The last comment concerns the annelation effect, i.e., the difference in basicity between azoles and benzazoles.[2] Using the data of pyrazole/indazole, 1-methylpyrazole/1-methylindazole, and the imidazole/benzimidazole pairs of Table V, the following equation can be calculated, always taking into account the symmetry effect:

$$\Delta\Delta G(\text{benzazole}) = -2.5 - 0.96\Delta\Delta G(\text{azole})$$

$$n = 7,\ r^2 = 0.989$$

For other related compounds we have found[2] a similar slope (0.93). To 1-*tert*-butyl-1*H*-benzimidazole (**18**) (-21.2) should correspond a value of -19.4 kcal mol^{-1} for 1-*tert*-butyl-1*H*-imidazole (**15**). The value, -17.1 (uncorrected) of Table IV seems again underestimated.

In conclusion, both methods (CI/MS/MS and ICR) yield comparable results. Part of the scatter in Figure 1 is expected due to the fundamental difference of process (1) and (2).

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Stereospecific Friedel–Crafts Alkylation of Aromatic Compounds: Synthesis of Optically Active 2- and 3-Arylalkanoic Esters[1]

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The alkylation of aromatic compounds, such as benzene, toluene, chlorobenzene, and naphthalene, with optically active (*S*)-alkyl 2-(sulfonyloxy)propionates and (*R*)-alkyl 3-(sulfonyloxy)butanoates in the presence of $AlCl_3$ afforded optically active (*S*)-alkyl 2-arylpropionates and (*S*)-alkyl 3-arylbutanoates in fair to good chemical yields (40–84%) and in good to excellent optical yields (61–97%). As usually occurs in Friedel–Crafts alkylation reactions, poor regioselectivity was observed.

We have recently reported the synthesis of (*S*)-methyl and (*S*)-ethyl 2-phenylpropionate as first examples of a Friedel–Crafts alkylation reaction with acyclic alkylating reagents, proceeding with good chemical yields (70–80%) and high stereospecificity (>97%) with inversion of configuration.[2] As an extension of these findings, we now report the results obtained in a detailed investigation on the synthetic usefulness and limitation of this alkylation reaction: using sulfonyloxy derivatives of optically active hydroxy esters **1** as the alkylating reagents, under $AlCl_3$ catalysis, the reaction afforded fair to good chemical and optical yields of the corresponding arylalkanoic esters **3** (Scheme I). In order to gain insight on the regioselectivity of the reaction, we have extended this study to the alkylation of some substituted benzenes and naphthalene.

Scheme I[a]

$$\underset{\mathbf{1}}{CH_3{}^*CH(OX)(CH_2)_nCOOR} + \underset{\mathbf{2}}{ArH} \xrightarrow{AlCl_3} \underset{\mathbf{3}}{CH_3{}^*CH(Ar)(CH_2)_nCOOR}$$

[a] **1a**: $n = 0$, X = SO_2CH_3, R = CH_3. **1b**: $n = 0$, X = SO_2CH_3, R = C_2H_5. **1c**: $n = 0$, X = SO_2Cl, R = CH_3. **1d**: $n = 0$, X = SO_2Tol, R = CH_3. **1e**: $n = 0$, X = SO_2Tol, R = C_2H_5. **1f**: $n = 0$, X = SO_2CF_3, R = C_2H_5. **1g**: $n = 1$, X = SO_2CH_3, R = CH_3. **1h**: $n = 1$, X = SO_2CH_3, R = C_2H_5. **1i**: $n = 1$, X = SO_2Tol, R = C_2H_5. **2a**: Ar = C_6H_5. **2b**: Ar = $CH_3C_6H_4$. **2c**: Ar = $C_{10}H_7$. **2d**: Ar = Cl-C_6H_4. **3a**: $n = 0$, Ar = C_6H_5, R = CH_3. **3b**: $n = 0$, Ar = C_6H_5, R = C_2H_5. **3c**: $n = 1$, Ar = C_6H_5, R = CH_3. **3d**: $n = 1$, Ar = C_6H_5, R = C_2H_5. **3e**: $n = 0$, Ar = *o*-, *m*-, and *p*-$CH_3C_6H_4$, R = C_2H_5. **3f**: $n = 1$, Ar = *o*-, *m*-, and *p*-$CH_3C_6H_4$, R = C_2H_5. **3g**: $n = 0$, Ar = 1- and 2-$C_{10}H_7$, R = CH_3. **3h**: $n = 0$, Ar = *o*-, *m*-, and *p*-ClC_6H_4, R = C_2H_5. **3i**: $n = 1$, Ar = *o*-, *m*-, and *p*-ClC_6H_4, R = C_2H_5.

Results

Alkylation of Benzene. We first examined the influence of the leaving group in the $AlCl_3$-mediated alkylation of benzene (**2a**), taken as a model reaction; in the previous report,[2] we employed, as alkylating reagents, (*S*)-methyl

(1) Presented in part at the XVII Convegno Nazionale della Divisione di Chimica Organica della SCI, Fiuggi (Italy). Azzena, U.; Piccolo, O. Abstract, 1987, P-5, p 49.

(2) Piccolo, O.; Spreafico, F.; Visentin, G.; Valoti, E. *J. Org. Chem.* **1985**, *50*, 3945.
(3) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.
(4) Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 2137.
(5) Azzena, U.; Delogu, G.; Melloni, G.; Piccolo, O. *Tetrahedron Lett.* **1989**, 4555.
(6) Rupe, H.; Van Walraven, F. *Helv. Chim. Acta* **1930**, *13*, 361.

