

Asymmetric Induction in the Michael Reaction by Means of Chiral Phase-transfer Catalysts derived from Cinchona and Ephedra Alkaloids

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Asymmetric induction in the Michael reaction has been achieved using alkaloidonium salts in a two-phase system with optical yields of up to 36 and 26% in the addition to $\alpha\beta$ -unsaturated ketones of thiols and nitroalkanes respectively. The presence of a hydroxy-group β to the 'onium function is essential to achieve substantial asymmetric syntheses.

1,4-ADDITION reactions of thiols to $\alpha\beta$ -unsaturated compounds are subject to asymmetric induction in high optical yields when chiral amines such as cinchona alkaloids are used as catalysts in homogeneous media.¹

If instead of the free amine a catalytic amount of its quaternary ammonium fluoride is used optically active thiol adducts are obtained also. The ammonium fluorides were prepared *in situ* from catalytic amounts of ammonium chlorides or bromides by addition of potassium fluoride.²

In order to verify the application of this type of asymmetric synthesis to a number of Michael donors and acceptors, we have now investigated the addition of nitroalkanes and of other nucleophiles to *trans*-chalcone, $\alpha\beta$ -unsaturated sulphoxides, and sulphones. Furthermore the effect on the optical yields of a number of variables such as (i) structural variations within the catalyst, (ii) the temperature, (iii) the solvent, and (iv) the nature of the added organic salt has been studied in detail.

The catalysts we used were *N*-benzylquininium chloride (QUIBEC) (30), *N*-(*o*-nitrobenzyl)quininium chloride (31), *N*-(*p*-nitrobenzyl)quininium chloride (32), *N*-(α -naphthylmethyl)quininium chloride (33), *N*-(β -naphthylmethyl)quininium chloride (34), *N*-benzyl-(*O*-benzoyl)-quininium chloride (35), *N*-benzylcinchonidinium chloride (36), *N*-benzylquinidinium chloride (37), *N*-benzyl-

cinchoninium chloride (38) *N*-dodecyl-*N*-methylephedrinium bromide (39), *N*-benzyl-*N*-methylephedrinium bromide (40), *N*-dodecyl-*N*-methylamphetaminium bromide (41), and *N*-dodecyl-*NN*-dimethyl-(3-hydroxy-3-phenylpropyl)ammonium bromide (42).

The reactions were carried out at room temperature in an organic solvent with a catalytic amount of the 'onium salts (30)–(42) and a large excess of inorganic salt (potassium fluoride, sodium hydroxide, or potassium *t*-butoxide).

RESULTS

In the addition of thiols to cyclohexenones (4) and (5), the results, reported in Table 1, indicate that among the catalysts tested *N*-(*o*-nitrobenzyl)quininium chloride (31) is the best optically active phase-transfer catalyst. Indeed addition of thiophenol (1) to cyclohex-2-en-1-one (4) afforded (–)-(6), $[\alpha]_{578}^{25} -23^\circ$, 35.6% optically pure.^{1a}

Cinchona alkaloid 'onium salts give higher asymmetric induction than the ephedra alkaloid derivative (39). With catalyst (42) no asymmetric induction was observed.

When the hydroxy-group at C-9 of quinine was esterified, (3-phenylthio)cyclohexanone (6) had $[\alpha]_{578}^{25} +1.2^\circ$. The sign of the optical rotation of (6) depends on the absolute configurations at C-8 and C-9 in catalysts (30)–(38). Quininium (30) and cinchonidinium (36) salts, having the same (8*S*, 9*R*) absolute configuration at C-8 and C-9, afforded (–)-(6), whereas quinidinium (37) and cinchoninium

TABLE 1
Reaction of carbonyl compounds with thiols in the presence of KF at 25 °C

Substrate	Catalyst	Solvent	Product	Yield (%)	$[\alpha]_{578}^{25} (^\circ)$ (C ₆ H ₆)	Optical yield (%)
(4)	(30)	PhMe	(6)	92	–16.4	22.5 ^a
(4)	(39)		(6)	80	–2.0	
(4)	(38)		(6)	75	+3.4	
(4)	(36)		(6)	87	–3.5	
(4)	(42)		(6)	75	0	
(4)	(30)	CCl ₄	(7)	94	→27.9	16.2 ^a
(4)	(31)		(8)	90	–19.0	35.6 ^a
(4)	(30)		(8)	92	–18.0	
(4)	(30)		(6)	85	–20.0	
(4)	(37)		(6)	81	+6.4	
(4)	(31)		(6)	85	–23.0	
(4)	(33)		(6)	90	–19.7	
(4)	(34)		(6)	80	–13.4	
(4)	(32)		(6)	75	–15.3	
(4)	(31)		(8)	90	–21.0	30.0
(4)	(30)		(8)	80	–21.2	
(5)	(31)		(9)	95	–5.7	
(5)	(30)	PhMe	(9)	75	–9.5	16.5 ^b

