Alkylation of Several Nucleophiles with Alkylsulfonium Salts

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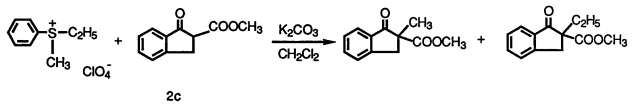
The reactions of dialkylphenylsulfonium salts (**1**) with several nucleophiles such as phenols, amine, enolate ion, and thiolate ions, have been investigated. The relative reactivities of the alkyl groups of sulfonium salts for the phenolate ion (hard nucleophile) were as follows; Me : Et:*i*-Pr= 1.0 : 1.34 : 3.44. In the alkylation of the *p*-toluenethiolate ion (soft nucleophile) with **1**, the opposite reactivity (Me : Et : *i*-Pr=1.0 : 0.22 : 0.03) was found. When a sulfonium salt (**1e**) having an optically active (*S*)-*s*-butyl group was reacted with a phenolate ion, an optically active (*R*)-*s*-butyl phenyl ether was obtained with an inversion of the configuration at the chiral carbon atom. A reaction mechanism via a sulfurane intermediate is proposed for the alkylation of the phenolate ion with alkylsulfonium salts. The relative reactivities for the alkylation of several nucleophiles with dialkylphenylselenonium salts (**12**) were also investigated.

S-Adenosylmethionine, a kind of methylsulfonium salt, is an important biological methylating agent and is known as a source of the methyl groups of such compounds as DNA, RNA, proteins, and biogenic amines.[1] The stereochemistry in the methylation of phenolate with *S*-adenosylmethionine was studied, and the S_N2-type process was proposed for enzymic systems.[2] In recent years a few studies have been published on the alkylation of oxygen, nitrogen, and carbon nucleophiles with alkylsulfonium salts as the alkylating reagents; a reaction mechanism via the S_N2 process was reported.[3] However, alkylsulfonium salts can also react with nucleophiles at a cationic sulfur atom as well as an α-carbon atom.

More recently, we have reported the first examples of asymmetric alkylation of β-keto esters with optically active alkylsulfonium salts.[4] The absolute configurations of (*S*)-(−)-2-methyl-2-methoxycarbonyl-1-indanone (**3a**) and (*R*)-(+)-2-ethyl-2-methoxycarbonyl-1-indanone (**3b**) were opposite when the enolate ion of 2-methoxycarbonyl-1-indanone (**2c**) was alkylated with an optically active (*S*)-ethylmethylphenylsulfonium salt (**1a**). However, the alkylation of **2c** with (*R*)-**1a** afforded (*R*)-(+)-**3a** and (*S*)-(−)-**3b**, as shown in the following Scheme:



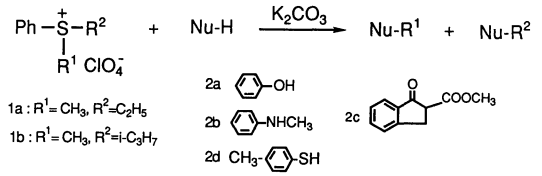
We propose a stereochemical course via the S–O sulfurane intermediate for this asymmetric alkylation. These findings suggest that the alkylation of nucleophiles with sulfonium salts could not be explained by only the S_N2 mechanism, although a sole S_N2 process was proposed for the alkylation, as mentioned above.[2,3] There has been no report concerning systematic studies of the alkylation of nucleophiles with alkylsulfonium salts focused on the S- and C-attacks by a nucleophile. We have investigated the relative reactivities of the alkyl groups of alkylsulfonium salts with several nucleophiles such as phenols, amine, enolate ion, and thiols. The stereochemistry was also studied regarding this alkylation; the reaction mechanism are discussed herein.

Results and Discussion

The Relative Reactivities of the Alkyl Groups of Sulfonium Salts. When phenol (**2a**) was alkylated with ethylmethylphenylsulfonium salt (**1a**) in dichloromethane in the presence of anhydrous potassium carbonate at room temperature, anisole (**4a**) and phenetole (**4b**) were obtained in 42 and 56% yields, respectively. Similarly, the alkylation of **2a** with isopropylmethylphenylsulfonium salt (**1b**) gave **4a** and isopropyl phenyl ether (**4c**) in 14 and 50% yields, respectively. The results are summarized in Table 1.

The relative reactivities of the alkyl groups of sulfonium salts (**1a** and **1b**) toward the phenolate ion were calculated based on the yields of **4a**, **4b**, and **4c** as Me:Et:*i*-Pr=1.00:1.34:3.44, since the product ratio can be regarded as being the relative reactivity of alkyl groups in these reactions. These results are quite different from the relative reactivities expected for S_N2 alkylation reactions on oxygen nucleophiles. For instance, the relative reactivity of sodium phenolate with methyl iodide and ethyl iodide in methanol at 42 °C has been reported as being Me:Et=1.00:0.21.[5] When *N*-methylaniline (**2b**) was alkylated with sulfonium salts **1a** and **1b**, the relative ratio of the products, (*N*,*N*-dimethylaniline (**5a**), *N*-ethyl-*N*-methylaniline (**5b**) and *N*-isopropyl-*N*-methylaniline (**5c**)) was calculated as being Me:Et:*i*-Pr=1.00:0.98:1.38 (Entries 3 and 4 in Table 1).[6] In the alkylation of 2-methoxycarbonyl-1-indanone (**2c**) with **1a** and **1b**, the relative reactivity of the alkyl groups was

