Since these enone dimerizations are thought to proceed through the triplet excited state,[3] quenching of the excited states of 1 and 2 was studied. The importance of the excited singlet state in these photoreactions could be determined by observing the fluorescence yield in the presence and absence of copper. When excited into the n,π* band at 335, however, the fluorescence of 2 is somewhat reduced, but not completely quenched, by the presence of Cu(I). We conclude that either Cu(I) can quench the n,π* singlet state or can facilitate intersystem crossing to the triplet state.

The transient enone triplets, generated by laser flash spectroscopy, were sensitive to oxygen in methanolic solution and were nearly completely quenched if precomplexed with copper triflate. Thus, the observed shift in regiochemistry toward the head-to-tail dimer may be attributed to more efficient quenching of the preferentially formed Cu(I)–head-to-head dimer complex.

Although the enhanced quenching of the head-to-head complex provides partial stereocontrol of these reactions, a mixture of regioisomers is still obtained. The shift in regiochemical preference obtained with copper closely resembles that observed in these systems upon alteration of solvent polarity. Comparable chemical yields are observed in the presence and the absence of the copper salt, and the quantum yield of photodimer is greatly reduced when copper is present. We, therefore, find no clear synthetically useful advantage in pre-complexation with copper salts as a means for regiocontrol in enone (2 + 2) cycloadditions.

Experimental Section

Commercial (Aldrich) samples of cyclopentenone and isophorone were distilled to 99% gas chromatographic purity. Solvents employed here were reagent grade, distilled before use.

Photodimerizations. In a typical experiment, enone (2 g, 15 mmol) was diluted to a solution volume of 20 mL with either methanol or dichloromethane. The resulting solution, having been purged by a nitrogen stream for 30 min and sealed into a glass test tube, was irradiated for 2 h at 254 or 350 nm. Quartz vessels were used for irradiations at 254 nm and Pyrex vessels were employed at 350 nm.

Irradiations conducted in dichloromethane were analyzed directly by GC. Those conducted in methanol were stripped of solvent and redissolved in diethyl ether. Having been washed with water, the solutions were dried over $MgSO_4$, filtered, and concentrated for analysis. Products were identified by comparison of ^1H and ^{13}C NMR spectral data and mass spectral fragmentation patterns with authentic samples.[1,2]

Photodimerizations in the Presence of Copper Triflate. To a 5-mL solution of enone prepared as above was added 1 mL of a saturated solution of CuOTf[10] (2 g in 10 mL solvent). The resulting dark blue-green solution was irradiated as above for 24 h at 254 or 350 nm. Products were worked up, analyzed, and identified as in the uncomplexed irradiations. Rates of reaction were determined by monitoring the absolute rates of appearance of product by GC and by observing the rate of disappearance of the vinyl proton of the starting material by proton NMR.

Fluorescence Quenching Studies. Solutions of isophorone (optical density of approximately 0.2) were excited by a source passing a beam from a high-pressure mercury arc through a monochromator blazed at 305 or 335 nm. Emission intensity, monitored at a right angle to the incident beam, was scanned from 325 to 400 nm, and the area under the emission curves was compared electronically. A solution containing a 1:1 ratio of enone to copper triflate was similarly scanned.

Phosphorescence Quenching Studies. Solutions (CH_2Cl_2 or CH_3OH) of 1 or 2 containing varying quantities of copper triflate were adjusted in concentration so that the resulting mixtures had an optical density between 0.1 and 0.2 at 355 or 265 nm. The resulting solutions were purged by a slow stream of nitrogen. Laser flash excitation with a N_2 laser or with the second harmonic of a Nd-YAG laser produced a transient with absorption at 295 nm. Transient decay rates were analyzed with a Biomation 8100 digitizer, coupled with either a PDP 11/34 or a PDP 11/70 computer, as previously described.[11]

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Registry No. 1, 930-30-3; 2, 78-59-1; CuOTf, 42152-44-3.

(10) Kochi, J. K.; Salomon, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 1889.
(11) Lindig, B. A.; Rodgers, M. A. J. *J. Phys. Chem.* **1979**, *83*, 1683.

