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Synthesis of New Chiral Phase-transfer Catalysts and Their Application to Michael Additions

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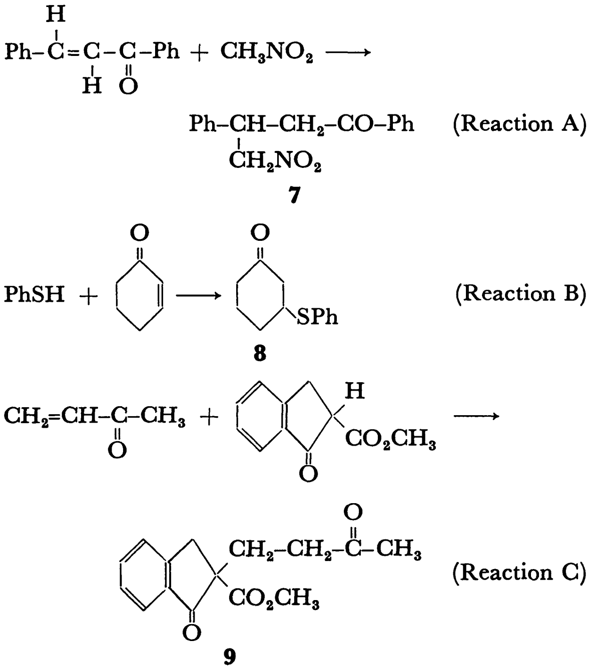
A series of chiral onium salts derived from (L)-(+)-methionine have been examined for the catalysis of Michael additions in phase-transfer conditions. The chemical yields are high, but no asymmetric induction was observed. Catalyst **6** represents the first example of an onium salt anchored to a polimeric matrix having a higher catalytic efficiency than its soluble counterpart.

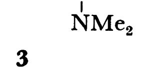
In the last few years much interest has been aroused by stereoselective syntheses under phase-transfer conditions in the presence of chiral "onium salts" as catalysts.[1)] The quaternary ammonium salts, usually derived from ephedra or cinchona alkaloids, must have a hydroxyl group in the β-position to the "onium" function in order for asymmetric induction and/or kinetic resolution[1,2)] to be observed. In the search for new chiral phase-transfer catalysts, we have now prepared onium salts containing the SO group as an asymmetric centre. The behaviour of the sulfinyl group, compared to other chiral groups, is indeed particularly influenced by ligands very different from each other from a stereoelectronic point of view; an oxygen, a lone pair and two aryl or alkyl groups. This accounts for the high conformational preference of sulfoxides as well as the high stereoselectivity in reactions involving chiral or prochiral groups α or β to the sulfur moiety.[3)]

For this reason we have investigated the behaviour of the chiral onium salts (**1**—**2**), derived from (L)-(+)-methionine, in a series of reactions carried out under phase-transfer conditions. These are the Michael additions of nitromethane to *trans*-chalcone and of thiophenol to 2-cyclohexen-1-one, [Reactions A and B respectively] and the addition of methyl vinyl ketone to methyl 1-oxoindan-2-carboxylate (Reaction C). For the sake of comparison the same reactions have been performed in homogeneous medium in the presence of catalytic amounts of catalysts **3** and **4**. The effect of the binding of the catalyst to a polymeric solid support [catalysts **5** and **6**] has also been examined.

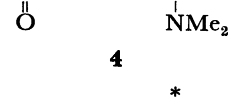

(Reaction A)
7
(Reaction B)
8
(Reaction C)
9

Results and Discussion

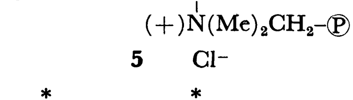
Synthesis of the Catalysts. All catalysts were prepared starting from commercial (L)-(+)-methionine (**10**), $[\alpha]^{20}_{546}$ $+28.7°$.