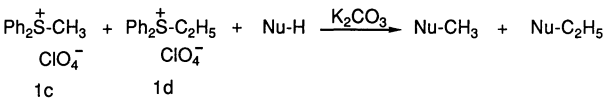
Table 1. Alkylation of Nucleophiles with Sulfonium Salts **1a** and **1b**



Entry	Nu-H	Sulfonium salts	Alkylated products/%[a]			Relative reactivity
			Nu-CH_3	Nu-C_2H_5	Nu-C_3H_7-*i*	CH_3 : C_2H_5 : *i*-C_3H_7
1	**2a**	**1a**	**4a** 41.8	**4b** 56.2		1 : 1.34 : 3.44
2	**2a**	**1b**	**4a** 14.4		**4c** 49.6	
3	**2b**	**1a**	**5a** 35.6	**5b** 34.9		1 : 0.98 : 1.38
4	**2b**	**1b**	**5a** 22.2		**5c** 30.7	
5	**2c**	**1a**	**3a** 25.7	**3b** 31.6		1 : 1.23 : 0.78[b]
6	**2c**	**1b**	**3a** 34.4		**3c** 26.8	
7	**2d**	**1a**	**6a** 71.8	**6b** 17.3		1 : 0.24 : 0.03
8	**2d**	**1b**	**6a** 94.9		**6c** 3.1	

a) Determined by GC. b) Ref. 4.

Table 2. Alkylation of Nucleophiles with Sulfonium Salts **1c** and **1d**



Entry	Nu-H	Solvent	Alkylated products/%[a]		Relative reactivity
			Nu-CH_3	Nu-C_2H_5	CH_3 : C_2H_5
1	**2a**	CH_2Cl_2	55.3	40.7	1 : 0.74
2	**2a**	Acetone	47.7	47.4	1 : 0.99
3	**2a**	CH_3CN	40.8	50.1	1 : 1.23
4	**2d**	CH_2Cl_2	72.0	14.5	1 : 0.20
5	**2d**	Acetone	82.1	15.6	1 : 0.19
6	**2d**	CH_3CN	73.8	15.4	1 : 0.21

a) Determined by GC.

calculated from the products ratio of **3a**, **3b**, and **3c** as Me:Et:*i*-Pr=1.0:1.23:0.78. (Entries 5 and 6).[4] Generally, the relative reactivity of the alkyl groups of alkyl halides toward several nucleophiles regarding S_N2 reactions is Me:Et:*i*-Pr=1.0:0.05:0.001.[7]

When *p*-toluenethiol (**2d**) was alkylated with **1a** and **1b** under similar conditions, the relative ratio of the products (methyl phenyl sulfide (**6a**), ethyl phenyl sulfide (**6b**), and isopropyl phenyl sulfide (**6c**)) were Me:Et:*i*-Pr=1.00:0.24:0.03 (Entries 7 and 8 in Table 1). In contrast to the alkylations of the phenolate ion, *N*-methylaniline, and the enolate ion, this result is similar to the relative reactivities of the alkyl groups for the S_N2 reactions.[7]

These results can be explained in terms of the hardness and softness of nucleophiles; the hardness of the nucleophiles increases in the following order: thiolate ion<enolate ion<amine<phenolate ion.[8] The relative reactivity of the alkyl groups of sulfonium salts toward a hard nucleophile, such as the phenolate ion, differs from the reactivities expected for ordinary S_N2 alkylation of a soft nucleophile, such as the thiolate ion.

The relative ratios shown in Table 1 were obtained by competitive alkylation of the two alkyl groups in the same molecule (**1a** and **1b**); in this case the leaving ability of alkyl phenyl sulfide was regarded as being nearly equal. The competitive alkylation of phenol (0.2 mmol) with diphenylmethylsulfonium salt (**1c**) (1.0 mmol) and diphenylethylsulfonium salt (**1d**) (1.0 mmol) was investigated in the presence of anhydrous potassium carbonate at room temperature; the results are summarized in Table 2. The ratios of *O*-ethylation vs. *O*-methylation were 0.74 to 1.23. In contrast, the relative ratios were almost 0.2 in the alkylations of *p*-toluenethiol with **1c** and **1d** under similar conditions (Entries 4, 5, and 6 in Table 2). The fact that a similar relative ratio was obtained in the

alkylation of the phenolate ion shown in Tables 1 and 2, indicates that the leaving ability of the sulfides in these alkylations can be regarded as being almost equal.

Substituent Effects of Nucleophiles. The alkylations of *p*-substituted phenols and *p*-substituted benzenethiols with dialkylphenylsulfonium salts (**1a** and **1b**) were investigated in the presence of potassium carbonate in dichloromethane. The relative ratio of the products, alkyl aryl ethers and alkyl aryl sulfides, are summarized in Table 3. A slight substituent effect was observed in the alkylations of the phenols; on the other hand the relative reactivity was almost the same in the alkylation of thiophenols.