0022-3263/91/1956-0183$02.50/0

Table I. Alkylation of 2a with 1

starting material (abs config)	t, h	T, °C	product (abs config)	% isol yield	$[\alpha]^{°C}_D$, deg (T °C, solvent, c)	% opt yield
1a (*S*)[a]	6	80	**3a** (*S*)	80	+105.7 (22, toluene, 6.2)[b]	97
1b (*S*)[a]	6	40	**3b** (*S*)	76	+65.7 (24, toluene, 10)[c]	91
1c (*S*)[a]	3	20	**3a** (*S*)	70	+109.8 (22, toluene, 6.2)[b]	>99
1e (*S*)	4	50	**3b** (*S*)	65	+67.8 (24, toluene, 10)[c]	94
1f (*S*)	2	25	**3b** (*S*)	40	+62.0 (24, toluene, 10)	86
1g (*R*)	2	0	**3c** (*S*)	63	+37.3 (20, neat, *l* = 1)[d]	88[e]
1g (*R*)	4	0–10	**3c** (*S*)[f]	57	+29.0 (20, neat, *l* = 1)[d]	69[e]
1h (*R*)	2	0–10	**3d** (*S*)[g]	65	+28.8 (25, neat, *l* = 1)[d,h]	88[e]
1i (*R*)	4	45	**3d** (*S*)	30	+22.3 (25, neat, *l* = 1)[d,h]	63[e]

[a] from ref 2. [b] Maximum specific rotation reported for **3a** is $[\alpha]^{22}_D$ = +109.2° (toluene, *c* 6.2).[3] [c] Maximum specific rotation reported for **3b** is $[\alpha]^{24}_D$ = +72.0° (toluene, *c* = 10).[3] [d] Observed rotation. [e] The optical yield was determined via LAH reduction to (*S*)-3-phenyl-1-butanol (**4**), by considering maximum observed rotation for the latter α^{25}_D = +39.0° (neat, *l* = 1).[4] [f] (*S*)-Methyl 3-chlorobutanoate (29% isolated yield, 80% optical yield) also recovered.[5] [g] (*S*)-Ethyl 3-chlorobutanoate (36% isolated yield, 93% optical yield) also recovered.[5] [h] Maximum observed rotation for **3d** is α^{25}_D = +32.6° (neat, *l* = 1).[6]

Table II. Alkylation of Toluene (2b), Naphthalene (2c), and Chlorobenzene (2d) with 1

reagents (abs config)	t, h	T, °C	product (abs config)	% isol yield	% of isomers[a]	% opt yield
1b (*S*), **2b**	4	30	**3e** (*S*)	84	35/32/33	not determined
1e (*S*), **2b**	4	40	**3e** (*S*)	41	44/23/33	not determined
1h (*R*), **2b**	1	0	**3f** (*S*)	60	40/27/33[b]	not determined
1d (*S*), **2c**	5	80	**3g** (*S*)	45	72/28	90[c]
1b (*S*), **2d**	12	40	**3h** (*S*)	48	53/18/29	65[d]
1e (*S*), **2d**	4	80	**3h** (*S*)	20	42/22/36	61[d]
1h (*R*), **2d**	5	0	**3i** (*S*)[e]	41	53/20/27	78[f]

[a] The isomeric ratio was determined by ^{1}H NMR spectroscopy, GLC, or HPLC; the attribution was not made except in the case of **3g**. [b] The ratio did not vary with the reaction temperature within −15 and +40 °C. [c] Evaluated by comparing the optical rotatory power of recovered **3g** with that of a similar mixture of authentic samples of the two isomers of known optical purity; see Experimental Section. [d] Determined via hydrogenation over Pd catalyst to **3b**. [e] (*S*)-Ethyl 3-chlorobutanoate (35% isolated yield, 79% optical purity) also recovered.[5] [f] Determined via hydrogenation over Pd catalyst to **3d**.

2-(mesyloxy)propionate (**1a**), (*S*)-ethyl 2-(mesyloxy)-propionate (**1b**), and (*S*)-methyl 2-[(chlorosulfonyl)oxy]-propionate (**1c**), obtaining good chemical yields and excellent optical yields of the corresponding (*S*)-methyl 2-phenylpropionate (**3a**) and (*S*)-ethyl 2-phenylpropionate (**3b**). We have now checked the reactivity of (*S*)-ethyl 2-[(*p*-tolylsulfonyl)oxy]propionate (**1e**) and of (*S*)-ethyl 2-[[(trifluoromethyl)sulfonyl]oxy]propionate (**1f**); the results obtained are reported in Table I, where a comparison with the previous data is shown.

Good chemical and optical yields of compounds **3a** and **3b** were usually obtained: however, the (methylsulfonyl)oxy group appears as the more attractive among the tested leaving groups, due to an easier preparation of the starting materials, which were obtained in almost quantitative yields; in fact, **1c** led to the formation of small amounts of chloro and/or sulfur derivatives as byproducts. In the preparation of the (*p*-tolylsulfonyl)oxy derivatives **1d** and **1e**, we sometimes obtained low chemical and optical yields, as well as competitive formation of the corresponding alkyl 2-chloropropionates; also the [(trifluoromethyl)sulfonyl]oxy derivative **1f**, prepared by using the expensive trifluoromethanesulfonyl chloride or anhydride, afforded a relatively low yield of the alkylated product. Our results also showed that, other things being equal, there was no relevant effect upon chemical or optical yields on going from methyl to ethyl esters.