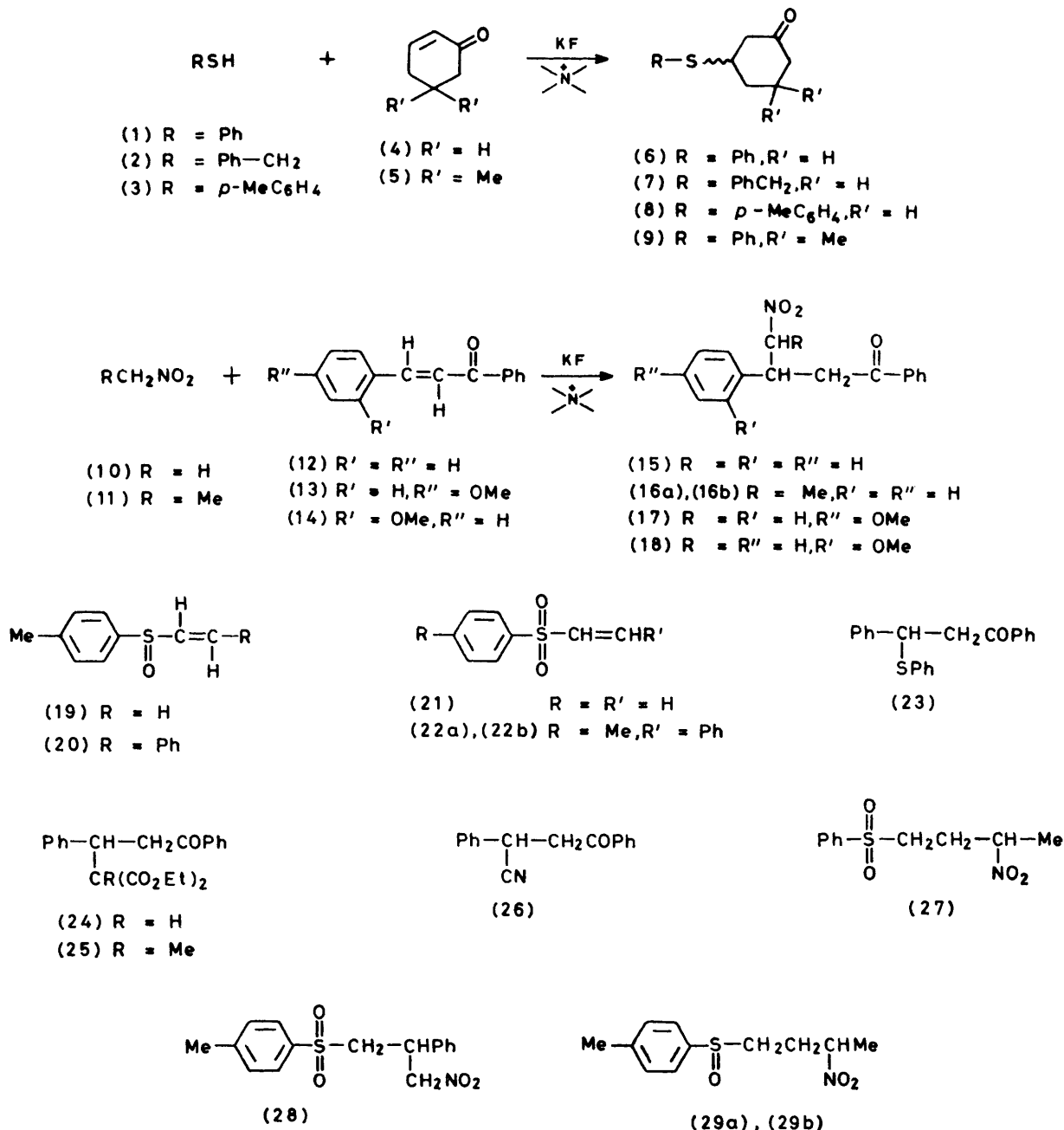
^a Based on the value reported ¹ in literature. ^b H. Wynberg, personal communication.

(38) salts, with (8*R*, 9*S*) configuration, gave (+)-(6). The presence of a methoxy-group at C-6 increases the enantiomeric excess of adduct (6) [see Table 1].

The results of the addition of nitromethane to chalcone (12) to give the nitroketone (15) are given in Table 2. The

cinchona alkaloid 'onium salt; the (−) and the (+) enantiomer is the prevailing one, respectively, with catalysts (30) and (31) and (37), having opposite configuration at C-8 and C-9.

When nitroethane (11) was used as donor in the reaction



highest asymmetric induction was obtained with the ephedrinium salts (40) and (39), the enantiomeric excess being 26.4% and 24%, respectively. When (−)-(*R*)-*NN*-dimethyl-*N*-dodecylamphetaminium bromide (41) was used as catalyst the nitroketone obtained was optically inactive. With the γ -hydroxy-derivative (42) the adduct had $[\alpha]_{578}^{21} + 2.5^\circ$.

Also in this case the sign of the optical rotation of (15) depends on the absolute configuration at C-8 and C-9 in the

with chalcone (12) in toluene in the presence of catalyst (39), two diastereoisomeric nitroketones (16a) and (16b) were obtained in a 1:1 ratio, $[\alpha]_{578}^{21} - 2.9^\circ$ and $[\alpha]_{578}^{21} - 5.0^\circ$, respectively. Their enantiomeric purity could not be determined.