Solvent Effect in the Alkylation. The solvent effects on the relative reactivities of the methylation and ethylation of the phenolate ion and thiolate ion with sulfonium salt **1a** were investigated. The ratio of *O*-ethylation vs. *O*-methylation in the alkylation of the phenolate ion (hard nucleophile) with **1a** increased in more polar solvents (Et/Me=1.34 in dichloromethane; 2.21 in acetonitrile; 2.39 in DMF). On the other hand, the solvent effect on the ratio of ethylation vs. methylation of the *p*-toluenethiolate ion (soft nucleophile) with sulfonium salt **1a** was not observed. As summarized in Table 4, the apparent solvent effect on the alkylation of phenolate ion (hard nucleophile) suggests the formation of ionic intermediate, such as an ion pair, as shown in the mechanism described later.

Table 3. Substituent Effect in the Alkylation of Nucleophiles with **1a** and **1b**

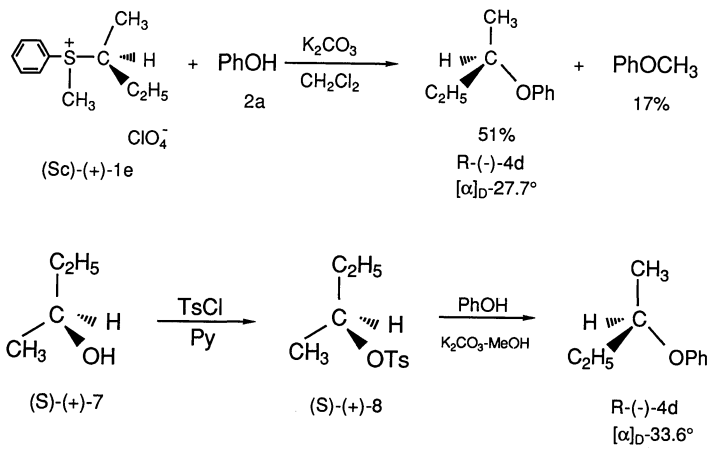
Entry	Nucleophile	Relative reactivity CH_3: C_2H_5: *i*-C_3H_7
1	*p*-$CH_3OC_6H_4OH$	1 : 1.48 : 2.18
2	C_6H_5OH	1 : 1.34 : 3.44
3	*p*-$NO_2C_6H_4OH$	1 : 1.60 : 3.88
4	*p*-$CH_3OC_6H_4SH$	1 : 0.23 : 0.03
5	*p*-$CH_3C_6H_4SH$	1 : 0.24 : 0.03
6	*p*-$NO_2C_6H_4SH$	1 : 0.26 : 0.03

Stereochemistry in the Alkylation of Phenolate Ion and Thiolate Ion with Sulfonium Salts. It is of interest to study stereochemistry regarding whether the configuration of the entering alkyl group toward nucleophiles is retained or inverted. The reaction between phenol or *p*-nitrobenzenethiol (**2e**) and the sulfonium salts containing optically active *s*-butyl groups was examined. The phenolate ion of **2a** was alkylated with a diastereomeric mixture of [(*S*)-(+)-*s*-butyl]methylphenylsulfonium perchlorate (**1e**) ($[\alpha]_D$ +3.29°) in the presence of anhydrous potassium carbonate in dichloromethane to give *s*-butyl phenyl ether (**4d**) ($[\alpha]_D$ −27.7°) in 51% yield and **4a** in 17% yield. The authentic (*R*)-*s*-butyl phenyl ether (**4e**) ($[\alpha]_D$ −33.6°) was obtained by a reaction of phenol with (*S*)-*s*-butyl tosylate (**8**) ($[\alpha]_D$ +9.6°) in the presence of anhydrous potassium carbonate in methanol, as shown in Scheme 1.

Table 4. Solvent Effect in the Alkylation of Nucleophiles with Sulfonium Salt **1a**

Entry	Nucleophile	Solvent	Alkylated products/%[a] Nu-CH_3	Nu-C_2H_5	Relative reactivity CH_3 : C_2H_5
1	**2a**	CH_2Cl_2	41.8	56.2	1 : 1.34
2	**2a**	CH_3CN	30.7	67.7	1 : 2.21
3	**2a**	DMF	25.5	60.8	1 : 2.39
4	**2d**	CH_2Cl_2	78.1	17.3	1 : 0.22
5	**2d**	CH_3CN	75.1	18.7	1 : 0.25
6	**2d**	DMF	74.4	17.7	1 : 0.24

a) Determined by GC.

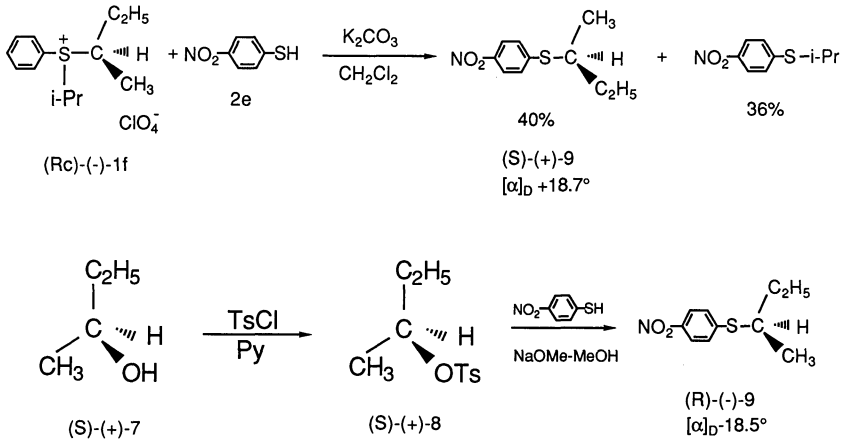


Scheme 1.