Besides sulfonyloxy derivatives of methyl and ethyl esters of 2-hydroxypropionic acid, we have also employed as alkylating reagents some sulfonyloxy derivatives of methyl and ethyl esters of 3-hydroxybutanoic acid; indeed, esters of 3-hydroxybutanoic acid are particularly attractive as chiral synthons, due to their ready availability in both enantiomeric forms in very high optical purity;[7] the results obtained in the alkylation of **2a** with (*R*)-methyl 3-(mesyloxy)butanoate (**1g**), which afforded (*S*)-methyl 3-phenylbutanoate (**3c**), and in the alkylation of **2a** with (*R*)-ethyl 3-(mesyloxy)butanoate (**1h**) and (*R*)-ethyl 3-[(*p*-tolylsulfonyl)oxy]butanoate (**1i**), which afforded (*S*)-ethyl 3-phenylbutanoate (**3d**), are also reported in Table I. It can be pointed out that with the esters of 3-hydroxybutanoic acid there is a remarkable advantage, in both chemical and optical yields, in using mesyloxy derivatives instead of (*p*-tolylsulfonyl)oxy derivatives; the result obtained with **1i** probably suffered from its very low solubility in the reaction mixture.

In comparison of the results obtained in the case of alkyl (mesyloxy)propionates **1a** and **1b** (*n* = 0) with those obtained in the case of the corresponding alkyl (mesyloxy)-butanoates **1g** and **1h** (*n* = 1), it is worth noting that the latter showed a higher reactivity in the $AlCl_3$-mediated alkylation of **2a**, affording satisfactory yields of the alkylated products also at 0 °C, although somewhat lower optical yields were obtained; furthermore, prolonged reaction times and relatively high reaction temperatures affected the optical yield in the synthesis of **3c**, without improvement of the chemical yield.

As a last remark, it has to be pointed out that under similar reaction conditions the sulfonyloxy derivatives may react with $AlCl_3$, affording (*R*)-2-chloropropionate and (*S*)-3-chlorobutanoate esters in good chemical yields and high optical purity.[5] In the presence of aromatic compounds, however, such a reaction is suppressed or reduced to a minimal amount; in case the chloro derivatives are formed, they can be easily separated from the alkylation products by distillation, due to their relatively low boiling points.

(7) Seebach, D.; Sutter, M. A.; Weber, R. H.; Zuger, M. F. *Org. Synth.* **1984**, *63*, 1.

(8) Menicagli, R.; Piccolo, O.; Lardicci, L.; Wis, M. L. *Tetrahedron* **1979**, *35*, 1301. Piccolo, O.; Menicagli, R.; Lardicci, L. *Tetrahedron* **1979**, *35*, 1751.

Alkylation of Substituted Benzenes and Naphthalene. The reactivity of compounds **1b**, **1d**, **1e**, and **1h** was tested toward toluene (**2b**), naphthalene (**2c**), and chlorobenzene (**2d**); the results obtained are reported in Table II.

With substituted benzenes, the regioselectivity of the present reaction did not differ from that usually observed in other Friedel–Crafts alkylation reactions, more particularly in the introduction of 2-propyl or 2-butyl groups;[9] it is, however, interesting to note that the reaction temperature did not affect the regioselectivity, as shown by the distribution of the regioisomers in the synthesis of **3f** from **1h**, which was nearly the same irrespective of the reaction temperature (−15/+40 °C), thus suggesting that the effect of reorientation on the observed isomer distributions in the alkylation product was small, if any.

Alkylations of **2c** and **2d** were studied in some detail, and optical yields as well as regioselectivity were determined. While the $AlCl_3$-mediated reaction of **1a** with **2c** afforded the corresponding chloro ester as the only reaction product, alkylation of **2c** was achieved with (*R*)-methyl 3-[(*p*-tolylsulfonyl)oxy]propionate (**1d**). The optical purity of the so obtained 72:28 mixture of (*S*)-methyl 2-(1- and 2-naphthyl)propionate (**3g**) was measured by comparing its optical rotatory power with the rotatory power of a similar mixture of authentic samples of known optical purity.[8] Alkylation of **2d** was achieved with **1b**, **1e**, and **1h**. The optical purity of the mixtures of regioisomers **3h** and **3i** was determined by dehalogenation to **3b** and **3d**, respectively; the chlorine atom was removed by hydrogenolysis catalyzed by Pd over charcoal.

While the naphthyl derivative was obtained with high optical yield (90%), comparable to that observed in the alkylation of **2a**, alkylations of **2d** proceeded with somewhat lower stereospecificity particularly in the case of **3h** (61%); this anomalous result was difficult to explain, and we have therefore investigated the last reaction carefully.

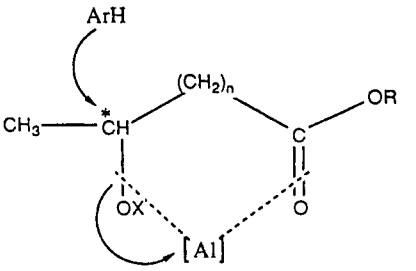
At first, we verified the optical stability of **1e** either under the reaction conditions, recovering where possible the unchanged starting material, or treating **1e** with $AlCl_3$ in CH_2Cl_2; loss of optical activity not exceeding 3–5% was observed.

As different amounts of alkyl 2-chloropropionates (as well as 3-chlorobutanotes) could be formed under the action of $AlCl_3$ on the alkylating reagents with inversion of configuration[5] (see footnotes *f* and *g* of Table I and footnote *f* of Table II), we wondered whether in the present case (*R*)-ethyl 2-chloropropionate could have been formed and have reacted with **2d**,[10] thus lowering the overall optical yield. However, in our hands, ethyl 2-chloropropionate did not react with **2d**, even by heating the reaction mixture up to 80 °C in the presence of $AlCl_3$ for several hours.

