quenched with a saturated aqueous solution of $(NH_4)_2SO_4$. The THF was removed in vacuo on a rotary evaporator with bath temperature maintained below 30 °C. The aqueous phase was washed with diethyl ether (2 × 50 mL), acidified to pH 1 (no lower!) with concentrated hydrochloric acid, salted with NaCl, and extracted with diethyl ether (3 × 50 mL). The extract was dried over $MgSO_4$, filtered, and evaporated leaving a tan solid residue. Crystallization from hexane provided 723 mg (65%) of cubane[^{13}C]carboxylic acid as white crystals: mp 124–125 °C; ^{1}H NMR δ 4.27 (m, 3 H), 4.00 (m, 3 H), 3.98 (m, 1 H) ppm; ^{13}C NMR δ 178.5 (enhanced), 49.4, 47.8, 45.2 ppm.

Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octyl Phenyl [^{13}C]Ketone. Phenyllithium in cyclohexane (Aldrich, 9.5 mL, 2 M, 18.9 mmol) was added dropwise over 15 min to a solution of cubane[^{13}C]-carboxylic acid (1.23 g, 8.31 mmol) in 35 mL of dry diethyl ether at −70 °C. The resulting reddish-brown heterogenous mixture was stirred at −70 °C for 0.5 h and then at room temperature for 0.5 h. It was recooled to −70 °C and quenched with 5 mL of ACS grade acetone. The mixture was warmed to room temperature, diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$ (20 mL) and water (20 mL), dried over $MgSO_4$, and filtered. The solvents were carefully removed in vacuo on a rotary evaporator with bath temperature maintained below 30 °C to give 2.65 g of crude ketone. Crystallization from methanol gave 1.54 g of cubyl phenyl ketone (89%) as beige crystals. Further purification by vacuum sublimation gave colorless crystals: mp 110–111 °C; IR (CCl_4) ν 2988, 1664, 1325, 947 cm^{-1}; ^{1}H NMR δ 7.81 (m, 2 H), 7.52 (m, 1 H), 7.43 (m, 2 H), 4.46 (m, 3 H), 4.14 (m, 1 H), 4.09 ppm (m, 3 H); ^{13}C NMR δ 198.2 (enhanced), 134.9, 132.8, 128.6, 127.9, 63.1, 50.9, 47.0, 45.2 ppm.

Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octyl Phenyl [^{13}C]Ketone (*p*-Tolylsulfonyl)hydrazone (6). Cubyl phenyl [^{13}C]ketone (0.87 g, 4.2 mmol) and tosylhydrazide (0.86 g, 4.6 mmol) were dissolved separately in minimal portions of hot absolute ethanol. The solutions were combined and stirred at room temperature for 3 days. (Do not heat!) The solvents were removed in vacuo, and the residue was crystallized from methanol to give 1.37 g of cubyl phenyl ketone tosylhydrazone (87%) as a white powder: mp 152 °C dec; IR (CCl_4) ν 3285, 2994, 1598, 1160 cm^{-1}; ^{1}H NMR δ 7.79 (m, 2 H), 7.42 (m, 3 H), 7.31 (m, 3 H), 7.02 (m, 1 H), 4.10 (m, 3 H), 3.97 (m, 1 H), 3.86 (m, 3 H), 2.45 ppm (s, 3 H); ^{13}C NMR δ 156.5 (enhanced), 140.8, 135.4, 130.8, 129.6, 129.5, 129.4, 128.0, 60.3, 49.3, 48.1, 44.3, 21.6 ppm.

9-Ethoxy-1-phenyl[1-^{13}C]pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (7) and 9-Ethoxy-9-phenyl[9-^{13}C]pentacyclo-[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (8). Cubyl phenyl [^{13}C]ketone tosylhydrazone (97 mg, 0.26 mmol) was added to a solution of sodium ethoxide in ethanol prepared earlier from 71 mg (3.1 mmol) of sodium and 3 mL of absolute ethanol. The reaction mixture was heated to reflux for 5 h. The solvent was carefully removed in vacuo on a rotary evaporator with bath temperature maintained below 30 °C. The residue was taken up in 30 mL of CH_2Cl_2, and the solution washed with a saturated aqueous solution of $NaHCO_3$ (2 × 15 mL) and water (2 × 15 mL) and then dried over $MgSO_4$, filtered, and evaporated, leaving a brown oil. Column chromatography on Merck grade 60 silica gel (230–400 mesh) with 1:10 EtOAc/hexane gave a mixture of the title compounds as a light yellow oil. The ^{13}C NMR spectrum was consistent with published data.[2f] Enhancements were observed only at 101.7 and 61.0 ppm.

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Registry No. 1, 109719-29-1; 2, 109719-35-9; 4, 109719-34-8; 6, 124687-69-0; 7, 124687-70-3; 8, 124716-13-8; $Ba^{13}CO_3$, 51956-33-3; $^{13}CO_2$, 1111-72-4; pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane[^{13}C]carboxylic acid, 112043-88-6; iodocubane, 74725-77-2; cubylithium, 72507-56-3; pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octyl phenyl [^{13}C]ketone, 124687-68-9.

A General Procedure for the Selective Oxidation of Sulfides to Sulfoxides by Nitric Acid: Tetrabromoaurate(III) Catalyst in a Biphasic System

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Tetrabromoaurate(III) is an efficient catalyst for the oxidation of sulfides to sulfoxides by nitric acid in a biphasic system (nitromethane/water). The system is selective and can be applied to the oxidation of any type of dialkyl and alkyl aryl sulfide and also of diaryl sulfides activated by electron-releasing substituents. The nature of the active species has been investigated in relation to the mechanistic aspects.