$\mathrm{CH_3\text{-}S\text{-}CH_2\text{-}CH_2\text{-}\underset{(+)N(Me)_2CH_2Ph}{\overset{*}{C}H}\text{-}CH_2OH}$

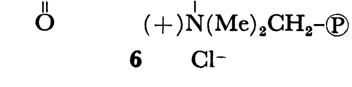
1 $\mathrm{Cl^-}$


$\mathrm{CH_3\text{-}\underset{O}{\overset{*}{S}}\text{-}CH_2\text{-}CH_2\text{-}\underset{(+)N(Me)_2CH_2Ph}{\overset{*}{C}H}\text{-}CH_2OH}$

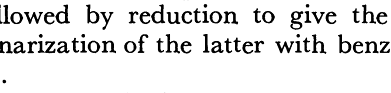
2 $\mathrm{Cl^-}$


$\mathrm{CH_3\text{-}S\text{-}CH_2\text{-}CH_2\text{-}\underset{NMe_2}{\overset{*}{C}H}\text{-}CH_2OH}$

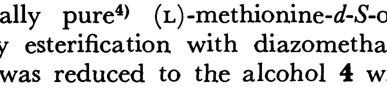
3


$\mathrm{CH_3\text{-}\underset{O}{S}\text{-}CH_2\text{-}CH_2\text{-}\underset{NMe_2}{\overset{*}{C}H}\text{-}CH_2OH}$

4


$\mathrm{CH_3\text{-}S\text{-}CH_2\text{-}CH_2\text{-}\underset{(+)N(Me)_2CH_2\text{-}\textcircled{P}}{\overset{*}{C}H}\text{-}CH_2OH}$

5 $\mathrm{Cl^-}$

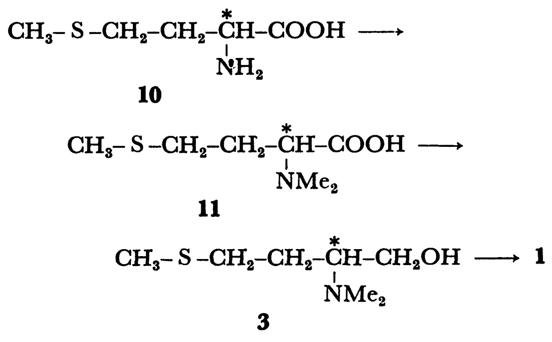

$\mathrm{CH_3\text{-}\underset{O}{\overset{*}{S}}\text{-}CH_2\text{-}CH_2\text{-}\underset{(+)N(Me)_2CH_2\text{-}\textcircled{P}}{\overset{*}{C}H}\text{-}CH_2OH}$

6 $\mathrm{Cl^-}$

The onium salt **1** was prepared by methylation of (+)-**10**, followed by reduction to give the alcohol **3** and quaternarization of the latter with benzyl chloride (Scheme 1).

Similarly **2** was obtained by methylation of diastereomerically pure[4)] (L)-methionine-*d*-*S*-oxide (**12**), followed by esterification with diazomethane to give **14**, which was reduced to the alcohol **4** with $LiAlH_4$ and quaternarizated to **2** with benzyl chloride (Scheme 2).

The catalysts **5** and **6** supported on a polymeric matrix were prepared by reaction of alcohols **3** and **4** with chloromethylated polystyrene in anhydrous DMF



$$CH_3\text{-}S\text{-}CH_2\text{-}CH_2\text{-}\underset{NH_2}{\overset{*}{C}H}\text{-}COOH \longrightarrow$$

10

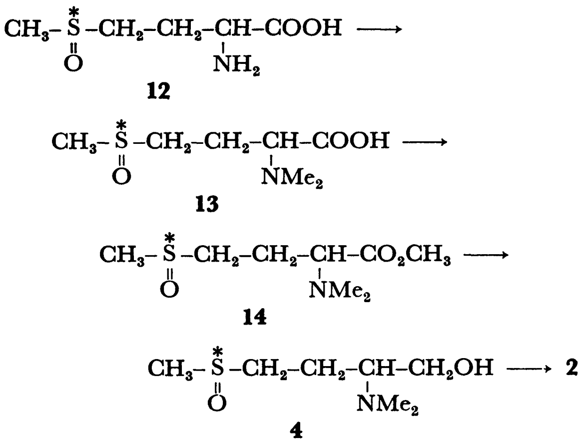
$$CH_3\text{-}S\text{-}CH_2\text{-}CH_2\text{-}\underset{NMe_2}{\overset{*}{C}H}\text{-}COOH \longrightarrow$$