On the basis of our experience,[11] we were not inclined to think that **3h** could have racemized under the dehalogenation reaction conditions, i.e., in the presence of Pd on charcoal; nevertheless, we have tested this reaction by varying the reaction conditions (temperature, time, catalysts from different sources), but, according to our expectations, the reaction product was always recovered with almost the same optical yield.

We then made the hypothesis that the stereospecificity of the Friedel–Crafts alkylation in the various positions of the aromatic nucleus could be different, thus affording the three regioisomers of **3h** in different optical yields; to test this hypothesis, we have obtained, by preparative HPLC, fractions of different composition in the three regioisomers; dehalogenation of such fractions afforded, in all cases, **3b** of almost the same optical purity (50–61%).

Scheme II



Finally, we have checked the optical stability of **3h**, as a mixture of regioisomers, under the conditions of the alkylation reaction; to our great surprise we found a loss of optical activity of 89%, without apparent change in the ratio of the regioisomers; on the other hand, a similar check made with the product of alkylation of benzene, **3b**, did not show loss of optical activity. As a possible explanation of this different behavior, we suggest that a coordination between $AlCl_3$ and the chlorine atom on the aromatic ring can enhance the electron-withdrawing effect of the latter and labilize the tertiary benzylic C–H bond, the detachment and reattachment of the hydrogen atom causing racemization. This effect is more conspicuous when a free or $AlCl_3$-coordinated carbalkoxy group is located α to the asymmetric carbon atom and therefore can also contribute to labilization of the same C–H bond. However, the carbalkoxy group alone is not able to produce racemization under the reaction conditions.

Discussion

The results reported show that high optical and chemical yields can be obtained in the asymmetric Friedel–Crafts alkylation of aromatic compounds with acyclic alkylating reagents, with $AlCl_3$ as a catalyst. To explain the high stereospecificity of this reaction, we confirm our proposal[2,5] on the formation of an intermediate complex between compounds **1** and the Lewis acid, followed by attack of **2** on the chiral carbon atom from the back side (Scheme II), in agreement with the suggestion of Suga and co-workers.[10] This hypothesis explains the small influence of the different leaving group under investigation (OX), as well as of R groups, on chemical and optical yields and regioselectivity; the differences observed in chemical and optical yields on going from sulfonyloxy derivatives of 2-hydroxypropionate to those of 3-hydroxybutanoate (i.e., from $n = 0$ to $n = 1$) can be attributed to the different stabilities of such intermediate complexes.

The requirement of a Lewis acid as a catalyst, and of a leaving group able to coordinate it, is further supported by the results reported in a recent paper, which show that complete racemization occurs in the alkylation of benzene with optically active (*S*)-methyl 3-[[(trifluoromethyl)-sulfonyl]oxy]butanoate, using trifluoromethanesulfonic acid both as a solvent and as a catalyst.[12] The stereochemical outcome of this reaction has been attributed to the intermediate formation of a carbenium ion; under our reaction conditions, the formation of similar carbenium

(9) Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry, a Century of Discovery*; Marcel Dekker Inc.: New York, 1984; Chapters 3 and 4 and references therein.

(10) Nakajima, T.; Masuda, S.; Nakashima, S.; Kondo, T.; Nakamoto, Y.; Suga, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2377.

(11) Piccolo, O.; Spreafico, F.; Visentin, G.; Valoti, E. *J. Org. Chem.* **1987**, *52*, 10.

(12) Efferberger, F.; Weber, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 142.

ions is likely not occurring, as well as scrambling of the leaving group that would cause racemization of compounds **1** without apparent reaction, contrary to what happens in other Friedel–Crafts alkylations.[10]

The low regioselectivity observed is, of course, a strong limitation to a general application of this reaction; however, either where there is not a problem of regioisomers, i.e., with benzene as aromatic substrate, or where the predominant formation of one regioisomer is foreseeable, or where the separation of regioisomers can be carried out in a simple way, this reaction seems convenient and easy to perform in order to obtain esters of optically active arylalkanoic acids of high optical purity with a reasonably good chemical yield.

Experimental Section

General Procedures. Boiling points are uncorrected. ^{1}H NMR spectra were recorded at 60 MHz on a Varian T 60 spectrometer, at 200 MHz on a Varian XL 200 spectrometer, and at 300 MHz on a Varian VXR 300 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded on a Finnigan Mat 1020-B mass spectrometer operating at 70 eV, interfaced with a Perkin-Elmer Sigma 3 gas chromatograph, equipped with a Supelco SP-2100 30-m capillary column (i.d. 0.25 mm). GLC analyses were performed with a Hewlett-Packard Model 5890 gas chromatograph equipped with a similar capillary column. HPLC analyses were performed with a Waters 510 liquid chromatograph equipped with a 3.1 × 30 cm Microporosil column, with 85/15 cyclohexane/CH_2Cl_2 as eluent, 1.1 mL/min flow, with a Philips spectrophotometric detector operating at 254 nm. The chromatograms were recorded with a Perkin-Elmer LC 100 integrator. Optical rotations were taken on a Perkin-Elmer 142 polarimeter using a 1-cm^3 capacity (10-cm path length) quartz cell. Optical rotatory powers of compounds **3a–d** are reported in Table I.

Starting Materials. Solvents were dried and distilled shortly before use. (*S*)-Methyl lactate and (*S*)-ethyl lactate were purchased from Aldrich; (*R*)-methyl 3-hydroxybutanoate ($[\alpha]_D^{22}$ = −23.4° (neat, d^{20}_4 = 1.05, optical purity >99%)) and (*R*)-ethyl 3-hydroxybutanoate ($[\alpha]_D^{24}$ = −19.0° (neat, d_4^{20} = 1.01, optical purity >99%)) were obtained via depolymerization of poly-((*R*)-3-hydroxybutanoic acid) (Fluka).[13]

The corresponding sulfonyloxy derivatives were obtained by using known procedures and were characterized as follows (optical purity confidently evaluated on the basis of the corresponding hydroxy esters).