Asymmetric Electrophilic Substitution on Phenols. 1. Enantioselective Ortho-Hydroxyalkylation Mediated by Chiral Alkoxyaluminum Chlorides

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A method has been developed for the asymmetric ortho-specific hydroxyalkylation of phenols with trichloroacetaldehyde in the presence of chirally modified aluminum chloride derivatives. Enantiomeric excesses of up to 80% were obtained by using (−)-menthoxy(ethyl)aluminum chloride in toluene at room temperature. A chelate transition state involving the chiral Lewis acid promoter and the reactants is proposed to account for both regio- and enantioselection.

The electrophilic aromatic substitution represented by Friedel–Crafts reaction is one of the most efficient procedures for formation of carbon–carbon bonds to aromatic rings.[1] Along this route we have been developing, in the

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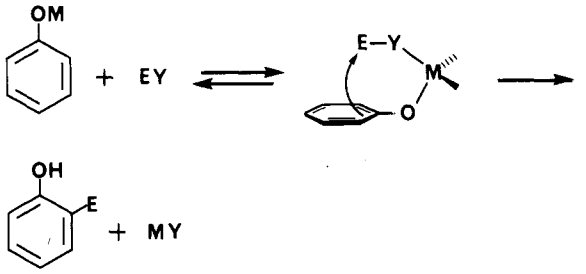
Table I. Effect of the Chiral Moiety L* in 3 on the Enantioselective Synthesis of 4b[a]

entry	chiral promoter	L*	yield,[b] %	$[\alpha]_{589}$, deg[c]	$[\alpha]_{546}$, deg[c]	CD, $10^{-3}[\vartheta]$,[d] deg cm^2 dmol^{-1}	ee,[e] %
1	**3a**	(−)-menthyl	97	−34.5	−42.3	−4.09	48.0
2	**3b**	(+)-neomenthyl	85	+3.5	+4.3	+0.41	6.2
3	**3c**	(−)-borneyl	79	−1.0	−1.2	−0.24	1.7
4	**3d**	(+)-*sec*-butyl	75				0.0
5	**3e**	(−)-8-phenylmenthyl	65	−17.9	−21.8	−1.97	23.8
6	**3f**	(+)-2,2,2-trifluoro-1-(9-anthryl)ethyl	80				0.0

[a] Conditions: phenol **1b**, 10 mmol; alkoxide **3**, 10 mmol; chloral, 10 mmol. At 15 ± 1 °C for 4 h. [b] Based on pure isolated compound. [c] 20 ± 1 °C (*c* 1.5, EtOH). [d] Circular dichroism (CD) of a 2 × 10^{-3} M solution in ethanol at 287 nm. [e] Enantiomeric excess was determined by 200-MHz ^{1}H NMR using Eu(hfc)$_3$.

Scheme I



phenolic domain, a general tactic for the C-ortho regiospecific elaboration of a variety of aromatic molecules, the essence of the reaction lying in the metal ion which, acting as a localized Lewis acid, serves as an activator of the electrophilic reagents as well as a stereosteering group.[2]

As can be seen in Scheme I, chelation around the metal through an oriented molecular complex involving both the phenolic substrate and the electrophile results in complete regiocontrol of the aromatic substitution (ortho substitution), and much evidence has accumulated for several reactions that involve such complexes as intermediates.[2,3]

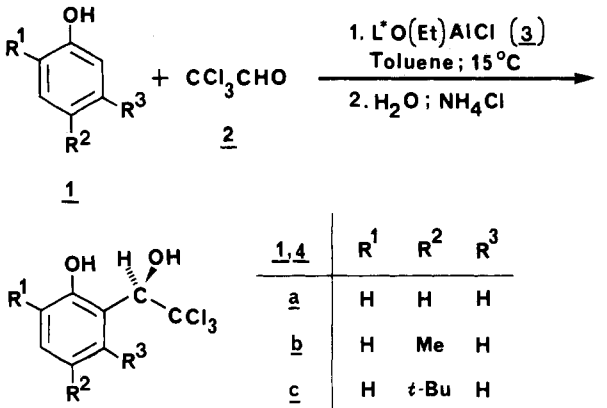
In order for this metal-bound mechanism to substantiate our hypothesis more firmly and even enlarge the synthetic scope of the reaction, we undertook a study aimed at the enantioselection of electrophilic substitution on phenols by using phenolates of metal ions carrying optically active ligand auxiliaries.

