C}}-CH=CH-C_6H_5$	" , H_2O_2	+29° "
"	5, H_2O_2	-34° "
p-$Cl-C_6H_4-CH=CH-\overset{O}{\overset{\Vert}{C}}-C_6H_5$	5, H_2O_2	-62° "
p-$O_2N-C_6H_4-CH=CH-\overset{O}{\overset{\Vert}{C}}-C_6H_5$	5, H_2O_2	-33° "
2-$C_{10}H_7-\overset{O}{\overset{\Vert}{C}}-CH=CH-C_6H_5$	5, H_2O_2	-31° "
$C_6H_5-\overset{O}{\overset{\Vert}{C}}-CH=CH-$ 	5, H_2O_2	-56° "
(E)$C_6H_5-CH=C(CH_3)NO_2$	5, H_2O_2	- 3° "

*Estimated on epoxide freed from catalyst. In some cases some starting alkene was still present. (E) chalcones were used and gave the corresponding epoxides.

We are investigating further the generality of alkaloid and alkaloid-salt catalysis in asymmetric syntheses.[13]

References and Notes

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2. G. Berti in "Topics in Stereochemistry" eds. N.L. Allinger and E.L. Eliel. Interscience, N.Y. 1973, Vol. 7, p. 93. Epoxidations using optically active peracids require at least molar quantities of the acid and are known to proceed in poor optical yields.
3. Optically pure epoxides have usually been prepared from optically pure olefins (e.g. Δ^4-3-oxosteroids) or other optically active precursors, see ref. 2 p. 166; see also M.N. Akhtar and D.R. Boyd, Chem. Comm., 916 (1975). For another approach to optically active epoxides, M. Igarashi and H. Midorikawa, Bull. Chem. Soc. Japan., 40, 2624 (1967).
4. Known as the Weitz-Scheffer reaction, see Ref. 2.
5. N.C. Yang and R.A. Finnegan, J. Am. Chem. Soc., 80, 5845 (1958).
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7. The use of optically active phase-transfer catalysts in asymmetric synthesis was described only recently; optical yields of 0%[a], 1%[b] and 6%[c] have been reported. The claim of a 97% enantioselective epoxide synthesis has been withdrawn.[d] a) S. Colonna and R. Fornasier, Synthesis, 531 (1975); b) T. Hiyama, H. Sawada, M. Tsukanaka and H. Nozaki, Tetrahedron Letters 3013 (1975); c) J.C. Fiaud, ibid., 3495 (1975); d) T. Hiyama, T. Mishima, H. Sawada and H. Nozaki, J. Am. Chem. Soc., 98, 641 (1976).
8. None of the epoxides reported in this paper had been prepared in optically active form before.
9. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley and Sons, N.Y. 1967, p. 466.
10. Great care was exercised to remove all of the catalyst and its degradation fragments from the product. Duplicate and blank experiments were performed. Experiments were carried out to ensure that the optical activity of the epoxides was not due to fortuitous resolution in the presence of the catalyst.
11. Optically active epoxides had analytical and/or spectral data in accord with their structure and with those reported for the known racemic substances.
12. This experiment was separately carried out on (-), (+) and racemic samples of epoxide 6b and proves that the enantiomers of 6b were indeed formed in different amounts.
13. For the enantioselective addition of thiols to electron-poor double bonds, see R. Helder, R. Arends and H. Wynberg, manuscript in preparation.