(−)-(*S*)-Methyl 2-(mesyloxy)propionate (1a): prepared as **1b**; see also ref 14; bp 80–82 °C (0.5 Torr); ^{1}H NMR (300 MHz) δ 1.62 (d, 3 H, *J* = 6.9, CH_3CH), 3.16 (s, 3 H, CH_3S), 3.82 (s, 3 H, CH_3O), 5.14 (q, 1 H, *J* = 6.9, CH); $[\alpha]^{25}_D$ = −56.4° (*c* = 1, $CHCl_3$).

(−)-(*S*)-Ethyl 2-(mesyloxy)propionate (1b): prepared according to ref 15; bp 85–86 °C (0.3 Torr) (lit.[15] bp 115 °C (2 Torr)); ^{1}H NMR spectrum in good agreement with literature data;[15] $[\alpha]^{22}_D$ = −53.0° (*c* = 1, $CHCl_3$) (lit.[16] $[\alpha]^{20}_D$ = −53.9° (*c* = 1, $CHCl_3$)).

(−)-(*S*)-Methyl 2-[(chlorosulfonyl)oxy]propionate (1c): prepared according to ref 17; bp 91 °C (3 Torr) (lit.[17] bp 70–71 °C (2 Torr)); ^{1}H NMR (300 MHz) δ 1.70 (d, 3 H, *J* = 7.0, CH_3CH), 3.82 (s, 3 H, CH_3O), 5.24 (q, 1 H, *J* = 7.0, CH); $[\alpha]^{25}_D$ = −81.4° (*c* = 1, $CHCl_3$).

(−)-(*S*)-Methyl 2-[(*p*-tolylsulfonyl)oxy]propionate (1d): prepared according to ref 18; bp 182–183 °C (1 Torr) (lit.[18] bp 170–173 °C (0.5 Torr)); ^{1}H NMR (60 MH) δ 1.45 (d, 3 H, *J* = 6, CH_3CH), 2.40 (s, 3 H, CH_3 tolyl), 3.60 (s, 3 H, CH_3O), 4.90 (q, 1 H, *J* = 6, CH), 7.35 (d, 2 H, *J* = 9, aromatic), 7.80 (d, 2 H, *J* = 9, aromatic); α^{20}_D = −61.1° (neat).

(−)-(*S*)-Ethyl 2-[(*p*-tolylsulfonyl)oxy]propionate (1e): prepared according to ref 19; bp 160–163 °C (0.4 Torr) (lit.[19] bp 164–166 °C (0.5 Torr)); ^{1}H NMR (60 MHz) δ 1.21 (t, 3 H, *J* = 7, CH_3CH_2), 1.51 (d, 3 H, *J* = 7, CH_3CH), 2.46 (s, 3 H, CH_3 tolyl), 4.12 (q, 2 H, *J* = 7, CH_2O), 4.93 (q, 1 H, *J* = 7, CH), 7.33 (d, 2 H, *J* = 9, aromatic), 7.85 (d, 2 H, *J* = 9, aromatic); $[\alpha]^{40}_D$ = −42.9° (neat) (lit.[19] $[\alpha]^{40}_D$ = −42.6° (neat, *d* = 1.1845)).

(−)-(*S*)-Ethyl 2-[[(trifluoromethyl)sulfonyl]oxy]-propionate (1f): prepared according to ref 20; bp 69–70 °C (15 Torr) (lit.[20] bp 68 °C (12 Torr)); ^{1}H NMR spectrum in good agreement with literature data;[20] $[\alpha]^{22}_D$ = −40.8° (*c* = 1, $CHCl_3$).

(−)-(*R*)-Methyl 2-(mesyloxy)butanoate (1g): prepared as **1h**; bp 98–100 °C (1 Torr); ^{1}H NMR (300 MHz) δ 1.52 (d, 3 H, *J* = 5.9, CH_3CH), 2.60 (dd, 1 H, J_{vic} = 4.1, J_{gem} = 16.1, CH_2), 2.80 (dd, 1 H, J_{vic} = 8.3, J_{gem} = 16.1, CH_2), 3.07 (s, 3 H, CH_3O), 3.76 (s, 3 H, CH_3S), 4.89–4.98 (complex m, 1 H, CH); α^{20}_D = −46.5° (neat).

(−)-(*R*)-Ethyl 2-(mesyloxy)butanoate (1h): prepared according to ref 21; bp 105–108 °C (0.5 Torr); ^{1}H NMR (60 MHz) δ 1.28 (t, 3 H, *J* = 7, CH_3CH_2), 1.50 (d, 3 H, *J* = 7, CH_3CH), 2.58–2.81 (m, 2 H, CH_2O), 3.01 (s, 3 H, CH_3S), 4.16 (q, 2 H, *J* = 7, CH_2O), 4.83–5.41 (m, 1 H, CH); α^{20}_D = −39.5° (neat).

(−)-(*R*)-Ethyl 2-[(*p*-tolylsulfonyl)oxy]butanoate (1i): prepared according to ref 21; bp 220–221 °C (1 Torr); ^{1}H NMR (60 MHz) δ 1.10–1.58 (complex m, 6 H, CH_3CH_2 and CH_3CH), 2.38–2.80 (m, 2 H, CH_2CH), 2.55 (s, 3 H, CH_3 tolyl), 4.16 (q, 2 H, *J* = 7, CH_2O), 5.10 (q, 1 H, *J* = 6, CH), 7.58 (d, 2 H, *J* = 9, aromatic), 8.03 (d, 2 H, *J* = 9, aromatic); $[\alpha]^{28}_D$ = −5.5° (*c* = 1, CH_3OH).