Sulfoxides are gaining considerable interest as intermediates in organic synthesis and recent studies have been devoted to increasing the range of such compounds or improving their method of preparation.[1]

We have recently reported a procedure for the selective oxidation of dialkyl sulfides to the corresponding sulfoxides in a biphasic system using tetrabutylammonium tetrachloroaurate(III), $TBA^+AuCl_4^-$, as catalyst.[2,3] This procedure, however, was not applicable to the oxidation of hindered dialkyl sulfides, alkyl aryl sulfides, and diaryl sulfides, which required reaction times that were too long.

In an attempt to improve the above process, tetrabutylammonium tetrabromoaurate(III), $TBA^+AuBr_4^-$, has

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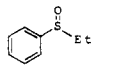
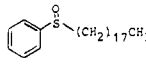
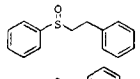
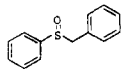
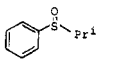
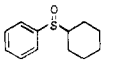
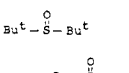
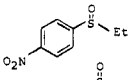
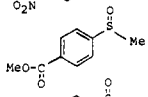
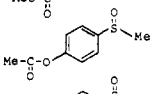
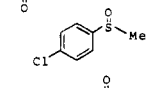
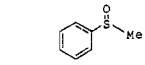
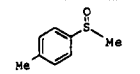
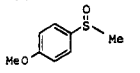
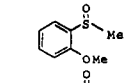
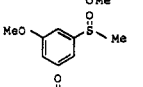
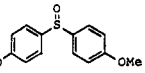
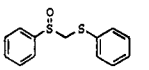
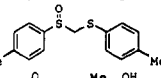
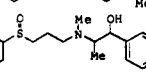
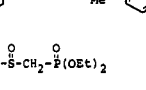
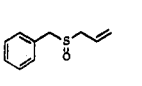
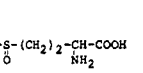
Table I. Oxidation of Sulfides with Nitric Acid in the Same Biphasic System but Using a Different Gold(III) Catalyst

sulfide (n)[a]	sulfoxide (n')[a]	$TBA^+AuBr_4^-$ reactn time (h)	$TBA^+AuBr_4^-$ yield[b] (%)	$TBA^+AuCl_4^-$ reactn time[c] (h)	$TBA^+AuCl_4^-$ yield[b] (%)
(1)[5]	 (1')[6]	0.5	91	6	92
(2)[7]	 (2')[7]	1.5	93	19	50
(3)[8]	 (3')[2]	2	92	10	50
(4)[9]	 (4')[6]	2	91	18	70
(5)[10]	 (5')[11]	2.5	95	26	44
(6)[12]	 (6')[12]	2	89	-	-
(7)	 (7')[13]	0.3	93	24	15
(8)[14]	 (8')	48	94	-	-
(9)[15]	 (9')[16]	28	87	23	10
(10)[17]	 (10')[17]	3	97	30	95
(11)[18]	 (11')[19]	2	88	6	75
(12)	 (12')[6]	1	93	1.5	5

sulfide (n)[a]	sulfoxide (n')[a]	$TBA^+AuBr_4^-$ reactn time (h)	$TBA^+AuBr_4^-$ yield[b] (%)	$TBA^+AuCl_4^-$ reactn time[c] (h)	$TBA^+AuCl_4^-$ yield[b] (%)
(13)[5]	 (13')[20]	0.3	89	3	92
(14)[21]	 (14')[17]	0.1	92	0.3	94
(15)[22]	 (15')[23]	0.1	93	-	-
(16)[17]	 (16')[17]	4	87	-	-
(17)[24]	 (17')[11]	0.7	92	-	-
(18)	 (18')[25]	15	78	-	-
(19)[26]	 (19')[27]	15	81	-	-
(20)	 (20')	16	89	-	-
(21)	 (21')	1.5	88	24	7
(22)[28]	 (22')[29]	2	86	-	-
(23)	 (23')[d]	1	95[d]	48	80

[a] Satisfactory elemental analyses were obtained for all compounds. Spectral data (IR, ^1H NMR, MS in chemical ionization) were in agreement with the proposed structure and with literature data when reported. [b] Yields were calculated on the starting sulfide and given on the pure isolated product. Purity was checked by analytical HPLC. [c] Reactions that, being too slow, could not be of practical utility were stopped before all the starting substrate had reacted. [d] Two diastereoisomers were obtained; their molar ratio was 5:3 in favor of the isomer with the same absolute configuration at the two chiral centers.

been used as a catalyst. In such conditions, the reaction was of general use mainly for the selective oxidation of the "thio group" and it succeeded also with substrates of biological interest.

The results of this investigation dealing with the mechanistic and synthetic aspects of the new system are reported in this paper.

Results and Discussion

The starting sulfide was added to a biphasic system made up of nitromethane and 10% aqueous nitric acid (1:2, v/v) that contains a catalytic amount of $TBA^+AuBr_4^-$. After being stirred for the time required, the extract in dichloromethane was washed with an aqueous solution of sodium thiosulfate to eliminate the catalyst and dried, and the solvent was distilled under reduced pressure. By this procedure several types of sulfides have been oxidized to the corresponding sulfoxide and the results are summarized in Table I and compared with those obtained with $TBA^+AuCl_4^-$ as catalyst.