As the first work along this line,[4] we describe the enantioselective ortho-hydroxyalkylation of phenols with trichloroacetaldehyde (chloral) mediated by chiral alkoxyaluminum compounds.[5]

Results and Discussion

In our search for possible chirally modified Lewis acids to promote asymmetric electrophilic substitution on phenols, we began by investigating chiral alkoxyaluminum chlorides, easily obtained from commercial diethylaluminum chloride and optically active alcohols. We have studied the reactions between 4-methylphenol (**1a**) and chloral (**2**) assisted by a variety of chiral alkoxides (**3a–f**),

Scheme II



1,4	R^1	R^2	R^3
a	H	H	H
b	H	Me	H
c	H	*t*-Bu	H
d	H	*t*-Oc	H
e	Me	H	H
f	*i*-Pr	H	H
g	*t*-Bu	H	H
h	Me	H	Me
i	Br	H	H
j	H	$-(CH{:}CH)_2-$	

leading to optically active 2-(2,2,2-trichloro-1-hydroxyethyl)-4-methylphenol (**4a**) (Scheme II). The effects of the chiral moiety L* in **3** were examined, and these are summarized in Table I.

The asymmetric inductions obtained ranged from 48% ee at most to zero according to the employed alkoxide, while chemical yields were above 65% in all cases. In contrast to the efficiency of the (−)-menthol catalyst (entry 1), the other employed alkoxides, viz. (+)-neomenthoxy (entry 2), (−)-borneoxy (entry 3), (−)-8-phenylmenthoxy (entry 5), (+)-2,2,2-trifluoro-1-(9-anthryl)ethoxy (entry 6), and (+)-*sec*-butoxy(ethyl)aluminum chloride (entry 4) gave inferior or no enantioselection.

It is noteworthy that the use of the (+)-neomenthol-based promoter **3b** resulted in production of dextrorotatory **4b** with opposite absolute configuration to that of the usual product (−)-**4b**, suggesting that the chiral carbon carrying the hydroxy group determines the product chirality.

Furthermore, comparison of entries 1 and 2 is particularly enlightening on the sensitivity of the reaction to the steric requirements of the chiral auxiliary; the enantiomeric excess drops dramatically from 48% to 6.2% by only changing the hydroxyl position from equatorial to axial.

The hydroxylalkylation reactions were carried out by adding the phenol and then chloral to a preformed solution of the chiral aluminum alkoxide in anhydrous toluene and allowing the resultant mixture to react at 15 °C for 4 h.

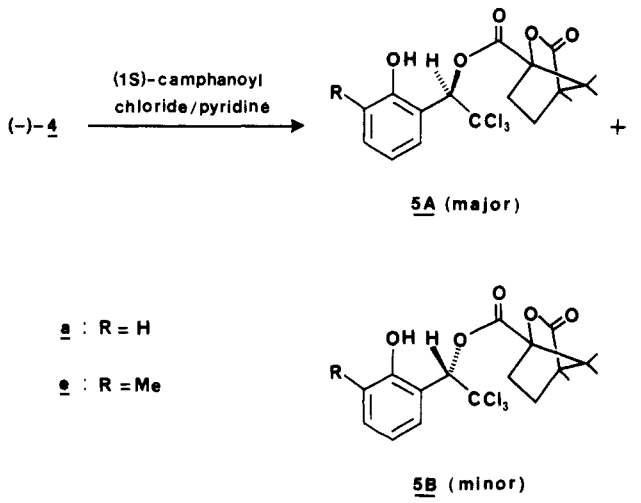
(1) Friedel, C.; Crafts, J. M. *C.R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392, 1450. Olah, G. A. "Friedel-Crafts and Related Reactions"; Interscience Publications: New York, 1963–1965; Vol. I–IV; Glatz, A. M. *Rev. Roum. Chim.* **1974**, *19*, 455.
(2) Casnati, G.; Casiraghi, G.; Pochini, A.; Sartori, G.; Ungaro, R. *Pure Appl. Chem.* **1983**, *55*, 1677.
(3) Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1980**, *110*, 352.
(4) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G. *J. Chem. Soc., Chem. Commun.* **1983**, 1210.
(5) For previous work on the use of chiral aluminum compounds in asymmetric synthesis see for example: Natta, G.; Farina, M.; Peraldo, M.; Bressan, G. *Makromol. Chem.* **1961**, *43*, 68; Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437; Samaddar, A. K.; Konar, S. K.; Nasiguri, D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1449; Giacomelli, G.; Lardicci, L.; Palla, F. *J. Org. Chem.* **1984**, *49*, 310.