Alkylation Reaction: General Procedure. The reactions were usually run with the aromatic substrate being used as solvent; only in the alkylation of **2c**, cyclohexane (15 mL) was used as solvent. **1** (15 mmol) was added dropwise to a stirred mixture of **2** (60 mmol) and $AlCl_3$ (30 mmol, 4 g) chilled at 0 °C, and the reaction mixture was stirred at the reported temperature for the indicated time. The reaction mixture was chilled at 0 °C, quenched by dropwise addition of 10% HCl (15 mL), and extracted with Et_2O (3 × 20 mL); the organic phase was collected, washed with water (3 × 20 mL), dried over anhydrous $CaCl_2$, and concentrated at reduced pressure; the crude product was purified by distillation at reduced pressure or flash chromatography and characterized as follows.

(+)-(*S*)-Methyl 2-phenylpropionate (3a): bp 100–103 °C (15 Torr) (lit.[22] bp 222 °C (760 Torr)); ^{1}H NMR (60 MHz) δ 1.47 (d, 2 H, *J* = 7, CH_3CH), 3.63 (s, 3 H, CH_3O), 3.70 (q, 1 H, *J* = 7, CH), 7.24 (s, 5 H, aromatic).

(+)-(*S*)-Ethyl 2-phenylpropionate (3b): bp 128–130 °C (15 Torr) (lit.[23] bp 105–107 °C (10 Torr)); ^{1}H NMR (60 MHz) δ 1.17 (t, 3 H, *J* = 7, CH_3CH_2), 1.46 (d, 3 H, *J* = 7, CH_3CH), 3.67 (q, 1 H, *J* = 7, CH), 4.24 (q, 2 H, *J* = 7, CH_2O), 7.26 (s, 5 H, aromatic).

(+)-(*S*)-Methyl 3-phenylbutanoate (3c): bp 110–112 °C (15 Torr) (lit.[24] bp 133–134 °C (22 Torr)); ^{1}H NMR (60 MHz) δ 1.26 (d, *J* = 7, 3 H, CH_3CH), 2.48 (d, *J* = 7, 2 H, CH_2CH), 2.93–3.53 (m, *J* = 7, 1 H, CH), 3.53 (s, 3 H, CH_3O), 7.16 (s, 5 H, aromatic).

(+)-(*S*)-Ethyl 3-phenylbutanoate (3d): bp 92–94 °C (10 Torr) (lit.[10] bp 118–119 °C (17 Torr)); ^{1}H NMR (60 MHz) δ 1.23 (t, *J* = 7, 3 H, CH_3CH_2), 1.53 (d, *J* = 7, 3 H, CH_3CH), 2.50 (d, *J* = 7, 2 H, CH_2CH), 2.93–3.50 (m, 1 H, CH), 4.05 (q, *J* = 7, 2 H, CH_2O), 7.18 (s, 5 H, aromatic).

(+)-(*S*)-Ethyl 2-(*o*-, *m*-, and *p*-Methylphenyl)propionate (3e). The ratio among the three isomers was determined by GLC: bp 70–76 °C (1 Torr); ^{1}H NMR (200 MHz) δ 1.13–1.25 (complex m, 3 H, CH_3CH_2, three isomers), 1.43–1.52 (complex m, 3 H, CH_3CH, three isomers), 2.32 (s, 3 H, CH_3 tolyl, one isomer), 2.34 (s, 3 H, CH_3 tolyl, one isomer), 2.37 (s, 3 H, CH_3 tolyl, one isomer),

(13) Seebach, D.; Zuger, M. F. *Helv. Chim. Acta* **1982**, *65*, 495.
(14) Scott, R. M.; Armitage, G. D. *Ger. Offen.* 2,650,434; *Chem. Abstr.* **1977**, *87*, 67990n. Rogers, R. B.; Genwick, B. C. *Eur. Pat. Appl.* 138,359; *Chem. Abstr.* **1985**, *103*, 195896x.
(15) Stephenson, L. M.; Speth, D. R. *J. Org. Chem.* **1979**, *44*, 4683.
(16) Azzolina, O.; Vercesi, D.; Ghislandi, V. *Farmaco, Ed. Sci.* **1988**, *43*, 469; *Chem. Abstr.* **1989**, *110*, 23438c.
(17) Seitetsu Kagagu Co., Ltd. *Jpn. Kokai Tokkyo Koho* JP 58 08,045 [83 08,045]; *Chem. Abstr.* **1983**, *98*, 143138k. It is noted that in *Chem. Abstr.* SO_2Cl_2 is erroneously substituted with S_2Cl_2.
(18) Freudenberg, K.; Rhino, F. *Chem. Ber.* **1924**, *57*, 1547.
(19) Kenyon, J.; Phillips, H.; Turley, H. G. *J. Chem. Soc.* **1925**, *127*, 399.
(20) Efferberger, F.; Burkard, U.; Willfarth, J. *Liebigs Ann. Chem.* **1986**, 314.
(21) Linstead, R. P.; Owen, L. N.; Webb, R. F. *J. Chem. Soc.* **1953**, 1221.
(22) Horner, L.; Winkler, H. *Justus Liebigs Ann. Chem.* **1965**, *685*, 1.
(23) Kadin, S. B. *J. Org. Chem.* **1966**, *31*, 620.
(24) Schroeter, G. *Chem. Ber.* **1907**, *40*, 1589.