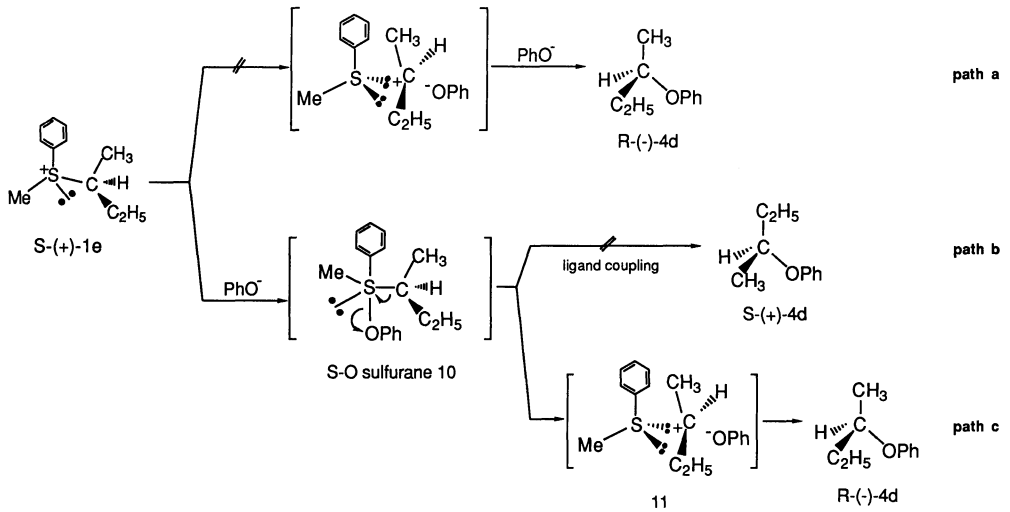
Since the configuration at the chiral carbon atom of (*S*)-*s*-butyl tosylate (**8**) inverts during this S_N2 reaction process, the configuration at the chiral carbon atom of authentic *s*-butyl phenyl ether (**4d**) was determined as being the (*R*)-configuration. Based on the optical rotation of the authentic (*R*)-(−)-**4d**, the configuration at the chiral carbon atom of (−)-**4d** derived from the sulfonium salt (**1e**) was determined as being the (*R*)-configuration; the optical purity of (−)-**4d** was estimated to be 82%, in comparison with authentic (−)-**4d**. This result shows that the net inversion of the configuration at the chiral carbon atom of **1e** took place in the alkylation of the phenolate ion.

When *p*-nitrobenzenethiol was also alkylated with a diastereomeric mixture of [(*R*)-(−)-*s*-butyl]isopropylphenylsulfonium perchlorate (**1f**) ($[\alpha]_D$ −2.44°) *s*-butyl *p*-nitrophenyl sulfide (**9**) (40% yield) ($[\alpha]_D$ +18.7°) and isopropyl *p*-nitrophenyl sulfide (36% yield) were obtained. The chiral carbon atom of (+)-**9** was assinged as being the (*S*)-configuration in comparison with the authentic (*R*)-*s*-butyl *p*-nitrophenyl sulfide (**9**) ($[\alpha]_D$ −18.5°), which was prepared by the alkylation of **2e** with (*S*)-*s*-butyl tosylate (**8**) ($[\alpha]_D$ +9.6°) in the presence of sodium methoxide in methanol. Thus, the optically active *s*-butyl group was transferred stereoselectively to the thiolate ion with 100%-inversion of the configuration, as shown in Scheme 2.

Reaction Mechanism. The relative reactivities and solvent effects observed exclude the S_N2 mechanism in the alkylation of hard nucleophiles such as the phenolate ion with alkylsulfonium salts. Alternatively, the following three processes are considered, as shown in Scheme 3. The first mechanism is an S_N1-like process by direct cleavage of the S–C bond of **1e**, giving *s*-butyl cation and methyl phenyl sulfide. The *s*-butyl cation readily reacts with the phenolate ion (path a). In the second mechanism, the phenolate ion attacks the cationic sulfur atom of **1e** to give S–O sulfurane intermediate **10**. The subsequent ligand coupling from **10** affords *s*-butyl phenyl ether **4d** (path b). The third mechanism is that the heterolytic bond cleavage of **10** once formed gives methyl phenyl sulfide, the *s*-butyl cation, and the phenolate ion (path



Scheme 2.



Scheme 3.

c). Path a is excluded since it is known that even the *t*-butyl cation is not formed from the *t*-butylethylmethylsulfonium salt.[9] Path b is also excluded since the ligand coupling product from sulfurane **10** is known to retain the starting configuration.[10] It is therefore considered that path c is the most plausible for this alkylation. The reason for an inversion of the asymmetric carbon atom of the *s*-butyl group of the product **4d** may be explained as follows. Since *s*-butyl cation interacts strongly with lone-pair electrons of methyl phenyl sulfide, the phenolate ion attacks selectively from the rear side of the cationic carbon atom of the *s*-butyl cation.[11] The solvent effects in the alkylation of phenols is explained as follows: the ionic intermediate **11** in path c is influenced by the polariry of the solvent.