The nitroalkane addition to ketone (12) is strongly influenced by steric factors; indeed chemical yields in the nitroethane addition are lower, even for a longer reaction time, than those with nitromethane.

TABLE 2
Addition of MeNO₂ to chalcone (12) at 20 °C in
toluene as solvent

Catalyst	Inorganic salt ^a	Time (days)	Yield (%)	$[\alpha]_{578}^{21}$ (°) (CH ₂ Cl ₂)
(39)	KF	3	60	-9.8
(39)	NaOH	3	55	-8.0
(39)	Bu ^t OK	1	70	-7.0
(40)	KF	3	50	-10.7 ^b
(41)	KF	6	60	0
(42)	KF	3	20	+2.5
(30)	KF	3	100	-4.1
(30)	NaOH	1	87	-5.3
(30)	Bu ^t OK	1	90	-4.1
(37)	KF	3	78	+3.4
(36)	KF	3	80	0
(31)	KF	3	60	-1.8

^a 1.5 Molar equivalents with respect to chalcone. ^b Enantiomeric excess 26.2.

Reaction of chalcones (13) (14) with catalyst (39) and KF in toluene in the presence of nitromethane (10) afforded adducts (17) and (18), $[\alpha]_D^{20}$ -9.1° and $[\alpha]_D^{21}$ -1.3°, respectively.

Effect of Temperature.—The degree of asymmetric induction in the addition of thiophenol (1) to cyclohex-2-enone (4) in toluene, using the quininium salt (30) as catalyst, decreases with the temperature. Thus the optical rotations of the adduct (6) obtained at -50, 25 and 70 °C were $[\alpha]_{578}^{25}$ -16.3°, -16.4°, and -1.3°, respectively. A similar situation was encountered in the addition of nitromethane to chalcone (12) with catalyst (39) and KF in toluene. When the reaction was performed at 0 and 74 °C, nitroketone (12) had $[\alpha]_{578}^{21}$ -10.2 and -4.5°, respectively.

Optical Stability of the Products.—When optically active 3-phenylthiocyclohexanone (6) was dissolved in methylene chloride or toluene in the presence of potassium fluoride and catalyst (30) and kept at room temperature, no racemisation occurred during the time (0.5–4 h) of the addition reaction. However, after 72–100 h some (15–20%) racemisation was observed. Nitroketone (15) is optically stable in toluene in the presence of KF and (39); its optical rotation did not change after 5 days reaction time. The enantiomeric purity of the product (15) was determined by using di-(+)-camphoylmethanatoeuropium(III) as ¹H n.m.r. shift reagent and has an accuracy of ±3%.²

Effect of the Solvent.—Non-polar aprotic solvents (PhMe and CCl₄) give higher asymmetric induction than solvents with high dielectric constants (MeCN, MeOH, and CH₂Cl₂) (Tables 3 and 4) in agreement with the results obtained by Wynberg in the alkaloid-catalysed addition of nitrosulphones to methyl vinyl ketone^{3a} and in the epoxidation reaction.^{3b}

Effect of Inorganic Salt.—When lithium fluoride was used as co-catalyst instead of potassium fluoride in the addition

TABLE 3

Solvent effect in the addition of thiophenol to cyclohex-2-enone with QUIBEC in the presence of KF at 25 °C for 4 h

Solvent	Yield (%)	$[\alpha]_{578}^{25}$ (°)
PhMe	92	-16.4
CCl ₄	85	-20.0
CH ₂ Cl ₂	70	-2.3
Cyclohexane	74	-6.0
MeCN	80	0
MeOH	86	0
Dioxan	61	-8.1

of thiophenol (1) to cyclohex-2-enone (4) only starting materials were recovered.

The use of an anion-exchange resin Amberlite IRA 900 (F⁻) as a source of fluoride ions instead of KF, in 1 : 1 ratio with the catalyst (30), does not substantially affect the enantiomeric purity of adduct (6), the optical rotations being $[\alpha]_{578}^{25}$ -15.6 and -16.4°, respectively. When the resin was in excess with respect to the ammonium salt (30) the adduct had $[\alpha]_D^{25}$ -1.35°. Recently, Michael addition aided by polymer-immobilized fluoride ion has been reported.⁴ In the addition of nitroalkanes to chalcone the nature of the inorganic salt added does not substantially affect the degree of asymmetric synthesis, whereas it influences the reaction rates, Bu^tOK and NaOH being more efficient than KF.