3.60–3.73 (complex m, 1 H, CH, two isomers), 3.94 (q, 1 H, J = 7, CH, one isomer), 4.03–4.21 (complex m, 2 H, CH_2O, three isomers), 7.02–7.29 (complex m, 4 H, aromatic, three isomers); mass spectra (GLC/MS), m/e (relative intensity) 192 ($M^{\bullet+}$, 13.9) and 119 ($M^{\bullet}$ - $COOC_2H_5$, 100) for the isomer with the lower GLC retention time (t_{R1}), 192 ($M^{\bullet+}$, 10.9) and 119 ($M^{\bullet+}$ - $COOC_2H_5$, 100) for the isomer with the intermediate GLC retention time (t_{R2}), and 192 ($M^{\bullet+}$, 10.8) and 119 ($M^{\bullet+}$ - $COOC_2H_5$, 100) for the isomer with the higher GLC retention time (t_{R3}). The specific rotations of the three isomers obtained via alkylation of **2b** with **1b** were $[\alpha]^{25}_D$ = +113° (cyclohexane, c = 1.1), for t_{R1}; $[\alpha]^{25}_D$ = +61° (cyclohexane, c = 1.1), for t_{R2}; and $[\alpha]^{25}_D$ = + 79° (cyclohexane, c = 1.1), for t_{R3}; these were calculated on enriched fractions of the three isomers obtained by spinning band distillation, assuming additivity of the rotatory powers.

(*S*)-Ethyl 3-(*o*-, *m*-, and *p*-Methylphenyl)butanoate (3f). The ratio among the three isomers was determined by GLC: bp 83–88 °C (1 Torr); ^{1}H NMR (300 MHz) δ 1.02–1.12 (complex m, 3 H, CH_3CH_2, three isomers), 1.12–1.30 (complex m, 3 H, CH_3CH, three isomers), 2.29 (s, 3 H, CH_3 tolyl, one isomer), 2.31 (s, 3 H, CH_3 tolyl, one isomer), 2.36 (s, 3 H, CH_3 tolyl, one isomer), 2.45–2.65 (complex m, 2 H, CH_2CH, three isomers), 3.15–3.38 (complex m, 1 H, CH, two isomers), 3.45–3.59 (m, 1 H, CH, one isomer), 4.03–4.19 (complex m, 2 H, CH_2O, three isomers), 6.99–7.11 (complex m, 4 H, aromatic, three isomers); mass spectra (GLC/MS), m/e (relative intensity) 206 ($M^{\bullet+}$, 6.8) and 119 ($M^{\bullet+}$ - $CH_2COOC_2H_5$, 100) for t_{R1}, 206 ($M^{\bullet+}$, 8.3) and 119 ($M^{\bullet+}$ - $CH_2COOC_2H_5$, 100) for t_{R2}, and 206 ($M^{\bullet+}$, 7.8) and 119 ($M^{\bullet+}$ - $CH_2COOC_2H_5$, 100) for t_{R3}.

(+)-(*S*)-Methyl 2-(1- and 2-Naphthyl)propionate (3g). The ratio between the two isomers was determined by GLC; assignments were made by comparing the ^{1}H NMR spectrum of **3g** with that of authentic samples[25] prepared according to ref 8; bp 123–125 °C (0.5 Torr); α isomer ^{1}H NMR (300 MHz) δ 1.66 (d, 3 H, J = 7.1, CH_3CH), 3.65 (s, 3 H, CH_3O), 4.51 (q, 1 H, J = 7.1, CH), 7.42–7.56 (m, 4 H, aromatic), 7.73–7.80 (m, 1 H, aromatic), 7.85–7.89 (m, 1 H, aromatic), 8.05–8.10 (d, 1 H, J = 8.1, aromatic); β isomer ^{1}H NMR (300 MHz) δ 1.59 (d, 3 H, J = 7.1, CH_3CH), 3.66 (s, 3 H, CH_3O), 3.89 (q, 1 H, J = aromatic), 7.76–7.83 (m, 3 H, aromatic); mass spectra (GLC/MS), m/e (relative intensity) 214 ($M^{\bullet+}$, 21.1) and 155 ($M^{\bullet+}$ - $COOCH_3$, 100) for the α isomer and 214 ($M^{\bullet+}$, 15.6) and 155 ($M^{\bullet+}$ - $COOCH_3$, 100) for the β isomer; specific rotation for recovered **3g** was $[\alpha]^{25}_D$ = +140.0° (benzene, c = 2.5); assuming additivity of rotatory powers, 90% optical purity was evaluated by comparison with the specific rotation of a similar mixture of authentic samples of known optical purity; maximum specific rotation for the α isomer is $[\alpha]^{25}_D$ = +181.3° (benzene, c = 2.5);[8] maximum specific rotation for the β isomer is $[\alpha]^{25}_D$ = +111.9° (benzene, c = 2.5).[8]