Many interesting and synthetically important reactions of sulfonium compounds involving sulfurane intermediates, which undergo a wide variety of subsequent reactions, have been reported. The reaction of triphenylsulfonium salt with phenyllithium,[12] 2,5-dihydrothiophenium salt with *n*-butyllithium,[13] and 1,2,4-trimethylthietanonium fluoroborate with *n*-butyllithium[14] are typical examples. Though we attempted to observe the sulfurane intermediate in the reaction of sulfonium salts with phenol by ^{1}H and ^{13}C NMR, however, no NMR signals corresponding to the intermedidate were detected.[15]

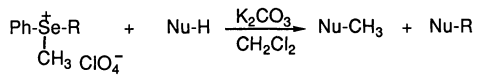
Alkylation of Nucleophiles with Alkylselenonium Salts. It is of interest to study the relative reactivity in the alkylation of nucleophiles with dialkylphenylselenonium salts in comparison with that of the dialkylphenylsulfonium salts. The reactions of the ethylmethylphenylselenonium salt (**12a**) and the isopropylmethylphenylselenonium salt (**12b**) with several nucleophiles were investigated; the results are summarized in Table 5. The relative reactivity of the alkyl groups toward phenol was calculated to be Me:Et:*i*-Pr=1:1.33:2.38; this ratio was similar to that of the alkylation of phenol with dialkylphenylsulfonium salts (**1a** and **1b**) (see Table 1). Similar relative reactivities of the alkyl groups in the alkylation of other nucleophiles such as *N*-methylaniline, 2-methoxycarbonyl-1-indanone, and *p*-toluenethiol with selenonium salts (**12a** and **12b**) were observed. These results thus suggest that the softness of the sulfur atom in **1** and the selenium atom in **12** is comparable.

Conclusion. In the alkylation of nucleophiles with sulfonium salts, the ratio of the relative reactivity of the alkyl groups on the sulfur atom showed an opposite order among the soft and hard nucleophiles. The reaction of the thiolate anion with sulfonium salts could be explained by the S_N2 mechanism, as reported previously; on the other hand, a new reaction mechanism via a sulfurane intermediate was proposed in the reaction of the phenolate anion with sulfonium salts.

Experimental

The melting points were determined on a Yamato MP-21 melting-point apparatus and were uncorrected. The ^{1}H NMR spectra were recorded on a JEOL PMX 60 SI spectrometer (60 MHz) in $CDCl_3$, unless otherwise indicated, with Me_4Si as an internal standard. The chemical shifts and coupling constants were recorded in δ (ppm) and Hz units. The infrared spectra were recorded on a Hitachi Model 260-10 spectrometer. The optical rotations were measured in a 1.0 dm or 0.5 dm cell on a JASCO DIP-140 polarimeter. The mass and high-resolution mass spectra were obtained on a JEOL JMS-DX 300 Mass spectrometer with a JEOL JMA 5000 mass data system at an ionizing voltage of 70 eV, with sample introduction via a direct probe or through a 1 m GC

Table 5. Alkylation of Nucleophiles with Selenonium Salts



12a: R = C_2H_5
12b: R = i-C_3H_7

Entry	Nu-H	Selenonium salt	Alkylated products/%[a]			Relative reactivity
			Nu-CH_3	Nu-C_2H_5	Nu-C_3H_7-*i*	CH_3:C_2H_5:*i*-C_3H_7
1	**2a**	**12a**	40.1	53.4		1:1.33:2.38
2	**2a**	**12b**	27.8		66.1	
3	**2b**	**12a**	58.3	37.7		1:0.65:1.01
4	**2b**	**12b**	48.0		48.5	
5	**2c**	**12a**	37.3	36.4		1:0.98:0.62
6	**2c**	**12b**	38.1		23.6	
7	**2d**	**12a**	83.9	14.8		1:0.18:0.04
8	**2d**	**12b**	95.4		3.9	

a) Determined by GC.

column containing 10% SE-30.

General Procedure for Alkylation of Several Nucleophiles with Dialkylphenylsulfonium Salts (1a and 1b). A mixture of dialkylphenylsulfonium salt **1** (0.5 mmol), nucleophile (0.5 mmol), and anhydrous potassium carbonate (0.7 mmol) was stirred in dry dichloromethane (5 cm^3) at room temperature for 3 days. After filtration of insoluble materials, the chemical yields of resulting alkylated products were determined by GC. The physical properties of the typical products are as follows:

2-Methyl-2-methoxycarbonyl-1-indanone (**5a**): Mp 57.5—58.0 °C (from hexane–ether); ^{1}H NMR ($CDCl_3$) δ=1.45 (3H, s), 2.95 (1H, d, J=17.0 Hz), 3.59 (1H, d, J=17.0 Hz), 3.62 (3H, s), and 7.16—7.80 (4H, m); MS m/z 204 (M^+), 190, 176, 161, and 145; Found: m/z 204.0779, Calcd for $C_{12}H_{12}O_3$: M, 204.0786.

2-Ethyl-2-methoxycarbonyl-1-indanone (**5b**): ^{1}H NMR ($CDCl_3$) δ=0.87 (3H, t, J=7.6 Hz), 1.98 (2H, q, J=7.6 Hz), 2.95 (1H, d, J=17.0 Hz), 3.69 (3H, s), 4.38 (1H, d, J=17.0 Hz), and 7.16—7.80 (4H, m); MS m/z 218 (M^+), 203, 190, 175, and 158; Found: m/z 218.0937, Calcd for $C_{13}H_{14}O_3$: M, 218.0942.