The salient characteristics of the catalytic system are the following:

(a) The oxidation rate is higher than that observed in the case of $TBA^+AuCl_4^-$ catalyst, by at least a factor of 10. Therefore, not only hindered dialkyl sulfides and alkyl aryl sulfides but also diaryl sulfides, activated by electron-donating substituents (17), are easily oxidized under mild conditions to the corresponding sulfoxides.

The intrinsically greater activity of the tetrabromoaurate(III) catalyst was evidenced by performing an experiment in which the rates of oxidation of methyl *p*-tolyl sulfide (13), using stoichiometric amounts (see Experimental Section) of $TBA^+AuCl_4^-$ and $TBA^+AuBr_4^-$, were measured. The disappearance of the sulfide and the formation of the sulfoxide were followed by HPLC. The measured half lives ($\tau_{1/2}$) were 180 and 15 min, respectively.[4]

(4) The measured rate values under these conditions are not comparable with those of Table I since the use of sulfuric acid [which does not reoxidize Au(I) to Au(III)] instead of nitric acid makes different the reaction conditions.

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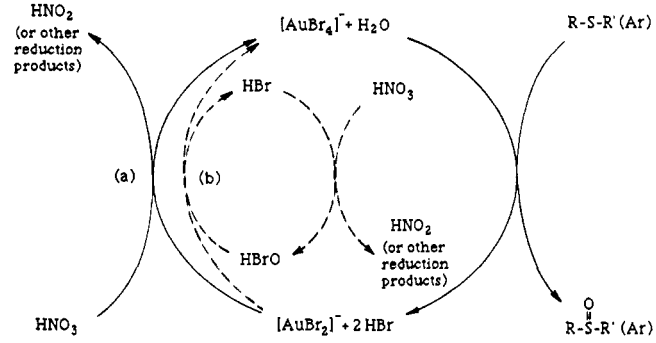
Scheme I



(b) The method is selective. Hence: (i) no sulfone formation is detected; (ii) the oxidation takes place at the sulfur atom even in the presence of other oxidable groups in the side chain of the sulfide, such as allyl (**22**), tertiary amino, and hydroxy groups (**20**); (iii) only one sulfur atom is oxidized to sulfoxide in the case of substrates **18** and **19**.

(c) The reactivity is enhanced by increasing the electron-donating ability of the substituents on the aryl moiety (NO_2 < COOMe < OCOMe < Cl < H < Me < OMe) as shown by para-substituted aryl methyl sulfides (**8–14**). Moreover, a methoxy group in the ortho or para position (**15**, **14**) causes a comparable activation of the substrate while the same group in the meta position (**16**) is completely ineffective.

(d) The catalytic system can be successfully applied to the oxidation of diethyl [(ethylthio)methyl]phosphonate (**21**), which represents a class of compounds of broad utility in organic synthesis.

The site specificity of the catalytic system was checked by performing the oxidation of allyl benzyl sulfide (**22**) and methyl 3-methoxyphenyl sulfide (**16**) with this system and with bromine. While Br_2 reacts with **22** and **16** to give 2,3-dibromopropyl benzyl sulfide and 4,6-dibromo-3-methoxyphenyl methyl sulfide, respectively, the tetrabromoaurate(III) system gives exclusively the corresponding sulfoxides.

The use of tetrabromoaurate(III) as catalyst has raised some additional questions concerning the nature of all active species in the system. In the catalytic cycle Au(III) is reduced to Au(I) with concomitant release of bromide ion into the solution (see Scheme I). If, under the same experimental conditions, Br^- is oxidized by nitric acid, it could, in turn, oxidize sulfide to sulfoxide. One experiment was set in which, keeping constant all other conditions, the $TBA^+AuBr_4^-$ catalyst was replaced by TBA^+Br^-. The new system was effective in catalyzing the oxidation of a reactive substrate such as *n*-Bu_2S to the corresponding sulfoxide while the addition of $TBA^+HSO_4^-$ instead of TBA^+Br^- had no catalytic effect. The catalytic role of the bromide was confirmed by an experiment in which the TBA^+Br^- catalyst was replaced by KBr. Under these conditions the oxidation to sulfoxide of *n*-Bu_2S was negligibly small. This prompted us to a more detailed investigation of all species formed in the tetrabromoaurate(III) and in the bromide anion catalytic systems. Three different sulfides were used as reference substrates: *n*-Bu_2S, *t*-Bu_2S (**7**), and L-(+)-methionine [(*S*)-2-amino-4-(methylthio)butyric acid] (**23**); the first two sulfides concentrate mainly in the organic phase while the last sulfide concentrates in water.

The composition of the catalytic system was analyzed (Experimental Section and supplementary material) (a) prior to the addition of sulfide, (b) during the oxidation reaction; and (c) after the total consumption of sulfide:

(a) Prior to the addition of the sulfide the aqueous phase contains only the NO_3^- anion while the nitromethane concentrates all the $TBA^+AuBr_4^-$ and a small quantity of NO_3^- ions. If the catalytic system is set aside for a long time (36 h), no significant changes in composition are observed.

(b) The addition of sulfide causes a rapid change in composition of the organic phase, which becomes colorless in a few seconds: the $[AuBr_4]^-$ species disappears and is replaced by $[AuBr_2]^-$, the concentration of sulfide decreases as the reaction time increases while, simultaneously, the sulfoxide concentration increases. The aqueous phase contains, apart from NO_3^-, a certain amount of NO_2^- and a small quantity of Br^- originating from the reduction of the gold catalyst (see Scheme I).