Catalysis in the reactions of inorganic salts in solid-liquid systems *via* lipophilic quaternary ammonium salts has already been reported.⁵

Michael addition to chalcone of diethyl malonate, diethyl α-methylmalonate, thiophenol, and potassium cyanide in the presence of catalyst (39) has also been studied. Yields and optical rotations of the adducts are reported in Table 5. The hydrocyanation did not occur in the absence

TABLE 4

Solvent effect in the addition of nitroethane to chalcone with catalyst (39) at 25 °C

Solvent	Yield (%)	$[\alpha]_{578}^{25}$ (°) (CH ₂ Cl ₂)
PhMe	60	-9.8
CCl ₄	64	-6.6
CH ₂ Cl ₂	10	-4.8
Cyclohexane	90	-2.8
Dioxan	10	-3.7
MeOH	9 ^a	0

^a A mixture of the 1 : 2 adducts is also formed.

TABLE 5

Addition of other nucleophiles to chalcone (12) in toluene at 20 °C in the presence of catalyst (39)

Inorganic salt	Adduct	Yield (%)	$[\alpha]_{578}^{21}$ (°) (CH ₂ Cl ₂)
KF	(23)	85	+32.9
NaOH	(24)	81	0
Bu ^t OK	(24)	76	0
KF	(24)	4	0
NaOH	(25)	60	0
KF	(26)	75	0

of acetone cyanohydrin or in the absence of the 'onium salt (39), in agreement with the results obtained by Liotta in the Michael addition to cholest-4-en-3-one.⁶ Only in the case of the addition product of thiophenol to (12) was it possible to evaluate the enantiomeric excess, which was found to be 5%.⁷ In the addition of diethyl malonate and diethyl α-methylmalonate satisfactory yields of adducts (24) and (25) were obtained using NaOH or Bu^tOK as inorganic salts (Table 5).

Reaction of nitroethane with phenyl vinyl sulphone (21) in toluene at room temperature with catalyst (40) gave the corresponding adduct (27) in a satisfactory chemical yield. Steric factors play an important role; indeed *trans*- and *cis*-*p*-tolyl styryl sulphone (22a) and (22b) with nitromethane and catalyst (40) at 70 °C for one week afforded the nitro-compound (28) $[\alpha]_{578}^{20}$ -3.3° and $[\alpha]_{578}^{20}$ +3.4°, respectively, in 36% yield.

Sulphoxides as Michael acceptors are less reactive than the corresponding sulphones; *trans*-*p*-tolyl styryl sulph-

oxide (20) was recovered unchanged after 7 days at 70 °C in the presence of (10) and (40). Reaction of *p*-tolyl vinyl sulphoxide (19) with nitroethane (11) and catalyst (40) for 24 h at 60 °C gave a 1 : 1 mixture of the two possible diastereoisomers (29a) and (29b), $[\alpha]_D^{25} 0^\circ$, in 46% yield.

The recovered sulphoxide (19) had $[\alpha]_D^{25} +13^\circ$ (2.7% enantiomeric excess),⁸ thus indicating that Michael addition of (10) to (19) is accompanied by kinetic resolution.

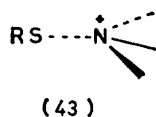
DISCUSSION

Although many factors involved in the Michael additions to activated double bonds have been described in this paper (structure of catalysts, donors, and acceptors, the solvent, and the nature of the inorganic salts added) the results do not allow a reasonable mechanism which rationalises the occurrence of asymmetric induction. Nevertheless some observation can be made. (i) The presence of a hydroxy-group β to the 'onium function in the catalyst is essential to achieve substantial asymmetric induction. (ii) With cinchona alkaloid 'onium salts the absolute configuration at C-8 and C-9 determines the stereochemical course of the addition. (iii) Comparison of the degree of asymmetric synthesis in the thiol addition to cyclohex-2-enone, and of nitromethane addition to (12), seems to lead to the conclusion that conformationally free ephedrinium salts are more efficient with the conformationally mobile chalcone. The opposite is true with the more rigid cyclohex-2-enone where cinchona 'onium salts are the catalysts of choice. (iv) The chiral ammonium fluoride salts formed *in situ* via exchange of the 'onium salt with potassium fluoride acts as the source of chirality.

The intervention of chiral ammonium fluorides as catalysts can also explain the occurrence of asymmetric induction obtained by using Amberlite IRA 900 F⁻ in the presence of catalyst (30).

The stereochemical results in the thiol addition to cyclohex-2-enone deserve some comment. A detailed mechanism to rationalize the relatively high enantiomeric excess of adducts (6) and (8), as well as the assignment of their absolute configuration,⁷ must await further studies. However, we note that the hydroxy-group at C-9 in the alkaloid greatly enhances the asymmetric induction. This effect has been observed earlier by Prelog and has been studied quantitatively.⁹ The effect is most probably due to hydrogen bonding between the hydroxy-group in the catalyst and the carbonyl group of the $\alpha\beta$ unsaturated ketone.¹⁰

Moreover, this reasoning is consistent with the strong solvent effect on the optical yield.^{3b} The formation of ion pairs such as (43) between thiolates and catalysts



could intervene in the addition of thiols (1) to $\alpha\beta$ unsaturated compounds (2), as previously suggested by Inoue.^{10c} They could control the direction of approach of

RS⁻ to the activated double bond of (4) and the extent of asymmetric induction.