2-Isopropyl-2-methoxycarbonyl-1-indanone (**5c**): ^{1}H NMR ($CDCl_3$) δ=0.76 (3H, d, J=6.8 Hz), 0.96 (3H, d, J=6.8 Hz), 2.86 (1H, q, J=6.8 Hz), 2.98 (1H, d, 18.0 Hz), 3.73 (1H, d, J=18.0 Hz), 3.97 (3H, s), and 7.30—7.89 (4H, m); MS m/z 232 (M^+), 201, 190, 172, and 157; Found: m/z 232.1079, Calcd for $C_{14}H_{16}O_3$: M, 232.1099.

General Synthetic Procedure of Dialkylphenylsulfonium Salts and Alkyldiphenylsulfonium Salts (1a, 1b, 1c, and 1d). To a mixture of silver perchlorate (25.0 g, 0.21 mmol) and alkyl phenyl sulfide (or diphenyl sulfide) (0.21 mol) in acetonitrile (110 cm^3) was added slowly an acetonitrile solution (10 cm^3) of alkyl iodide (0.60 mol) at 0 °C; the mixture was stirred for 2 days at room temperature. After the insoluble materials (AgI) were filtered off the solvent was evaporated and the residue washed with ether. The resulting crude product was purified by recrystallization from acetone–ether to give dialkylphenylsulfonium perchlorate **1a** and **1b** (or alkyldiphenylsulfonium perchlorate **1c** and **1d**) in 74—100% yield.

Ethylmethylphenylsulfonium Perchlorate (**1a**):[4a] Mp 84.5 °C (acetone–ether) (lit, mp 84.5 °C); ^{1}H NMR (acetone-d_6) δ=1.40 (3H, t, J=7.2 Hz), 3.52 (3H, s), 3.92 (2H, q, J=7.2 Hz), and 7.76—8.33 (5H, m).

Isopropylmethylphenylsulfonium Perchlorate (**1b**):[4a] Syrup; ^{1}H NMR (acetone-d_6) δ=1.31 (3H, d, J=7.0 Hz), 1.58 (3H, d, J=7.0 Hz), 3.28 (3H, s), 4.20 (0.5H, q, J=7.0 Hz), 4.30 (0.5H, q, J=7.0 Hz), and 7.53—8.00 (4H, m).

Diphenylmethylsulfonium Perchlorate (**1c**):[16] Mp 78—79 °C (acetone–ether) (lit, mp 73—74 °C); ^{1}H NMR (acetone-d_6) δ=3.92 (3H, s), and 7.57—8.23 (10H, m).

Diphenylethylsulfonium Perchlorate (**1d**):[4a] Mp 81—81.5 °C (acetone–ether) (lit, mp 81—81.5 °C); ^{1}H NMR (acetone-d_6) δ=1.51 (3H, t, J=7.8 Hz), 4.41 (2H, q, J=7.8 Hz), and 7.60—8.23 (10H, m).

[(*S*)-(+)-*s*-Butyl]methylphenylsulfonium Perchlorate (**1e**).[4a] To a mixture of silver perchlorate (1.93 g, 9.31 mmol) and (*S*)-(+)-*s*-butyl phenyl sulfide ($[\alpha]_D$ +16.2° (*c* 1.50, MeOH)) (1.54 g, 9.27 mmol) in 5 cm^3 of acetonitrile, which was prepared from (*R*)-(−)-s-butyl bromide[4] ($[\alpha]_D$ −22.9° (*c* 4.91, EtOH)) and thiophenol, was added slowly a solution of methyl iodide (12.1 g, 85.2 mmol) in acetonitrile (5 cm^3) at 0 °C; the mixture was stirred for 2 days at room temperature. After the insoluble materials (AgI) were filtered, the solvent was evaporated and the residue washed with ether to give [(*S*)-(+)-*s*-butyl]methylphenylsulfonium perchlorate (**1e**) (1.70 g, 95% yield): Syrup; $[\alpha]_D$ +3.29° (*c* 4.18, MeOH); ^{1}H NMR (acetone-d_6) δ=1.31 (3H, t, J=7.2 Hz), 1.31 (1.5H, d, J=7.2 Hz), 1.58 (1.5H, d, J=7.2 Hz), 1.62 (2H, q, J=7.2 Hz), 3.43 (1.5H, s), 3.47 (1.5H, s), 4.11 (1H, q, J=7.2 Hz), and 7.67—8.25 (5H, m).

Preparation of Authentic (*R*)-(−)-*s*-Butyl Phenyl Ether (4d). A mixture of phenol (141 mg, 1.49 mmol) and anhydrous potassium carbonate (300 mg, 2.17 mmol) in 8 cm^3 of dry methanol was stirred at room temperature. After addition of a methanol solution (7 cm^3) of (*S*)-(+)-*s*-butyl tosylate (**8**) ($[\alpha]_D$ +9.54° (*c* 4.01, $CHCl_3$)), the reaction mixture was refluxed for 6 h. The product was extracted with ether and the extracts dried over $MgSO_4$. After the ether was removed, the resulting crude product was purified by silica-gel column chromatography (pentane/ether=10/1) to give (*R*)-(−)-*s*-butyl phenyl ether (**4d**) in 63% yield: $[\alpha]_D$ −33.6° (*c* 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.96 (3H, t, J=6.6 Hz), 1.26 (3H, d, J=6.0 Hz), 1.63 (2H, q, J=6.6 Hz), 4.27 (1H, m), and 6.67—7.45 (5H, m); MS m/z 150 (M^+), 135, 121, 93, and 57; Found: m/z 150.1068, Calcd for $C_{10}H_{14}O$: M, 150.1044.