(c) At the end of the reaction the organic phase turns red. It again contains the $[AuBr_4]^-$ ion, in a concentration comparable to that of the initial solution (above 90%), and no $[AuBr_2]^-$. The sulfide has been replaced by an equivalent amount of sulfoxide. The aqueous phase contains NO_3^-, NO_2^- (in a quantity that is ca. 1/10 of that corresponding to the oxidized sulfide), and a trace amount of Br^- (see Scheme I). The gas phase, in equilibrium with the liquid, contains NO (checked by mass spectrum), which appears to be the major product of reduction of nitric acid. The catalytic cycle can be repeated several times by successive addition of new aliquots of sulfide. Starting with L-methionine (**23**), two diastereoisomers, having a different configuration at the sulfur atom, are formed. Their molar ratio, measured directly on the reaction mixture by HPLC, is ca. 5:3. The more abundant isomer can be obtained in a pure form by crystallization from acetone–ethanol (1:1 v/v) of the raw material and has the same absolute configuration at the carbon and sulfur chiral centers.[30]

The catalytic system containing TBA^+Br^- instead of $TBA^+AuBr_4^-$, as catalyst was also studied in detail.

(a) Before the addition of sulfide, the biphasic system contains Br^- in the organic phase in a quantity comparable to that of the added TBA^+Br^-, NO_3^-, and a trace amount of Br^- in the aqueous phase. We can also exclude the presence of detectable amounts of $HBrO_3$. The oxidized species of the HBr may be HBrO,[31] although it was not detectable by HPLC due to its inherent instability.

(b) In the presence of added sulfide, different results are obtained depending on the type of substrate. *n*-Bu_2S is oxidized to the corresponding sulfoxide with a rate and a selectivity comparable to those observed in the tetrabromoaurate(III) system. In the aqueous phase, apart from NO_3^-, there was also the appearance of NO_2^-. Also *t*-Bu_2S (**7**) reacts with a rate similar to that observed when the

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gold catalyst is used, but the corresponding sulfoxide is only a minor component while a complex mixture of organic compounds is detected in the organic phase. It is possible that the sulfoxide is formed in the first instance but this undergoes a further transformation under the action of the oxidizing system. No reaction is observed in the case of L-methionine (**23**).

The above-reported results are in agreement with the catalytic cycle shown in Scheme I, from which it is evident that the reduced species $[AuBr_2]^-$ can be reoxidized to $[AuBr_4]^-$ by either (pathway a) HNO_3 and/or (pathway b) by the HBrO that can derive[31] from HBr produced in the first step of the reaction.

The reoxidation of Au(I) to Au(III) is undoubtedly faster than the oxidation of sulfide to sulfoxide by HNO_3 and/or HBrO. In fact, L-methionine (**23**) [which is completely oxidized to the corresponding sulfoxide by the tetrabromoaurate(III) system in 1 h] is unaffected by the bromide system after 2 h. With a much longer reaction time its concentration slowly decreases but only a trace amount of sulfoxide is formed.

These results indicate that the bromide anion, although capable of catalyzing the oxidation of some reactive sulfides to the corresponding stable sulfoxides, only plays, at best, a very marginal role in the case of the tetrabromoaurate(III) system. The simplest explanation is that the eventual products of oxidation of HBr by nitric acid react preferentially with Au(I) (pathway b in Scheme I) instead of with sulfide. Therefore, beyond any reasonable doubt, a halogen aurate(III) species is the active oxidant in the metal-catalyzed system, and the detailed mechanism should not differ from that found in the stoichiometric oxidation of sulfides by tetrachloroaurate(III), that is, an atom-transfer process with formation of a sulfonium cation, $[(SR_2X)^+$ (X = halogen)] which hydrolyzes to sulfoxide.[32]

Experimental Section

Equipment. Melting points are uncorrected and were determined with a Buchi apparatus. ^1H NMR spectra were recorded on Varian FT-80A and VXR 300 spectrometers (TMS internal standard). Mass spectra were recorded on Hewlett-Packard 5988A and HP 88A spectrometers equipped with a 5870A data system. IR spectra were recorded as films or Nujol mulls on Perkin-Elmer 337 and 297 grating spectrophotometers. Analytical high performance liquid chromatography (HPLC) was performed on a Waters Associates chromatograph (Waters Associates, Milford, MA) equipped with a U6K universal injector, two M510 solvent delivery systems, and temperature control module (TMC). Different detectors were used. They include M490 programmable multiwavelength detector, Waters 990 photo diode array (PDA), M410 refractive index (RI), M430 conductivity detector, and LS-5 luminescence spectrometer (Perkin-Elmer). Chromatographic data were collected and processed on a Waters 840 chromatography control and data station. High resolution gas chromatography (HRGC) was performed on a Carlo Erba Fractovap 4160 or a Hewlett-Packard Mod 7620A instrument with FID detector. HRGC column: Alltech Bonded FSOT RSL-300 (polyphenylmethylsiloxane), 10 m × 0.53 mm (i.d.), 1.2 μm film thickness. HPLC columns: Waters IC-PAK anion column (4.6 × 50 mm) and Guard column; Hypersil ODS column, 5 μm, 4.0 × 250 mm; Hamilton PRP-1 column, 10 μm, 4.0 × 50 mm. Analytical data (C, H, N, and S) were obtained from Mikroanalytisches Labor Pascher, Remagen-Bandorf (Germany).