11

$$CH_3\text{-}S\text{-}CH_2\text{-}CH_2\text{-}\underset{NMe_2}{\overset{*}{C}H}\text{-}CH_2OH \longrightarrow \mathbf{1}$$

3

Scheme 1.



$$CH_3\text{-}\underset{O}{\overset{*}{\overset{}{S}}}\text{-}CH_2\text{-}CH_2\text{-}\underset{NH_2}{CH}\text{-}COOH \longrightarrow$$

12

$$CH_3\text{-}\underset{O}{\overset{*}{S}}\text{-}CH_2\text{-}CH_2\text{-}\underset{NMe_2}{CH}\text{-}COOH \longrightarrow$$

13

$$CH_3\text{-}\underset{O}{\overset{*}{S}}\text{-}CH_2\text{-}CH_2\text{-}\underset{NMe_2}{CH}\text{-}CO_2CH_3 \longrightarrow$$

14

$$CH_3\text{-}\underset{O}{\overset{*}{S}}\text{-}CH_2\text{-}CH_2\text{-}\underset{NMe_2}{CH}\text{-}CH_2OH \longrightarrow \mathbf{2}$$

4

Scheme 2.

as solvent (see Experimental).

Michael Additions. The reactions with catalysts **1**, **2**, **5**, and **6**, were carried out at room temperature under solid-liquid phase-transfer conditions in toluene as solvent in the presence of an excess of solid KF. In the case of catalysts **3**, **4** the reactions were performed in the same solvent and in the absence of the inorganic salt.

The results collected in the Table show that conversion into the Michael adducts is more efficient under phase-transfer conditions with catalysts **1**, **2** than in homogeneous medium with catalysts **3** and **4**. The difference is particularly noticeable in the nitromethane addition to *trans*-chalcone; a reaction which occurs only in the presence of the onium salts and potassium fluoride. In homogeneous medium methioninol *S*-oxide (**4**) is a more efficient catalyst than the corresponding sulfide (**3**).

As far as soluble "onium" salts are concerned, catalyst **1** is more efficient than catalyst **2** in the nitromethane addition to *trans*-chalcone, whereas the latter is more efficient in the addition of thiophenol to 2-cyclohexen-1-one. Both **1** and **2** gave similar results in the Michael addition of methyl vinyl ketone to methyl 1-oxoindan-2-carboxylate. The same behaviour was observed with catalysts **5** and **6** supported on a polimeric matrix. It should also be pointed out that in Reactions A and B the yields obtained with catalyst **6** are equal or higher than those obtained with the corresponding soluble onium salts (**2**). To the best of our knowledge this is the first example of an onium salt supported on a polimeric matrix having a catalytic efficiency comparable to that of the corresponding soluble onium salt.[5,6]

TABLE 1. MICHAEL ADDITIONS AT ROOM TEMPERATURE IN THE PRESENCE OF CHIRAL CATALYSTS 1—6 IN TOLUENE AS SOLVENT

Catalyst	Yield/%		
	Reaction A[a]	Reaction B[b]	Reaction C[c]
(**3**)	0	40	45[d]
(**1**)	99	68	88[e]
(**5**)	75	93	85[d]
(**4**)	0	54	57[f]
(**2**)	35	87	86[d]
(**6**)	54	96	89[d]
(**15**)	50	80	99[g]

a) Nitromethane 75 mmol, *trans*-chalcone 5 mmol, catalyst 0.5 mmol, 3 d; KF 7.5 mmol in the case of "onium" catalysts. b) Thiophenol 5 mmol, 2-cyclohexen-1-one 6.25 mmol, catalyst 0.02 mmol, 4 h; KF 7.5 mmol in the case of "onium" catalysts. c) Methyl vinyl ketone 4 mmol, methyl 1-oxoindan-2-carboxylate 2 mmol, catalyst 0.025 mmol, KF 2.5 mmol in the case of "onium" catalysts. d) For 3 d. e) For 20 h. f) For 4 d. g) For 3 h.