(+)-(*S*)-Ethyl 2-(*o*-, *m*-, and *p*-Chlorophenyl)propionate (3h). The ratio among the three isomers was determined by GLC or HPLC: ^{1}H NMR (300 MHz) δ 1.18–1.24 (complex m, 3 H, CH_3CH_2, three isomers), 1.46–1.51 (complex m, 3 H, CH_3CH, three isomers), 3.67 (q, 1 H, J = 7.3, CH, one isomer), 4.06–4.24 (complex m, 3 H, CH, two isomers, and CH_2O, three isomers), 7.16–7.39 (complex m, 4 H, aromatic, three isomers); mass spectra (GLC/MS), m/e (relative intensity) 212 ($M^{\bullet+}$, 1.9), 177 ($M^{\bullet+}$ - Cl, 68.9), and 139 ($M^{\bullet+}$ - $COOC_2H_5$, 100) for t_{R1}, 214 ($M^{\bullet+}$ + 2, 9.6), 212 ($M^{\bullet+}$, 30.1), and 139 ($M^{\bullet+}$ - $COOC_2H_5$, 100) for t_{R2}, and 214 ($M^{\bullet+}$ + 2, 3.8), 212 ($M^{\bullet+}$, 12.6), and 139 ($M^{\bullet+}$ - $COOC_2H_5$, 100) for t_{R3}; the specific rotations of the three isomers obtained via alkylation of **2d** with **1e** were $[\alpha]^{25}_D$ = +29° ($CHCl_3$, c = 1), for t_{R1}; $[\alpha]^{25}_D$ = +21° ($CHCl_3$, c = 1), for t_{R2}; and $[\alpha]^{25}_D$ = +88° ($CHCl_3$, c = 1), for t_{R3}; these were calculated on enriched fractions of the three isomers obtained by preparative HPLC, assuming additivity of the rotatory powers; the mixture was further characterized by dehalogenation to **3b**.

(*S*)-Ethyl 3-(*o*-, *m*-, and *p*-Chlorophenyl)butanoate (3i). The ratio among the three isomers was determined by GLC: ^{1}H NMR (200 MHz) δ 1.19 (t, 3 H, J = 7, CH_3CH_2, three isomers), 1.30 (d, 3 H, J = 7, CH_3CH, three isomers), 2.47–2.59 and 2.65–2.74 (complex m, 2 H, CH_2CH, three isomers), 3.21–3.31 (m, 1 H, CH, one isomer), 3.75–3.88 (m, 1 H, CH, two isomers), 4.05–4.20 (complex m, 2 H, CH_2O), 7.11–7.38 (complex m, 4 H, aromatic, three isomers); mass spectra (GLC/MS), m/e (relative intensity) (no molecular ion) 191 ($M^{\bullet+}$ - Cl, 51.8) and 139 ($M^{\bullet+}$ - $CH_2COOC_2H_5$, 100) for t_{R1}, 228 ($M^{\bullet+}$ + 2, 2.3), 226 ($M^{\bullet+}$, 8.8), 152 (100), and 139 ($M^{\bullet+}$ - $CH_2COOC_2H_5$, 77.9) for t_{R2}, and 228 ($M^{\bullet+}$ + 2, 3.9), 226 ($M^{\bullet+}$, 11.0), 152 (67.6), and 139 ($M^{\bullet+}$ - $CH_2COOC_2H_5$, 100) for t_{R3}; the mixture was further characterized by dehalogenation to **3d**.

Dehalogenation of 3h and 3i. In a typical procedure, 10 mmol of **3h** (or **3i**) dissolved in 20 mL of absolute EtOH was hydrogenated at atmospheric pressure in the presence of 10% Pd over charcoal (0.3 g) for 6 h at 25 °C. The catalyst was removed by filtration and the solvent evaporated; distillation at reduced pressure afforded compound **3b** (or **3d**) in almost quantitative yield.

(+)-(*S*)-3-Phenyl-1-butanol (4) by LAH Reductions of 3c or 3d. In a typical procedure, 10 mmol of **3c** (or **3d**) dissolved in 5 mL of anhydrous Et_2O was added dropwise with vigorous stirring to a mixture of LAH (0.27 g, 7 mmol) in 20 mL of Et_2O. After 5 h of stirring at room temperature, the reaction mixture was chilled to 0 °C, quenched by dropwise addition of 10% HCl (20 mL), and extracted with Et_2O. The organic phase was washed with brine (2 × 20 mL) and dried over anhydrous $CaCl_2$. Evaporation of the solvent and vacuum distillation afforded **4** in 78–92% yield: bp 100 °C (1 Torr) (lit.[6] bp 117.5 °C (10 Torr)); ^{1}H NMR (60 MHz) δ 1.23 (d, J = 7, 3 H, CH_3), 1.53–1.98 (m, 2 H, CH_2CH), 2.52–3.08 (m, 1 H, CH), 3.16 (br s, 1 H, OH), 3.4 (t, J = 7, 2 H, CH_2O), 7.20 (s, 5 H, aromatic).

Registry No. **1a**, 63696-98-0; **1b**, 63696-99-1; **1c**, 98064-20-1; **1d**, 71283-66-4; **1e**, 57057-80-4; **1f**, 84028-88-6; **1g**, 130378-36-8; **1h**, 130378-37-9; **1i**, 130378-38-0; **2a**, 71-43-2; **2b**, 108-88-3; **2c**, 91-20-3; **2d**, 108-90-7; **3a**, 28645-07-0; **3b**, 42253-99-6; **3c**, 1441-20-9; **3d**, 1134-71-0; **3e** (ortho isomer), 130378-39-1; **3e** (meta isomer), 130378-43-7; **3e** (para isomer), 130378-44-8; **3f** (ortho isomer), 130378-40-4; **3f** (meta isomer), 130378-45-9; **3f** (para isomer), 1461-11-6; **3g** (1-naphthyl isomer), 22561-78-0; **3g** (2-naphthyl isomer), 119393-06-5; **3h** (ortho isomer), 130378-41-5; **3h** (meta isomer), 130405-70-8; **3h** (para isomer), 130405-71-9; **3i** (ortho isomer), 130378-42-6; **3i** (meta isomer), 130378-46-0; **3i** (para isomer), 130378-47-1; **4**, 2031-46-1.

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