

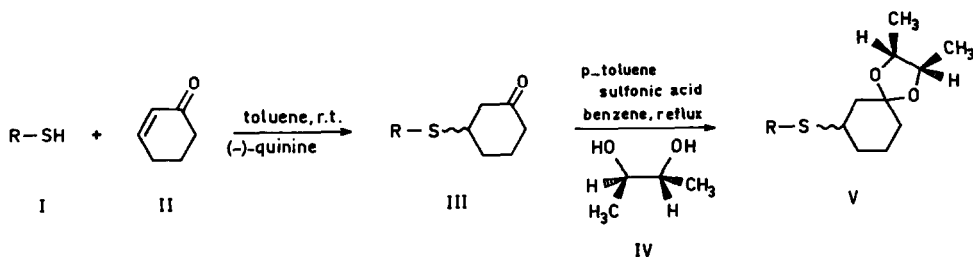
ALKALOID CATALYZED ASYMMETRIC SYNTHESIS III¹
THE ADDITION OF MERCAPTANS TO 2-CYCLOHEXENE-1-ONE;
DETERMINATION OF ENANTIOMERIC EXCESS USING ¹³C NMR.

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
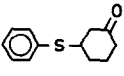

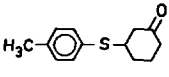
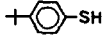
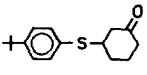
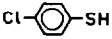
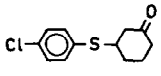
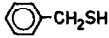
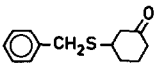
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(Received in UK 20 April 1977; accepted for publication 10 May 1977)

The addition of mercaptans to α,β -unsaturated systems is an important reaction in biosynthetic processes² as well as in synthesis.³ We wish to report the formation in excellent yields of a series of β -ketosulfides in enantiomeric excess up to 50% by the addition of mercaptans to 2-cyclohexene-1-one in the presence of catalytic quantities of quinine.⁴



A typical experiment follows: Thiophenol (I, R = phenyl; 1.10 g, 10.0 mmol) and 2-cyclohexene-1-one (II; 1.20 g, 12.5 mmol) were dissolved in 25 ml dry toluene containing 25 mg (0.08 mmol) sublimed (-)-quinine and the reaction mixture was allowed to stand for 5 hours at room temperature. The product could be isolated readily by removal of the catalyst by extraction with dilute hydrochloric acid followed by evaporation of the solvent. Thus 1.90 g (94%) of 3-phenylthiocyclohexanone (III, R = phenyl) was obtained as a colorless oil; enantiomeric excess 41%, $[\alpha]_{578}^{21} = +29.7^\circ$, $[\alpha]_{365}^{21} = +267^\circ$ (c = 2.00, benzene). The table lists the results of the addition reaction with several mercaptans under the same conditions.

Mercaptan	Adduct ⁵	bp (mm Hg) (°C)	mp (°C)	rotation (benzene)		chem. yield (%)	enant. excess (%)
				$[\alpha]_{578}^{21}$	conc. $\left(\frac{g}{100\text{ ml}}\right)$		
		110 (0.08)		+29.7°	2.00	94	41
		147-9 (0.07)		+32.2°	2.01	86	46
			47-51	+22.8°	2.00	89	45
			60-61	+17.0°	2.00	95	22
		100-15 (0.01-0.005)		-10.3°	3.60	82	6

Direct determination of the enantiomeric excess of the ketosulfides failed. The corresponding diastereomeric ketals (V) were then prepared using an excess of R-(-)-butane-2,3-diol.⁶ When chromatographic separation of these diastereomeric ketals proved difficult and laborious (for 3-phenylthiocyclohexanone (III, R = phenyl) an estimate of 40% enantiomeric excess was made using HPLC), we turned to ¹³C nmr spectroscopy. The diastereomeric ketals (V) gave distinct ¹³C nmr spectra capable of reliable integration.⁷

A reasonable mechanism to rationalize the relatively high asymmetric induction (optimization experiments in progress have achieved induction of 70% in selected cases), as well as an absolute configurational assignment must await further studies.

References and notes:

- For earlier papers see a) H. Wynberg and R. Helder, *Tetrahedron Lett.*, 4057 (1975); b) R. Helder, J.C. Hummelen, R.W.P.M. Laane, J.S. Wiering and H. Wynberg, *Tetrahedron Lett.*, 1831 (1976).
- See for example I.H. Hall, K.H. Lee, E.C. Mar, C.O. Starnes and T.G. Waddell, *J. Med. Chem.*, **20**, 333 (1977).
- See for example the first step in an elegant grandisol synthesis: B.M. Trost and D.E. Keeley, *J. Org. Chem.*, **40**, 2013 (1975).
- While this work was in progress other examples of asymmetric induction in thiol addition reactions became known: a) K. Ueyanagi and S. Inoue, *Macromolek. Chem.*, **178**, 235 (1977); b) V.N. Gogte, Poona, India, personal communication (1976); c) K. Yamaguchi and Y. Minoura, *Chem. Ind. (London)*, 478 (1975).
- (+)-3-Phenylthiocyclohexanone (III, R = phenyl) has been reported earlier (P. Chamberlain and G.H. Whitham, *J. Chem. Soc. Perkin II*, 130 (1972)). All other adducts were new compounds that gave analytical and spectroscopic data in agreement with the structure assigned.
- For the use of diastereomeric ketals of R-(-)-butane-2,3-diol see a) J. Casanova and E.J. Corey, *Chem. Ind. (London)*, 1664 (1961); b) J.J. Plattner and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 1758 (1971).
- For a full account of the technique see H. Hiemstra and H. Wynberg, *Tetrahedron Lett.*, submitted for publication.