Starting Materials. Sulfides **1**, **7**, **12**, **18**, **21**, and **23** are commercially available and were used without further purification. The remaining sulfides (except **20**) were prepared either by reaction of thiols with the appropriate haloalkane in phase-transfer conditions (PTC)[33] or according to references cited in Table I.

Preparation of *N*-[3-(Phenylthio)propyl]-L-(−)-ephedrine (20). A sligth variation of the method of Landini[33] was used. A benzene solution (50 mL) of thiophenol (11 g, 0.1 mol) and 1,3-dibromopropane (20.2 g, 0.1 mol) was reacted with an aqueous solution (20 mL) of sodium hydroxide (4.4 g, 0.11 mol) under phase-transfer conditions (TBA^+Br^-, 0.16 g, 0.5 mmol). After 2 h of stirring at 20 °C, the reaction mixture was extracted with CH_2Cl_2, the organic layer was washed with water and dried over Na_2SO_4, and the solvent was distilled under reduced pressure. The residue was chromatographed on an open column of silica gel (Si60, 0.040–0.063 mm, eluent cyclohexane) from which 3-bromopropyl phenyl sulfide was obtained (68% yield): IR (liquid film) 1600, 1490, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.10 (m, 5 H), 3.43 (t, J = 6.75 Hz, 2 H), 3.00 (t, J = 6.75 Hz, 2 H), 2.09 (quintet, J = 6.75 Hz, 2 H). A mixture of 3-bromopropyl phenyl sulfide(4.62 g, 2.0 mmol), L-(−)-ephedrine [(1*R*,2*S*)-2-(methylamino)-1-phenyl-1-propanol] (3.30 g, 2.0 mmol) and Et_3N (6.07 g, 6.0 mmol) was heated to reflux for 2 h, then cooled, treated with water, and extracted with CH_2Cl_2. The organic layer was washed with water and dried over Na_2SO_4, and the solvent was distilled under reduced pressure. The residue was chromatographed on an open column of silica gel (Si60, 0.040–0.063 mm, eluent cyclohexane/AcOEt/Et_3N, 65/30/5, v/v) from which *N*-[3-phenylthio)propyl]-L-(−)-ephedrine (**20**) was obtained (88% yield): IR (liquid film) 3450, 1245, 1070, 1005, 735, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (m, 10 H), 4.75 (d, J = 5.60 Hz, 1 H), 3.34 (br s, 1 H, D_2O exchangeable), 2.95–2.43 (m, 5 H), 2.18 (s, 3 H), 1.95–1.50 (m, 2 H), 0.88 (d, J = 6.78 Hz, 3 H).

Preparation of Tetrabutylammonium Tetrabromoaurate(III) ($TBA^+AuBr_4^-$). CH_2Cl_2 (200 mL) and TBA^+Br^- (4.25 g, 13.20 mmol) were added to a solution of tetrabromoauric acid, obtained by dissolving gold metal (2.00 g, 10.15 mmol) in a mixture of hydrobromic (60 mL, 48% in water) and nitric (20 mL, 89% in water) acids and then boiling the solution to remove all nitrogen oxides.[34] After 10 min of stirring the organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The solid residue was recrystallized from CH_2Cl_2/*n*-hexane: yield 94%, mp 176–7 °C; IR (Nujol) 1165, 1030, 885, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23 (m, 2 H), 1.75–1.60 (m, 2 H), 1.49 (sextet, J = 7.24 Hz, 2 H), 1.04 (t, J = 7.24 Hz, 3 H). Anal. Calcd for $C_{16}H_{36}NAuBr_4$: C, 25.32; H, 4.78; N, 1.84. Found: C, 25.34; H, 4.83; N, 1.68.

Preparation of Tetrabutylammonium Tetrachloroaurate(III) ($TBA^+AuCl_4^-$). The title compound was prepared according to the procedure of ref 2: mp 161–2 °C; IR (Nujol) 1485, 1350, 1030, 880, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23 (m, 2 H), 1.73–1.60 (m, 2 H), 1.48 (sextet, J = 7.24 Hz, 2 H), 1.03 (t, J = 7.24 Hz, 3 H). Anal. Calcd for $C_{16}H_{36}NAuCl_4$: C, 33.06; H, 6.24; N, 2.41. Found: C, 32.80; H, 6.30; N, 2.40.

Preparation of Tetrabutylammonium Dibromoaurate(I) ($TBA^+AuBr_2^-$). The title compound was prepared by reduction of the corresponding tetrabromoaurate(III) with di-*n*-butyl sulfide. $TBA^+AuBr_4^-$ (1 mmol) was dissolved in nitromethane (2 mL) and treated with sulfuric acid (4 mL, 1.0 M) and *n*-Bu_2S (1 mmol). After 24 h of stirring at 20 °C, the colorless organic phase, with some CH_2Cl_2 added (50 mL), was separated, washed with water, and dried over Na_2SO_4. The solvent was evaporated and the colorless solid residue crystallized from CH_2Cl_2/*n*-hexane: yield 92%; mp 87–88 °C; IR (Nujol) 1025, 880, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26 (m, 2 H), 1.75–1.60 (m, 2 H), 1.48 (sextet, J = 7.43 Hz, 2 H) 1.02 (t, J = 7.43 Hz, 3 H). Anal. Calcd for $C_{16}H_{36}NAuBr_2$: C, 32.07; H, 6.05; N, 2.34. Found: C, 31.57; H, 6.01; N, 2.45.