Table II. Asymmetric Hydroxyalkylation of Phenols 1 with Chloral 2 Assisted by Menthoxy(ethyl)aluminum Chloride 3a[a]

entry	starting phenol	product[b]	yield,[c] %	$[\alpha]_{589}$, deg[d]	$[\alpha]_{546}$, deg[d]	CD, $10^{-3}[\vartheta]$,[e] deg cm^2 dmol^{-1}	ee,[f] %	abs confign
1	phenol	**4a**	96 (98)	−29.1	−35.9	−2.88	33.7	*R*[h]
2	4-methylphenol	**4b**	97 (98)	−34.5	−42.3	−4.09	48.0	*R*[i]
3	4-*tert*-butylphenol	**4c**	97 (98)	−25.3	−30.8	−3.49	41.3	*R*[i]
4	4-octylphenol[g]	**4d**	94 (98)	−16.8	−20.6	−2.12	33.0	*R*[i]
5	2-methylphenol	**4e**	65 (91)	−19.5	−22.4	+2.81	76.2	*R*[h]
6	2-isopropylphenol	**4f**	78 (90)	−3.9	−3.9	+4.43	54.4	*R*[i]
7	2-*tert*-butylphenol	**4g**	53 (89)	+10.4	+13.5	+5.15	35.8	*R*[i]
8	2,5-dimethylphenol	**4h**	55 (92)	−1.0	+1.3	+15.05	80.1	*j*
9	2-bromophenol	**4i**	51 (85)	−8.6	−10.2	−0.73	7.9	*j*
10	2-naphthol	**4j**	52 (93)	−10.6	−11.8	+1.09	6.0	*j*

[a] Conditions: 15 ± 1 °C, 4 h; 1:3 mole ratio, 1:1. [b] Analytical and spectroscopic data are given in supplementary material. [c] Based on pure isolated compound; values in parentheses refer to yield based on reacted starting phenol. [d] See note *c* for Table I. [e] Circular dichroism (CD) of a 2×10^{-3}M solution in ethanol; λ_{max} **4a**, 280; **4b**, 287; **4c**, 285; **4d**, 288; **4e**, 287; **4f**, 286; **4g** 286; **4h**, 288; **4i** 280; **4j**, 333 nm. [f] See note *e* for Table I. [g] Octyl = 1,1,3,3-tetramethylbutyl. [h] By X-ray analysis on (1*S*)-camphanoyl derivatives (see text). [i] Tentative assignment by ^{1}H NMR correlation to camphanoyl esters of **4a** and **4e** (see text). [j] Not determined.

Scheme III



Cooling from 15 to −52 °C did not improve the induction (41% ee) and heating to 70 °C also had little effect (32.3% ee). As expected, dilution from 0.17 to 0.04 M had no effect whereas an increase in concentration from 0.17 to 0.75 M gave inferior ee (20%). The most promising condition for providing maximum chemical and optical yields of **4a** involved treatment of an equimolar mixture of phenol and chloral with 1.0 molar equivalent of **3c**, whereas use of a lower catalyst-to-phenol ratio caused the enantioselectivity to drop noticeably.

This initial study pointed out that (−)-menthoxy(ethyl)aluminum chloride (**3c**) is a promising stoichiometric promoter for the enantioselective and regiospecific ortho-hydroxyalkylation of phenols with chloral under mild conditions. The next task was to extend this method to various phenols to evaluate the effects of the ring structure on the extent of the asymmetric induction. As the results summarized in Table II indicate, the reaction indeed appears to be ortho-specific and general, the enantioselection degree depending markedly upon the structure of the employed phenols.

Two observations are worthy of specific comment. First, the nature of phenol para substituents seems to have no effect on the extent of enantiodifferentiation nor on the stereochemical behavior of the reaction. Second, the effect of alkyl groups at the ortho position is reflected in enhanced stereoselection, reaching ca. 80% ee when methyl group is involved (entries 5 and 8).