This could also explain why in solvents with high dielectric constant such as MeCN, MeOH, and CH₂Cl₂, where (43) is likely to be present as a loose ion pair,^{*} the enantiomeric purities (0–3.5%) of (3-phenylthio)-cyclohexane are substantially lower than in solvents such as PhMe and CCl₄.[†]

The influence of the configuration at C-8 and C-9 in the alkaloid 'onium salts on the sign of the optical rotation of adduct (6) as well as the favourable effect of a methoxy-group at C-6 on the asymmetric synthesis tally with the results previously found by Prelog in cyanohydrin formation⁹ and by Wynberg in Michael addition.^{1e} On the other hand *N*-benzylquininium chloride (30) and *N*-benzylquinidinium chloride (37) also gave opposite enantiomers in the conversion of alkenes into epoxides with H₂O₂ under phase-transfer conditions.¹²

The stereochemical course of the thiol addition to cyclohex-2-enone in heterogeneous conditions in the presence of 'onium salts as catalysts is the reverse of that obtained for the same reaction carried out in homogeneous medium,^{1a} with the corresponding chiral cinchona alkaloid, so that a prevalence of (–)- or (+)-(6), respectively, can be obtained depending on the method used.

EXPERIMENTAL

Light petroleum had b.p. 40–60 °C. Solvents were dried over molecular sieves. ¹H N.m.r. spectra were recorded with Varian A-60 and/or Varian HA 100 instruments. Optical rotations were measured with a Perkin-Elmer 241 and/or Perkin-Elmer 141 polarimeters. Potentiometric titrations were carried out with a Metrohm Potentiograph type E 576 using silver and calomel electrodes, the latter isolated by means of a potassium sulphate bridge.

Optically Active Catalysts.—(–)-*N*-Benzylquininium chloride (30) (+)-*N*-benzylquinidinium chloride (37), (+)-*N*-benzylcinchoninium chloride (38), (–)-(1*R*, 2*S*)-*N*-dodecyl-*N*-methylephedrinium bromide (39), (+)-*N*-dodecyl-*NN*-dimethyl-(3-hydroxy-2-phenylpropyl)ammonium bromide (42), (–)-(1*R*, 2*S*)-*N*-benzyl-*N*-methylephedrinium bromide (40), and (–)-(*R*)-*N*-dodecyl-*NN*-dimethylamphetaminium bromide (41) were prepared as previously described.^{13–15}

(–)-*N*-Benzylcinchonidinium chloride (36). This was prepared by adding benzyl chloride (10 mmol) to a solution of chinchonidine (10 mmol) in anhydrous acetone (100 ml). After 5 days at 75 °C the precipitate was filtered off, dissolved in hot water and evaporated to dryness to give compound (36) in 50% yield, m.p. 212–213 °C (decomp.), $[\alpha]_D^{20} -175.4^\circ$ (*c* 0.5 in H₂O) (Found: C, 74.0; H, 6.9; N, 6.6. C₂₈H₂₉ClN₂O requires C, 74.2; H, 6.9; N, 6.65%).

(–)-*N*-(*o*-Nitrobenzyl)quininium chloride (31). This was prepared by adding *o*-nitrobenzyl chloride (10 mmol) to a solution of quinine (10 mmol) in absolute ethanol (40 ml) and heating at 80 °C for 20 h. The reaction mixture was diluted with diethyl ether, the precipitate filtered off, and crystallized from acetone–diethyl ether to afford (31) in 60% yield,

^{*} Under phase-transfer conditions the nature of the solvent also influences the degree of association of the quaternary 'onium salt.¹¹

[†] Recently an inverse relationship between the dielectric constant and the enantiomeric yield has been reported.^{3b}

m.p. 188–190 °C (decomp.); $[\alpha]_{578}^{21} - 131.6^\circ$ (c 0.7 in $\text{CH}_2\text{-Cl}_2$) (Found: C, 65.0; H, 6.2; N, 8.2. $\text{C}_{27}\text{H}_{30}\text{ClN}_3\text{O}_4$ requires C, 65.4; H, 6.1; N, 8.5%).

(–)-N-(*p*-Nitrobenzyl)quininium chloride (32). This was prepared in the same way in 55% yield; compound (32) had m.p. 178–180 °C, $[\alpha]_{578}^{21} - 216.8^\circ$ (c 0.5 in EtOH) (Found: C, 64.9; H, 6.1; N, 8.3. $\text{C}_{27}\text{H}_{30}\text{ClN}_3\text{O}_4$ requires C, 65.4; H, 6.1; N, 8.5%).

(–)-N-(α -Naphthylmethyl)quininium chloride (33). This was prepared in the same way in 65% yield; compound (33) had m.p. 216–218 °C (decomp.) (from ethanol–water), $[\alpha]_{578}^{21} - 518.9^\circ$ (c 0.35 in EtOH) (Found: C, 74.1; H, 6.6; N, 5.3. $\text{C}_{31}\text{H}_{33}\text{ClN}_2\text{O}_2$ requires C, 74.3; H, 6.6; N, 5.6%).