Oxidation Reactions. Oxidation Catalyzed by $TBA^+AuX_4^-$ (X = Cl, Br). In a typical experiment the sulfide (5.0 mmol) was dissolved in nitromethane (8 mL) and treated with aqueous HNO_3 (16 mL, 25.0 mmol, 1.56 M) in the presence of $TBA^+AuBr_4^-$ or $TBA^+AuCl_4^-$ (0.25 mmol). The two-phase reactions were carried out in a round-bottom flask under magnetic stirring (400 rpm) at room temperature; the reaction progress monitored by ^1H NMR and/or HPLC, HRGC. When no more sulfide was present, the

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mixture was extracted with CH_2Cl_2 (in the case of **20'** after neutralization with Na_2CO_3), washed with a saturated solution of $Na_2S_2O_3$ to eliminate the catalyst, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on an open column of silica gel (Si60, 0.040–0.063 mm), eluting with AcOEt/cyclohexane (50/50, v/v) (the sulfoxide **20'** was eluted with AcOEt/cyclohexane/Et_3N, 50/45/5, v/v). The purity of the compounds was checked by HPLC or HRGC. The reactions that were too slow to be of practical utility were stopped before all the starting substrate had reacted. The yields given in Table I refer to pure isolated products. The physical and spectroscopic data of the newly synthesized sulfoxides are listed below.

4-Nitrophenyl ethyl sulfoxide (8'): mp 76–78 °C; IR (Nujol) 1510, 1340, 1055, 855, 745, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (dd, AA'BB', J = 8.87 Hz, 4 H), 3.31–2.56 (m, 2 H), 1.24 (t, J = 7.50 Hz, 3 H).

***N*-[3-(Phenylsulfinyl)propyl]-L-(−)-ephedrine (20'):** IR (liquid film) 3390, 1445, 1090, 1030, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (br s, 5 H), 7.22 (br s, 5 H), 4.63 (d, J = 5.61 Hz, 1 H), 3.43 (br s, 1 H, D_2O exchangeable), 2.87–2.30 (m, 5 H), 2.15–2.07 (m, 3 H), 1.85–1.44 (m, 2 H), 0.92 (d, J = 6.71 Hz, 3 H).

Diethyl [(ethylsulfinyl)methyl]phosphonate (21'): IR (liquid film) 1260, 1040, 970, 800, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.40–3.97 (m, 4 H), 3.37–2.66 (m, 4 H), 1.39 (t, J = 7.90 Hz, 3 H), 1.37 (t, J = 7.20 Hz, 6 H).

Oxidation of L-Methionine (23) Catalyzed by $TBA^+AuX_4^-$ (X = Br, Cl). The reaction procedure was that already described. When the oxidation was complete (1 h in the case of $TBA^+AuBr_4^-$ and 48 h in the case of $TBA^+AuCl_4^-$), 8 mL of water and 4 mL of nitromethane were added to the reaction mixture and the two phases separated. The aqueous phase was extracted twice with a solution of activated liquid anion exchanger Amberlite LA-2 [11128-96-4] (16 mL) in *n*-hexane (16 mL) (to remove the excess nitric acid), washed with *n*-hexane, toluene, and chloroform, and evaporated under reduced pressure.

Oxidation of Methyl *p*-Tolyl Sulfide (13) by $TBA^+AuX_4^-$ (X = Br, Cl) under Stoichiometric Conditions. Methyl *p*-tolyl sulfide (0.1 mmol) dissolved in nitromethane (4 mL) was treated with 8 mL of sulfuric acid (1 M) and the stoichiometric amount of $TBA^+AuX_4^-$ (0.1 mmol). The composition of the reaction mixture, while being stirred at room temperature, was monitored by RP HPLC.

When the oxidation was complete (1.5 h in the case of $TBA^+AuBr_4^-$ catalyst, 20 h in the case of $TBA^+AuCl_4^-$) the reaction mixture was extracted with CH_2Cl_2, washed with a saturated aqueous solution of $Na_2S_2O_3$ to eliminate the gold complex, and dried over Na_2SO_4, and the solvent was evaporated. The solid residue of methyl *p*-tolyl sulfoxide was chromatographed on an open column of silica gel (Si60, 0.040–0.063 mm, eluent AcOEt/cyclohexane 50/50, v/v) and characterized.

Oxidation with Bromine. 3-Methoxyphenyl methyl sulfide (16) (0.77 g, 5.0 mmol, in 10 mL of CH_2Cl_2) and potassium hydrogen carbonate (1 g, 10.0 mmol, in 10 mL of water) were treated with bromine (1.60 g, 10.0 mmol, in 10 mL of CH_2Cl_2). After being stirred for 0.5 h at 20 °C, the colorless organic layer was separated, washed with water, and dried over Na_2SO_4, and the solvent was distilled under reduced pressure. The solid residue was pure 4,6-dibromo-3-methoxyphenyl methyl sulfide: mp 97–9 °C, yield 89%; IR (Nujol) 1560, 1460, 1260, 855, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (s, 1 H), 6.67 (s, 1 H), 3.90 (s, 3 H), 2.48 (s, 3 H).

The same procedure was used for the reaction of **allyl benzyl sulfide (22)** (0.82 g, 5.0 mmol) with bromine (0.80 g, 5.0 mmol), which yields 2,3-dibromopropyl benzyl sulfide as an oil (87%): IR (liquid film) 1500, 1455, 1420, 1240, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.25 (m, 5 H), 3.77 (s, 2 H), 3.75–3.53 (m, 3 H), 3.17–2.87 (m, 2 H).