Compounds **4** can be enriched in the major enantiomer by crystallization from suitable benzene–hexane solvent mixtures. Thus, for example, an 8:2 (v:v) benzene–hexane solution of (−)-**4a** (76.2% ee) left racemic crystals whose mother liquors enriched to 94% ee and, similarly, (−)-**4b** (42.5% ee) was enriched up to 81% ee, by using a 6:3 benzene:hexane solvent mixture. As expected, the optically active alcohol auxiliary can be recovered (>80% recovery) after aqueous quenching of the reaction mixture without any appreciable racemization and can be recycled.

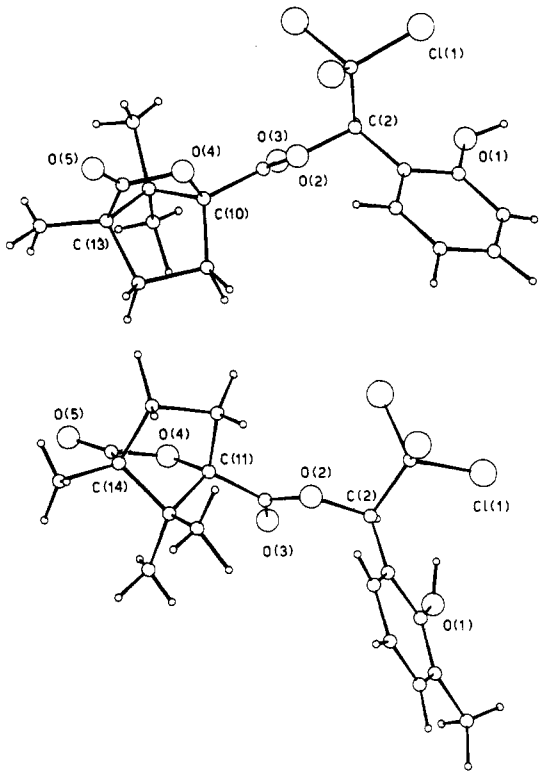


Figure 1. Computer-generated perspective view of the final X-ray models of **5Aa** (above) and **5Ae** (below). Particular note should be taken of the relative stereodisposition of C(2) and C(10) in **5Aa** and C(2) and C(11) in **5Ae**.

Configurational Assignments. In order to establish unambiguously the absolute configuration at the carbinol carbon, (−)-**4a** (ca. 80% ee) and (−)-**4e** (ca. 90% ee) were converted into the corresponding diastereomeric (1*S*)-camphanoyl derivatives **5A** and **5B** as outlined in Scheme III.

Chromatographic separation and subsequent crystallization from a hexane/benzene (8:2) solvent mixture then allowed the major diastereoisomers **5Aa**, and **5Ae** to be easily purified. The complete structural connectivity was

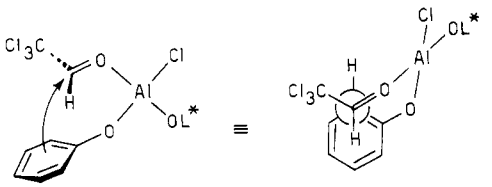


Figure 2. Chelate transition-state model for the aluminum-mediated ortho-specific hydroxyalkylation of phenols (L* denotes the chiral component).

rigorously established to be as in **5Aa** and **5Ae** by X-ray crystal structure analysis (Figure 1). Given the fact that the configuration of the camphanoyl carbon, C(10) in **5Aa** and C(11) in **5Ae**, is *S*, the configuration of the C(2) carbinol carbon is *R* in both the molecules.

The configurational assignments of the other carbinols in Table II were further attempted by 200-MHz ^{1}H NMR chemical shift nonequivalence studies[6] on the (1*S*)-camphanoyl derivatives of **4**. Since the ^{1}H NMR signal due to the methyl group of the camphanoyl moiety at ca. 1.0 ppm in structure **5A** (major diastereoisomer) appears consistently at lower field than that of the corresponding group in structure **5B** (minor diastereoisomer),[7] we can confidently assign *R* absolute configuration to other optically enriched carbinols **4** from this asymmetric reaction.[8]

Conclusions

The results herein nicely confirm our basic mechanistic model for the ortho-specific alkylation on metal phenolates. Indeed, the reaction key lies in the intermediacy of a quite rigid chelate transition state (Figure 2, *re* face attack depicted) in which the metal serves three functions; (a) activation of the chloral carbonyl carbon by coordination; (b) regiocontrol of the process by keeping the reacting sites of the two reactants, i.e. carbonyl carbon of chloral and ortho-carbon of phenol, into proximity; (c) proper orientation of the prochiral carbonyl compound with chirality transfer from the auxiliary ligand.