(–)-N-(β -Naphthylmethyl)quininium chloride (34). This was prepared as described above in 55% yield; compound (34) had m.p. 231–232 °C (decomp.) (from EtOH) $[\alpha]_{578}^{21} - 233.2^\circ$ (c 1.0 in 96% EtOH) (Found: C, 74.1; H, 6.6; N, 5.6. $\text{C}_{31}\text{H}_{33}\text{ClN}_2\text{O}_2$ requires C, 74.3; H, 6.6; N, 5.6%).

(+)-N-Benzyl-O-benzoylquininium chloride (35). This was prepared by adding benzyl chloride (10 mmol) to a solution of *O*-benzoylquinine (10 mmol) {m.p. 139–140 °C, $[\alpha]_{\text{D}}^{21} + 116^\circ$ (c 1.0 in EtOH) [lit.,¹⁶ m.p. 141.5–143 °C, $[\alpha]_{\text{D}}^{22} + 119.5^\circ$ (c 1.0 in EtOH)]} in anhydrous acetone (60 ml) and refluxing for 2 days. After evaporation of the solvent the residue was washed with diethyl ether to give compound (35) in 30% yield, m.p. 137–139 °C (decomp.), $[\alpha]_{\text{D}}^{25} + 29.3^\circ$ (c 0.9 in EtOH), Cl^- content 90% by potentiometric titration.

Thiol Addition.—In a typical experiment thiophenol (1) (5 mmol) and cyclohex-2-enone (4) (6.25 mmol) were added under magnetic stirring in a nitrogen atmosphere to dry toluene (12.5 ml) containing the 'onium salt (0.02 mmol) and potassium fluoride (7.5 mmol), and the reaction mixture was allowed to stand for 4 h at room temperature. The product could be isolated by diluting the reaction mixture with methylene chloride: the organic layer was washed with 10% aqueous sodium hydroxide and water, and evaporated to dryness. The residue was chromatographed on silica with ether–light petroleum (1:9) and then (1:1). 3-Phenylthiocyclohexanone (6) had b.p. 110 °C at 0.08 mmHg, (lit.,^{1a} b.p. 110 °C at 0.8 mmHg). In a blank experiment it was shown that the catalyst (30) is not eluted under the chromatographic conditions used for the purification of (6).

Table 1 lists the results of the addition reaction with other mercaptans under the same conditions, together with yields, optical rotation, and enantiomeric excesses. ¹H N.m.r. spectra were in agreement with the assigned structures. 3-Benzylthiocyclohexanone (7) had b.p. 112 °C at 0.01 mmHg (lit.,^{1a} b.p. 110–115 °C at 0.01–0.005 mmHg). 3-*p*-Tolylthiocyclohexanone (8) had b.p. 150 °C at 0.08 mmHg (lit.,^{1a} b.p. 147–149 °C at 0.07 mmHg). 5,5-Dimethyl-3-phenylthiocyclohexanone (9) had n_{D}^{20} 1.5600 (Found: C, 71.6; H, 7.6. $\text{C}_{14}\text{H}_{18}\text{OS}$ requires C, 71.7; H, 7.7%).

In an ancillary experiment Amberlite IRA 900 (F^-), exchange capacity 3.4 milliequiv. g^{-1} (0.02 mol) was used instead of KF under the conditions described above for 23 h reaction time. The resin was filtered off and solvent was evaporated. The residue was purified by column chromatography to give adduct (6) in 85% yield, $[\alpha]_{578}^{21} - 15.6^\circ$ (c 2.1 in C_6H_6). When the reaction was repeated at 0 °C for 3 h using Amberlite IRA 900 (F^-) (0.01 mol) in excess with respect to catalyst (30), 3-phenylthiocyclohexanone (6) was obtained in 80% yield, $[\alpha]_{578}^{21} - 1.35^\circ$ (c 2.0 in C_6H_6).

Racemisation of 3-Phenylthiocyclohexanone (6).—In a typical experiment adduct (6), $[\alpha]_{578}^{21} - 16.4^\circ$ (c 2.0 in C_6H_6) (239 mg), was added with stirring to a suspension of *N*-benzylquininium chloride (30) (2.5 mg) and KF (109 mg) in anhydrous toluene. After 72 h at room temperature the potassium fluoride was filtered off and the solvent evaporated. The residue was chromatographed on silica with ether–light petroleum (1:9 and then 1:1) to give 3-phenylthiocyclohexanone (6) (88%), $[\alpha]_{578}^{21} - 13.2^\circ$ (c 2.0 in C_6H_6) and diphenyl disulphide (10 mg), identified by g.l.c. analysis.

Blank Experiment.—When thiophenol (1) (5 mmol) was reacted for 1 day with cyclohex-2-enone (4) (6.25 mmol) in dry toluene (12.5 ml) containing only *N*-benzylquininium chloride (0.02 mol), 3-phenylthiocyclohexanone (6) was obtained in 7% yield, $[\alpha]_{578}^{21} - 4.7^\circ$ (c 2.0 in C_6H_6).