Oxidation of Di-*n*-butyl Sulfide, Di-*tert*-butyl Sulfide (7), and L-Methionine (23) Catalyzed by TBA^+Br^-. The sulfide (5.0 mmol) was dissolved in nitromethane (8 mL) and treated with aqueous HNO_3 (16 mL, 25.0 mmol, 1.56 M) in the presence of catalytic amounts of TBA^+Br^- (0.25 mmol). The composition of the reaction mixture (separately for the organic and aqueous phase) was analyzed as described in the supplementary material. In the case of methionine, the procedure used allowed the detection of all different stereoisomers.[35] In the absence of TBA^+Br^- catalyst [either complete absence of bromide ion or presence of KBr alone (0.25 mmol)] the oxidation reaction becomes exceedingly slow.

Analytical Investigation of the Species Formed in the Catalytic Cycles. Since the biphasic system contains a rather complex mixture of species, different analytical procedures were employed for their identification. Hence the simple anions (NO_3^-, NO_2^-, and Br^-) were analyzed by high performance ion exchange chromatography (HPIEC) while the complex anions $[AuBr_4]^-$ and $[AuBr_2]^-$ were determined by reverse phase high performance liquid chromatography (RP HPLC). The neutral organic molecules were determined by RP HPLC or HRGC, depending upon the value of absorbance of the corresponding chromophore and the thermal stability of the compound.

All species were identified by comparison with an authenticated sample of the pure product. The species with adequate absorbance were also determined on line, using a photo diode array detector (PDA).

The composition of the reaction mixture was monitored separately for the aqueous and the organic phase.

Aqueous Phase. From time to time 10 μL of this phase was dissolved in 250 μL of water, and 15 μL of the resulting solution was injected into the chromatograph. HPIEC columns: Hamilton PRP-1 (4.0 × 50 mm, 10 μm packing), which retains the gold species and other hydrophobic organic materials, and IC-PAK A (4.6 × 50 mm) for anion separation. Detector: Waters 430 conductometer. Eluent: potassium benzoate 0.001 M. Flow rate: 1.0 mL/min.

In the case of methionine the sample to be analyzed requires a pretreatment by which the methionine derivatives, containing a primary aminic group, are converted into 1-(alkylthio)-2-alkylisoindoles whose characteristics of hydrophobicity and fluorescence allow them to be detected by RP HPLC.[35] By this procedure the different diastereoisomers of methionine sulfoxides and even the enantiomers of the starting amino acid can be resolved. Therefore from time to time 50 μL of the aqueous phase was dissolved in 500 μL of sodium borate buffer (0.4 M, pH = 10) and 100 μL of the resulting solution treated with 100 μL of reagent [50 mg of *o*-phthalic aldehyde, 1.25 mL of CH_3OH, 11.2 mL of sodium borate buffer (0.4 M, pH = 10), and 74 mg of *N*-acetyl-L-(+)-cysteine]. A few minutes after the mixing of the reagents, 10 μL of solution was injected into the chromatograph. RP HPLC column: Hypersil ODS (4.0 × 250 mm, 5 μm packing). Detector: fluorimeter (5 nm slit EX, 330 λ_{EX}; 5 nm slit EM, 418 λ_{EM}; response time 3 s). Temperature: 25 °C. Mobil phase: isocratic 100% A (CH_3CN/aqueous CH_3COONa 0.05 M, 5/95, v/v, pH = 7.5) for 30 min, then linear gradient from 100% A to 85% A and 15% B (CH_3CN) for 5 min and continuing for 30 min more. Flow rate: 1.0 mL/min. K'_1((*S*)-methionine (*R*)-sulfoxide) = 14.9; K'_2((*S*)-methionine (*S*)-sulfoxide) = 16.0; α = 1.07). The identification of different stereoisomers has been performed by comparison with samples of pure isomers prepared by literature methods.[29]

Organic Phase. The organic phase was also analyzed by RP HPLC.

From time to time 20 μL of the organic phase was dissolved in 250 μL of CH_3OH and 10 μL of the resulting solution injected in the chromatographic system. Column: Hamilton PRP-1, 4.0 × 50 mm (10 μm packing). Detectors: M490 programmable multiwavelength spectrometer (254, 220, and 205 nm) or 990 PDA. Temperature: 25 °C. Mobile phase: linear gradient from 100% A (CH_3CN/H_2O, 10/90, v/v, 0.005 M $TBA^+HSO_4^-$) to 100% B (CH_3CN/H_2O, 90/10, v/v, 0.005 M $TBA^+HSO_4^-$) for 10 min, then continuing for 5 min more. Flow rate: 2.0 mL/min.

In these conditions it is possible to separate not only the neutral organic species but also the gold-complexed species $[AuBr_4]^-$ and $[AuBr_2]^-$ because they form ionic couples with the TBA^+ added to the mobile phase.

Similarly, from time to time, 20 μL of the organic phase was dissolved in 150 μL of CH_3OH and 1 μL of the resulting solution

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injected into the HRGC. Column: RSL-300 (polyphenylmethylsiloxane) (10 m × 0.53 mm i.d.) bonded FSOT (1.2 μm film). Temperature: 90 °C for 2 min, then to 230 °C at 25 °C/min. Flow rate: 4 mL/min He. Detector: FID 250 °C. Injector: splitter 1:40, 250 °C.