The last relevant feature of the new phase-transfer catalysts **1** and **2** in comparison with the "classical" *N*-dodecyl-*N*-methyl-ephedrinium bromide (**15**),[1] is that they give higher conversions into the Michael adducts in Reactions A and B, but they are less active than **15** in the reaction of methyl vinyl ketone with methyl 1-oxoindan-2-carboxylate (Reaction C).[7] This suggests that among these catalysts there is selectivity, depending on the nature of the Michael donors and acceptors.

Finally the polymer supported catalysts **5** and **6**, as is normal for this type of reactions, are easily removed from the reaction mixture by a simple filtration and retain their catalytic efficiency after several reactions.[6] Although it was hoped that the optically active catalysts **1**—**6** might lead to asymmetric induction in the chiral Michael adducts, unfortunately all samples were obtained in a racemic form.[8] These results were particularly frustrating in the case of catalysts **2**, **6** in view of the known ability of the sulfinyl group to promote asymmetric induction.[3,9]

Experimental

General. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Infrared spectra were recorded on a Perkin-Elmer 377 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian HA 100 and/or a Varian A 390 instrument.

Materials. (L)-Methionine-*d*-*S*-oxide was prepared according to the literature; $[\alpha]_D^{20}$ +127° (*c* 1.15, 1 mol dm^{-3} HCl); lit,[4] $[\alpha]_D^{24}$ +131° (*c* 1.8, 1 mol dm^{-3} HCl). It has the (*S*,*S*) absolute configuration.[4] Methyl 1-oxoindan-2-carboxylate was obtained by literature methods.[10]

N,N-*Dimethyl-(*L*)-methionine.* (L)-(+)-Methionine (**10**) was methylated by reductive condensation with formaldehyde and hydrogen in the presence of palladized charcoal for 18 h according to Bowman.[11] The product, obtained in 86% yield, had mp 186 °C, $[\alpha]_D^{20}$ +57.0° (*c* 1, H_2O) lit,[12] mp 187 °C, $[\alpha]_D^{20}$ +57.9° (H_2O).

N,N-*Dimethyl-(*L*)-methioninol.* Boron trifluoride etherate (12.2 mmol) was added dropwise under nitrogen at room temperature to a stirred suspension of sulfide **11** (10 mmol) and $NaBH_4$ (12.2 mmol) in anhydrous tetrahydrofuran (40 ml). The mixture was stirred for 15 h, then a second aliquot of boron trifluoride (12.2 mmol) and $NaBH_4$ (12.2 mmol) was added. The mixture was stirred for 48 h, then ethanol (10 ml) was added and the suspension was acidified to pH 1 with 3 mol dm^{-3} hydrochloric acid. The mixture was evaporated off *in vacuo.* Water (15 ml) was added to the residue.

The insoluble material was filtered off and NaOH was added to the solution up to pH 10. Extraction with diethyl ether and evaporation of the solvent afforded the title compound in 75% yield. It had n_D^{20} 1.4949, $[\alpha]_D^{20}$ +35.0° (*c* 1.1, CH_2Cl_2). Compound **3** had been previously obtained[13] by reduction of *N,N*-dimethyl methionine methyl ester with $LiAlH_4$.

Benzyldimethyl (3-Methylthio-1-hydroxymethylpropyl)ammonium Chloride. Compound **1** was obtained by reaction of **3** (2.75 mmol) with benzyl chloride (2.8 mmol) in ethanol (15 ml) at 50 °C for 24 h. After evaporation of the solvent under vacuum and treatment of the residue with pentane, compound **1** was obtained (67%), n_D^{21} 1.5605, $[\alpha]_D^{20}$ +26.9° (*c* 4.95, EtOH). Found: C, 58.00; H, 8.30; N, 4.83%. Calcd for $C_{14}H_{24}ClNOS$: C, 58.02; H, 8.35; N, 4.83%.

N,N-*Dimethyl-(*L*)-methionine-*d-S-*oxide.* Sulfoxide **12** was methylated as described above in the case of sulfide **10** with a 5 h reaction time. Compound **13** (81%) had mp 196—197 °C, $[\alpha]_D^{20}$ +141.0° (*c* 1.1, 1 mol dm^{-3} HCl). Found: C, 43.40; H, 7.78; N, 7.23%. Calcd for $C_7H_{15}NO_3S$: C, 43.50; H, 7.82; N, 7.25%.