Synthesis of Optically Active Nitroketones.—In a typical experiment nitromethane (10) (75 mmol) and *trans*-chalcone (12) (5 mmol) were added with stirring to dry toluene (50 ml) containing the 'onium salt (0.5 mmol) and potassium fluoride (7.5 mmol) and the reaction mixture was allowed to stand for a suitable time. Methylene chloride was added, and the organic layer was washed with 2N HCl and water and evaporated under vacuum. The residue was chromatographed on silica with ether–light petroleum (1:9 and then 3:7). Optically active 3-phenyl-4-nitro-1-phenylbutan-1-one (15) had m.p. 91–93 °C (lit.,¹⁷ m.p. 101–102 °C for the racemic compound). Reactions with inorganic salts other than KF were carried out by the same procedure. The results are listed in Table 2. In a blank experiment it was shown that the stirring is unnecessary. When the reaction was repeated in the absence of KF the starting material (12) was recovered quantitatively.

Under typical reaction conditions *trans*-4-methoxychalcone (13) after 3 days gave optically active 3-*p*-methoxyphenyl-4-nitro-1-phenylbutan-1-one (17) in 31% yield, $[\alpha]_{\text{D}}^{20} - 9.1^\circ$ (c 6.0 in CH_2Cl_2), m.p. 55–56 °C (lit.,¹⁸ m.p. 63–65 °C for the racemic compound). 3-*o*-Methoxyphenyl-4-nitro-1-phenylbutan-1-one (18) obtained in the same way in 41% yield, had n_{D}^{20} 1.5700, $[\alpha]_{\text{D}}^{20} - 1.3^\circ$ (c 3.6 in CH_2Cl_2) (Found: C, 68.5; H, 5.8; N, 4.8. $\text{C}_{17}\text{H}_{17}\text{NO}_4$ requires C, 68.2; H, 5.7; N, 4.7%).

Reaction of *trans*-chalcone (12) (5 mmol) with nitroethane (6 mmol), KF (7.5 mmol), and catalyst (39) in dry toluene (50 ml) afforded, after 12 days reaction, 3-phenyl-4-nitro-1-phenylpentan-1-one (16a), (16b) (43% yield), as a mixture of diastereoisomers in 1:1 ratio, which were separated by column chromatography on silica with ether–light petroleum (1:9). Nitroketones (16a) and (16b) had $[\alpha]_{578}^{20} - 2.9^\circ$ (c 3.0 in CH_2Cl_2) and $[\alpha]_{578}^{20} - 5^\circ$ (c 3.0 in $\text{CH}_2\text{-Cl}_2$), and m.p. 66–68 and 90–92 °C, respectively (lit.,¹⁷ m.p. 67 and 100 °C, respectively, for the racemic compounds).

Chalcone (12) was reacted with nitromethane (10), KF, and catalyst (39) for 4 days under the conditions described above in solvents other than toluene; the results are listed in Table 4. In methanol as solvent the reaction mixture is homogeneous and the mono-adduct (15), m.p. 99–100 °C, $[\alpha]_{578}^{25} 0^\circ$ (c 3.0 in CH_3Cl_2) was formed in 9% yield, together with an isomeric mixture of 4-nitro-1,3,5,7-tetraphenylheptane-1,7-diones in 5% yield, which after separation by fractional crystallization from ethanol had m.p. 153–154 and 227–228 °C, respectively (lit.,¹⁹ m.p. 155–156 and 223–225 °C, respectively).

Michael Addition of Nucleophiles other than Nitroalkane to Chalcone (12).—Thiophenol (5 mmol) and chalcone (1) (5 mmol) were added with magnetic stirring under a nitrogen

atmosphere to dry toluene (50 ml) containing catalyst (39) (0.5 mmol) and potassium fluoride (7.5 mmol), and the reaction was allowed to stand for 3 days at room temperature. The reaction mixture was diluted with methylene chloride, the organic layer was washed with 10% aqueous sodium hydroxide and with water, and evaporated to dryness. The residue was chromatographed on silica with ether–light petroleum (1 : 9) to give in 85% yield 1,3-diphenyl-3-phenylthiopropion-1-one (23), m.p. 110–112 °C, $[\alpha]_{578}^{20} + 32.9^\circ$ (c 4.6 in CH_2Cl_2) (Found: C, 79.1; H, 5.6. $\text{C}_{21}\text{H}_{18}\text{OS}$ requires C, 79.2; H, 5.7%).

Diethyl malonate (25 mmol) and chalcone (12) (5 mmol) were added with magnetic stirring to dry toluene (50 ml) containing catalyst (39) (0.5 mmol) and sodium hydroxide (7.5 mmol). After 5 h the reaction mixture was diluted with methylene chloride, and the organic layer was washed with 2N HCl and water, and evaporated to dryness. The residue was chromatographed on silica with ether–light petroleum (1 : 9) to give in 81% yield the racemic γ -benzoyl- α -ethoxycarbonyl- β -phenylbutyrate (24), m.p. 68–70 °C (lit.²⁰ m.p. 71 °C). When the reaction was repeated using Bu^tOK instead of KOH, the racemic adduct (24) was obtained in 76% yield after 6 h reaction, m.p. 67–69 °C. When KF was used as inorganic salt adduct (24) was formed in 4% yield after 7 days reaction time, m.p. 65–68 °C.