Detection of NO Gas in Equilibrium with the Reaction Solution. The oxidation of n-Bu_2S was performed as described above. At the end of the reaction the GC-MS analysis of the gaseous phase [HP 5988A spectrometer, HP Ultra 1 (cross-linked methyl silicone) column (25 m × 0.32 mm, 0.17 μm film thickness), 70 °C, He carrier] revealed the presence of a discrete amount of NO and the absence of oxygen and other nitrogen oxides. Under strictly analogous conditions but in the absence of the sulfide as reducing agent, no NO formation was observed.

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Registry No. 1, 622-38-8; 1′, 4170-80-3; 2, 622-38-8; 2′, 114045-22-6; 3, 13865-49-1; 3′, 114045-23-7; 4, 831-91-4; 4′, 833-82-9; 5, 3019-20-3; 5′, 4170-69-8; 6, 7570-92-5; 6′, 3324-82-1; 7, 107-47-1; 7′, 2211-92-9; 8, 7205-60-9; 8′, 114129-36-1; 9, 3795-79-7; 9′, 114129-35-0; 10, 50910-13-9; 10′, 114045-25-9; 11, 123-09-1; 11′, 934-73-6; 12, 100-68-5; 12′, 1193-82-4; 13, 623-13-2; 13′, 934-72-5; 14, 1879-16-9; 14′, 3517-99-5; 15, 2388-73-0; 15′, 38452-13-0; 16, 2388-74-1; 16′, 13150-72-6; 17, 3393-77-9; 17′, 1774-36-3; 18, 3561-67-9; 18′, 114129-34-9; 19, 17241-04-2; 19′, 83212-58-2; 20, 124461-76-3; 20′, 124461-77-4; 21, 54091-78-0; 21′, 124461-78-5; 22, 6937-97-9; 22′, 114045-26-0; 23, 63-68-3; 23′ (isomer 1), 3226-66-2; 23′ (isomer 2), 23631-84-7; $TBA^+AuBr_4^-$, 17769-65-2; $TBA^+AuCl_4^-$, 17769-64-1; $TBA^+AuBr_2^-$, 50481-01-1; TBA^+Br^-, 1643-19-2; thiophenol, 108-98-5; 1,3-dibromopropane, 109-64-8; L-(−)-ephedrine [(1*R*,2*S*)-2-(methylamino)-1-phenyl-1-propanol], 299-42-3; tetrabromoauric acid, 17083-68-0; 3-bromopropyl phenyl sulfide, 3238-98-0.

Supplementary Material Available: Figure 1, HPLC and HRGC chromatograms for the oxidation of di-*tert*-butyl sulfide catalyzed by $TBA^+AuBr_4^-$ (2 pages). Ordering information is given on any current masthead page.

A New Rearrangement of Alkoxybenzyl Anions

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Alkyl groups migrate from oxygen to carbon in alkyl aryl ethers which have been metalated in benzylic positions. 2,6-Dimethylanisole provides a variety of 2,6-dialkylphenols and their ethers in 45–80% yields. Rearrangement products are obtained in 10–30% yields from other dimethylanisoles and from methylanisoles. The reactions appear to proceed, like Wittig rearrangements, by homolytic cleavage of the alkyl–oxygen bond followed by recombination of the resulting radical pair in a different way. The rearrangements can be avoided by using *methyl* ethers and working at or below room temperature.

In attempting to prepare dianion 1 by refluxing 2,6-dimethylanisole (**6d**) with 2 equiv of Lochmann's base (n-BuLi/KO-t-Bu)[1] in heptane, we obtained products from dianion **2** instead which indicated that the methyl group migrates from oxygen to benzylic carbon in at least 70% yield. We have studied the scope and mechanism of this unexpected rearrangement to learn where it is synthetically useful and also how it can be avoided, permitting reactions of alkoxybenzyl anions without rearrangement. Some products and yields obtained in this study are given in Chart I and Table I.

Methylanisoles. Since the simplest mechanisms for this rearrangement do not require a second methyl group on the ring, we tried methylanisoles (**3a–c**) as starting materials (reactions 1, 3, and 5). Rearrangement products were obtained in every case, but the total yields of rearrangement products (14–29%) were much lower than with 2,6-dimethylanisole (**6d**), with the simple rearrangement products **4d–f**, obtained in 11–14% yields, being accompanied by products containing s-Bu groups (**4j,k**, formed by benzylic metalation of ethyl groups followed by alkylation with diethyl sulfate) and i-Pr groups (**4i**, derived by benzylic metalation of ethyl groups followed by methylation via *inter*molecular rearrangement). That these further reactions were not observed in the para case is consistent with it being more difficult in general to metalate alkyl groups para to alkoxy groups than either ortho (favored by chelation[2-5]) or meta (favored by resonance effects). This generalization also explains why the main nonrearrangement products come from dealkylation–metalation–dialkylation in the ortho and meta cases (**4g,h**) but from dealkylation–monoalkylation in the para case (**4c**). Since ring metalation ortho to methoxyl groups is well known,[6] the formation of a small amount of **7b** in the para case is not surprising.

It should be noted that in these reactions in refluxing heptane, the methyl groups are completely lost from the starting anisoles **3a–c**. When these reactions were repeated at room temperature (reactions 2, 4, and 6), the methyl groups were largely retained in the products. The yields of propylanisoles **3f–h** from metalation–alkylation were 49, 80, and 26%, respectively. In the ortho case, dealkylation–metalation–dialkylation gave an additional 25% of the propylphenetol **4g**, and small amounts of rearrangement products were observed, but from these and examples below involving di- and trimethylanisoles, *the rearrangement can be avoided by working with methyl*

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