Alkylation of Phenol with Sulfonium Salt (1e). A mixture of [(*S*)-(+)-*s*-butyl]methylphenylsulfonium perchlorate (**1e**) (375 mg, 1.33 mmol) ($[\alpha]_D$ +3.29° (*c* 4.18, MeOH)), phenol (125 mg, 1.33 mmol) and anhydrous potassium carbonate (238 mg, 1.72 mmol) in dry dichloromethane (15 cm^3) was stirred at room temperature for 3 days. After filtration of insoluble materials, the resulting reaction mixture was purified by silica gel column chromatography (pentane/ether=10/1) to give a mixture of two alkylated products of phenol, which were separated by GPC to give anisole (**4a**) (17%) and (*R*)-(−)-*s*-butyl phenyl ether (**4d**) (51%): $[\alpha]_D$ −27.7° (*c* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.96 (3H, t, J=6.6 Hz), 1.26 (3H, d, J=6.0 Hz), 1.63 (2H, q, J=6.6 Hz), 4.27 (1H, m), and 6.67—7.45 (5H, m); MS m/z 150 (M^+), 135, 121, 93, and 57; Found: m/z 150.1068, Calcd for $C_{10}H_{14}O$: M, 150.1044.

Preparation of (*S*)-(+)-*s*-Butyl Tosylate (8). A solution of (*S*)-(+)-*s*-butanol (**7**) (3.04 g, 41 mmol; from Aldrich Chemical Company, Inc. $[\alpha]_D^{20}$ +11° (neat)) in 30 cm^3 of pyridine was cooled to 0 °C. After the addition of tosyl chloride (10.0 g, 52 mmol) in 40 cm^3 of pyridine, the solution was stirred at room temperature for 2 days. The product was extracted three times with ether and the combined organic extracts washed with water, dried over $MgSO_4$, and the solvent removed in vacuo. The resulting crude product was purified by silica-gel column chromatography (hexane/AcOEt=5/1) to give (*S*)-(+)-*s*-butyl tosylate (**8**) in 80% yield: $[\alpha]_D$ +9.6° (*c* 4.01, $CHCl_3$); IR (neat) 1350, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.83 (3H, t, J=6.6 Hz), 1.22 (3H, d, J=6.2 Hz), 1.52 (2H, q, J=6.6 Hz), 2.41 (3H, s), 4.55 (1H, m), and 7.30 and 7.76 (4H, A_2B_2, J=8.6 Hz); MS m/z 228 (M^+), 171, 113, 99, and 57; Found: m/z 228.0839, Calcd for $C_{11}H_{16}O_3S$: M, 228.0820.

Preparation of (*R*)-(−)-*s*-Butyl Phenyl Sulfide. Thiophenol (1.54 g, 14.0 mmol) was added to 25 cm^3 of methanol solution of sodium methoxide with stirring and the mixture was cooled to 0 °C. After the addition of *s*-butyl tosylate (2.13 g, 9.35 mmol) ($[\alpha]_D$ +9.6° (*c* 4.01, $CHCl_3$)) in 20 cm^3 of

methanol, the solution was stirred at room temperature for 2 days. The product was extracted three times with ether; and the combined organic extracts were then washed with water and dried over $MgSO_4$. After the solvent was removed in vacuo the resulting crude product was purified by distillation to give (*R*)-(−)-*s*-butyl phenyl sulfide in 85% yield: bp 120—123 °C (1.5 mmHg); $[\alpha]_D$ −23.5° (*c* 1.29, MeOH); ^1H NMR ($CDCl_3$) δ=1.00 (3H, t, *J*=7.0 Hz), 1.26 (3H, d, *J*=7.0 Hz), 1.57 (2H, q, *J*=7.0 Hz), 3.16 (1H, m), and 7.14—7.50 (5H, m).

Preparation of [(*R*)-(−)-*s*-Butyl]isopropylphenylsulfonium Perchlorate (1f). A mixture of silver perchlorate (1.49 g, 7.20 mmol) and (*R*)-(−)-*s*-butyl phenyl sulfide (1.20 g, 7.21 mmol) ($[\alpha]_D$ −23.5° (*c* 1.29, MeOH)) in 10 cm^3 of nitromethane was cooled to 0 °C. After the addition of isopropyl iodide (6.58 g, 38.7 mmol) in 10 cm^3 of nitromethane at 0 °C, the mixture was stirred for 2 days at room temperature. After the insoluble materials were filtered, the solvent was evaporated and the residue washed with ether to give [(*R*)-(−)-*s*-butyl]isopropylphenylsulfonium perchlorate (**1f**) in 91% yield: Pale yellow syrup; $[\alpha]_D$ −2.44° (*c* 2.37, MeOH); ^1H NMR (acetone-d_6) δ=1.16 (3H, t, *J*=7.6 Hz), 1.44 (3H, d, *J*=6.6 Hz), 1.54 (3H, d, *J*=6.6 Hz), 1.64 (2H, q, *J*=7.6 Hz), 1.66 (3H, d, *J*=6.6 Hz), 4.20—4.80 (2H, m), and 7.12—8.18 (5H, m); IR (neat) 1090 cm^{-1}.