N,N-*Dimethyl-(*L*)-methionine-*d-S-*oxide Methyl Ester.* Acid **13** (27 mmol) was dissolved in methanol (50 ml), cooled at 0 °C, and esterified with an ethereal solution of diazomethane. The usual work up afforded the crude ester which was purified by column cromatography (SiO_2, CH_2Cl_2/CH_3OH 9: 1). Compound **14** (80%) had mp 55—57 °C, $[\alpha]_D^{20}$ +20.9° (*c* 2.1, CH_2Cl_2). Found: C, 46.27; H, 8.25; N, 6.71%. Calcd for $C_8H_{17}NO_3S$: C, 46.35; H, 8.27; N, 6.76%.

N,N-*Dimethyl-(*L*)-methioninol-*d-S-*oxide.* Ester **14** (4 mmol) was added at 0 °C under nitrogen to a stirred suspension of $LiAlH_4$ (6 mmol) in anhydrous diethyl ether (40 ml). The mixture was stirred at room temperature for 6 h, monitoring the reaction by IR. Excess of hydride was destroyed and the mixture was evaporated off. The residue was extracted with dichloromethane and the organic layer evaporated off. The alcohol **4** (78%) had mp 58—61 °C, $[\alpha]_D^{20}$ +100.4° (*c* 1.04, CH_2Cl_2). Found: C, 46.70; H, 9.56; N, 7.75%. Calcd for $C_7H_{17}NO_2S$: C, 46.89; H, 9.56; N, 7.81%.

Benzyldimethyl (3-Methylsulfinyl-1-hydroxymethylpropyl)ammonium Chloride. Onium salt **2** was obtained by reaction of **4** with benzyl chloride with a 48 h reaction time as described above in the case of **1**. Compound **2**, a viscous oil, (66%) had $[\alpha]_D^{20}$ +51.1° (*c* 2.0, CH_3OH). Found: C, 55.02; H, 7.88; N, 4.60%. Calcd for $C_{14}H_{24}ClNO_2S$: C, 54.98; H, 7.91; N, 4.58%.

Poly(styrene-divynilbenzene) Onium Salts (5 and 6). Equimolecular amounts of commercial anion-exchange resin in the chloride form Biobeads S-X1 (Cl^-); exchange capacity 1.25 mequiv. Cl/g and sulfide **3** or sulfoxide **4** were heated at 60 °C under stirring in DMF as solvent (10 ml for 1 mmol of substrate) for 3 d.

The resin was filtered off, washed with absolute ethanol, water, 1 mol dm^{-3} HCl, water, absolute ethanol, and anhydrous diethyl ether. The exchange capacity of **5** and **6**, determined by Volhard's method, were 1.156 and 0.84 mequiv Cl/g, respectively.

Michael Additions. Michaels additions of nitromethane to *trans*-chalcone, of thiophenol to 2-cyclohexene-1-one, and of methylvinyl ketone to methyl 1-oxoindan-2-carboxylate in homogeneous and phase-tranfser conditions were carried on according to procedures described in the literature.[2a,14] Reactions with polymer supported catalysts **5** and **6** were performed as the corresponding reactions in the presence of soluble onium salt, except that at the end of the reaction the catalysts **5** and **6** were removed by simple filtration. Adducts **7**—**9** had physical and spectroscopic properties identical to those of reference samples prepared according to known procedures.[2a,14] Compounds **7**, **8**, and **9**, obtained by using **15** as catalyst had $[\alpha]_{578}^{21}$ −9.8° (*c* 2, CH_2Cl_2),[2a] $[\alpha]_{578}^{25}$ −2.0° (*c* 2, C_6H_6),[2a] and $[\alpha]_{578}^{25}$ −2.56° (*c* 2, C_6H_6); 3.3% e.e.[14]

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7) The adducts obtained by using **15** as catalyst are optically active (see Experimental).

8) In ancillary experiments it was shown that also a diastereomeric mixture of sulfoxides **2** gave racemic Michael adducts.

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