Using diethyl α -methylmalonate as donor instead of diethyl malonate, and sodium hydroxide as inorganic salt, after 5 h reaction the reaction adduct ethyl γ -benzoyl- α -ethoxycarbonyl- α -methyl- β -phenylbutyrate ester (25) was isolated in 60% yield, m.p. 88–89 °C (from cyclohexane) (lit.²⁰ m.p. 95 °C).

Acetone cyanohydrin (6 mmol) and chalcone (12) (5 mmol) were added with stirring to dry toluene (50 ml) containing catalyst (39) (0.5 mmol) and potassium cyanide (6 mmol). After 7 days the reaction mixture was diluted with methylene chloride, and the organic layer washed with water and evaporated to dryness. The residue was chromatographed on silica with ether–light petroleum (1 : 9) to give racemic 2-cyano-2-phenylethyl phenyl ketone (26), m.p. 124 °C, (lit.¹⁷ m.p. 126 °C). When the reaction was repeated in the absence of either KCN or acetone cyanohydrin only starting chalcone (12) was recovered.

Michael Addition to $\alpha\beta$ -Unsaturated Sulphones.—Phenyl vinyl sulphone (21) (5 mmol) and nitroethane (50 mmol) were added with magnetic stirring to dry toluene (50 ml) containing catalyst (40) and KF (7.5 mmol). After 8 h at room temperature the reaction was diluted with methylene chloride, and the organic layer washed with 2N HCl and evaporated to dryness. The residue was chromatographed on silica with ether–light petroleum (1 : 1) and then ether, to give the adduct 3-nitro-1-phenylsulphonylbutane (27) in 70% yield, $[\alpha]_{578}^{20} - 0.57^\circ$ (c 5.0 in CH_2Cl_2), m.p. 41–42 °C (Found: C, 49.6; H, 5.4; N, 5.7. $\text{C}_{10}\text{H}_{13}\text{NO}_4$ requires C, 49.4; H, 5.4; N, 5.75%). When the adduct (–)-(27) was treated under the reaction conditions described above in the absence of catalyst (40) for 5 days at room temperature, racemic (27) was quantitatively recovered.

p-Tolyl *trans*-styryl sulphone (22a) (5 mmol) and nitromethane (75 mmol) were added with magnetic stirring to dry toluene (50 ml) containing KF (7.5 mmol) and catalyst (40) (0.5 mmol). After 7 days at 70 °C the reaction mixture was diluted with methylene chloride, and the organic layer

washed with 2N HCl and evaporated to dryness. The residue was chromatographed on silica using ether–light petroleum (3 : 7 and then 1 : 1) to give 1-nitro-2-phenyl-3-*p*-tolylsulphonylpropane (28) in 36% yield, m.p. 94–96 °C, $[\alpha]_{578}^{20} - 3.3^\circ$ (c 1.2 in Me_2CO) (Found: C, 60.0; H, 5.4; N, 4.2. $\text{C}_{16}\text{H}_{17}\text{NO}_4\text{S}$ requires C, 60.2; H, 5.35; N, 4.4%). When the reaction was repeated starting from *cis*-styryl-*p*-tolyl sulphone (22b) (–)-(28) was obtained in 38% yield, m.p. 93–95 °C, $[\alpha]_{578}^{20} + 3.4^\circ$ (c 1.3 in Me_2CO). Both (+)- and (–)-(28) were optically stable under the reaction conditions in the absence of catalyst (40).

Reaction of $\alpha\beta$ -Unsaturated Sulphoxides with Nucleophiles.—*p*-Tolyl vinyl sulfoxide (19) (2 mmol) and nitroethane (5 mmol) were added to dry toluene (20 ml) containing catalyst (40) (0.02 mmol) and KF (0.3 mmol), and heated with stirring at 70 °C for 24 h. After the usual work-up the crude reaction mixture was chromatographed on silica with ether–light petroleum (1 : 1) to give optically active *p*-tolyl vinyl sulfoxide in 20% yield; $[\alpha]_{\text{D}}^{20} + 13^\circ$ (c 1.0 in Me_2CO), 13% enantiomeric excess,⁸ and a diastereoisomeric mixture of 3-nitro-1-*p*-tolylsulphinybutane (29a), (29b) in a 1 : 1 ratio by ^1H n.m.r. spectroscopy in the presence of $\text{Eu}(\text{tfc})_3$ shift reagent, $[\alpha]_{\text{D}}^{20} 0$ (c 2.9 in Me_2CO), m.p. 60–65 °C (Found: C, 58.3; H, 6.6; N, 6.2. $\text{C}_{11}\text{H}_{15}\text{NO}_3\text{S}$ requires C, 58.1; H, 6.65; N, 6.2%).

When the reaction was repeated under the same conditions with *p*-tolyl *trans*-styryl sulfoxide (20) only starting material was recovered.

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