Preparation of (*R*)-(−)-*s*-Butyl *p*-Nitrophenyl Sulfide (9). *p*-Nitrobenzenethiol (345 mg, 2.22 mmol) was added to 10 cm^3 of methanol solution of sodium methoxide with stirring; the mixture was then cooled to 0 °C. After the addition of (*S*)-(+)-*s*-butyl tosylate (**8**) ($[\alpha]_D$ +9.6° (*c* 1.83, $CHCl_3$)) in 10 cm^3 of methanol, the solution was refluxed for 1 day. The product was extracted with ether, and the combined organic extracts washed with water, dried over $MgSO_4$. After the solvent was removed in vacuo, the resulting crude product was purified by preparative TLC (Merck Kieselgel $60F_{254}$) (hexane/ether=1/1) to give (*R*)-(−)-*s*-butyl *p*-nitrophenyl sulfide (**9c**): $[\alpha]_D$ −18.5° (*c* 3.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.03 (3H, t, *J*=7.6 Hz), 1.36 (3H, d, *J*=6.8 Hz), 1.63 (2H, q, *J*=7.6 Hz), 3.10—3.63 (1H, m), and 7.30 and 8.06 (4H, A_2B_2, *J*=9.0 Hz); MS *m/z* 211 (M^+), 195, 182, 155, and 139; Found: *m/z* 211.0705, Calcd for $C_{10}H_{13}O_2NS$: M, 211.0667.

Alkylation of *p*-Nitrobenzenethiol with Sulfonium Salt (1f). A mixture of [(*R*)-(−)-*s*-butyl]isopropylphenylsulfonium perchlorate (**1f**) (992 mg, 3.21 mmol; $[\alpha]_D$ −2.44° (*c* 2.37, MeOH)), *p*-nitrobenzenethiol (**2e**) (546 mg, 5.32 mmol) and anhydrous potassium carbonate (736 mg, 5.32 mmol) in dry dichloromethane (20 cm^3) was stirred at room temperature for 4 days. After filtration of insoluble materials, the resulting reaction mixture was purified by silica-gel column chromatography (hexane/ether=20/1) and then GPC to give isopropyl *p*-nitrophenyl sulfide (36%) and pale yellow syrup of (*S*)-(+)-*s*-butyl *p*-nitrophenyl sulfide (**9**) (40%); $[\alpha]_D$ +18.7° (*c* 2.09, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.03 (3H, t, *J*=7.6 Hz), 1.36 (3H, d, *J*=6.8 Hz), 1.63 (2H, q, *J*=7.6 Hz), 3.01—3.63 (1H, m), 7.30 and 8.06 (4H, A_2B_2, *J*=9.0 Hz); MS *m/z* 211 (M^+), 195, 182, 155, 139; Found: *m/z* 211.0706, Calcd for $C_{10}H_{13}O_2NS$: M, 211.0667. Isopropyl *p*-nitrophenyl sulfide (**9b**); ^1H NMR ($CDCl_3$) δ=1.36 (6H, d, *J*=6.6 Hz), 3.34 (1H, m), and 7.30 and 8.06 (4H, A_2B_2, *J*=9.0 Hz); MS *m/z* 197 (M^+), 182, 167, 155, and 139; Found: *m/z* 197.0553, Calcd for $C_9H_{11}O_2NS$: M, 197.0510.

Synthesis of Isopropylmethylphenylselenonium Salt (12b). Isopropyl phenyl selenide was prepared by the reaction of sodium benzenethiolate and isopropyl iodide in ethanol under a nitrogen atmosphere in 83% yield; isopropyl phenyl selenide: bp 60 °C (1 mmHg, 1 mmHg=133.322 Pa); ^1H NMR ($CDCl_3$) δ=1.39 (6H, d, *J*=7.0 Hz), 3.42 (1H, m), and 7.15—7.67 (5H, m); MS *m/z* 200 (M^+), 158, 117, 105, 93, and 78. To a mixture of silver perchlorate (3.44 g, 16.6 mmol) and isopropyl phenyl selenide (3.49 g, 17.5 mmol) in nitromethane (25 cm^3) was added slowly a nitromethane solution of methyl iodide (5.50 g, 38.7 mmol) at 0 °C, and the mixture was stirred for 1 day at room temperature. After the insoluble materials were filtered off, the solvent was evaporated and the residue was washed with ether to give pure selenonium salt **12b** in 93% yield: oil, ^1H NMR ($CDCl_3$) δ=1.41 (3H, d, *J*=7.0 Hz), 1.59 (3H, d, *J*=7.0 Hz), 3.13 (3H, s), 4.20 (1H, m), and 7.57—7.93 (5H, m).

Similarly, ethylmethylphenylselenonium perchlorate (**12a**) was prepared by ethylation of methyl phenyl selenide with ethyl iodide in acetonitrile in 82% yield: Mp 69—70.5 °C (acetone-ether); ^1H NMR (acetone-d_6) δ=1.46 (3H, t, *J*=7.8 Hz), 3.26 (3H, s), 3.81 (2H, q, *J*=7.8 Hz), and 7.60—8.20 (5H, m).

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