Although it is premature to fully rationalize the stereochemical results on the basis of proper stereocorrelation models, especially due to the absence of evidence about the stereochemical array of aluminum in the complex, the synthetic results in this study hold promise that a variety of enantioselective and regiospecific reactions on phenols can be reached[9] and that a new avenue in stereocontrolled carbon–carbon bond-forming reactions on aromatics can be opened starting from nonchiral reactants by using chirally modified Lewis acid promoters.

Experimental Section

Melting points were obtained on a electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were determined on a Bruker CXP 200 spectrometer at 200 MHz. Chemical shifts are expressed in ppm relative to Me_4Si as internal standard. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer in KBr pellets unless otherwise stated. UV spectra for solutions in 95% ethanol were measured on a Jasco UVIDEC 505 spectrophotometer. Optical rotations were recorded on a Autopol III polarimeter with 1-dm tube at 589 and 546 nm. CD spectra were measured by using a Jasco J-500A spectropolarimeter with DP-500N data processor in spectrograde 95% ethanol solution. Preparative-layer chromatography was performed with Merck silica gel GF254 using hexane–ethyl acetate mixtures as eluant. Microanalyses were carried out by Istituto di Chimica Farmaceutica dell'Universita' degli Studi di Parma, Italy. The calculations were carried out on the Cyber 76 computer of the Consorzio per la Gestione del Centro di Calcolo Elettronico Interuniversitario dell'Italia Nord-Orientale, CINECA, Casalecchio, Bologna with the financial support of the University of Parma, and the GOULD-SEL 32/77 computer of the Centro di Studio per la Strutturistica Diffrattometrica del CNR.

Enantiomeric excesses were determined by direct method of ^{1}H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$ [hfc = 3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]. This resulted in a downfield shift of the methine singlet of compounds **4** into the signal-free region between δ 5 and 6. The signals for the two enantiomers were shifted by different amounts and became well separated and measurable.

Materials. All chemicals were reagent-grade and were used without further purification except chloral, which was distilled under N_2.

Toluene was dried and stored over molecular sieves. Diethylaluminum chloride (1 M hexane solution) was purchased from Aldrich. The chiral alcohols in this study were (–)-menthol, $[\alpha]^{20}_D$ –49° (*c* 10, ethanol), from Carlo Erba; (+)-neomenthol, $[\alpha]^{20}_D$ +20° (*c* 10, ethanol), from Fluka; (–)-borneol, $[\alpha]^{29}_D$ –19° (*c* 5, ethanol), from Fluka; (*S*)-(+)-butan-2-ol, $[\alpha]^{20}_D$ +15°, from Fluka, (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, $[\alpha]^{25}_D$ –29° (*c* 6, in chloroform), from EGA-Chemie. (–)-8-Phenylmenthol, $[\alpha]^{24}_D$ –23.7° (*c* 2.5, ethanol), was synthesized from (+)-pulegone (from EGA-Chemie) following the reported procedure.[10] (1*S*)-Camphanoyl chloride, $[\alpha]^{20}_D$ –4.4° (*c* 1.1, benzene), mp 62–65 °C, was prepared from (1*S*)-ω-camphanic acid (from Fluka) and $SOCl_2$ according to the literature.[11]

(–)-(*R*)-2-(2,2,2-Trichloro-1-hydroxyethyl)-4-methylphenol (4b). Typical Procedure. To a solution of diethylaluminum chloride (10 ml of 1 M hexane solution) in anhydrous toluene (10 mL) a solution of (–)-menthol (1.56 g, 10 mmol) in toluene (10 mL) was added dropwise at 0 °C during 15 min, while a stream of dry nitrogen was passed. After stirring at room temperature for 1 h, 4-methylphenol (1.08 g, 10 mmol) was added dropwise as a solution in 10 mL of toluene. After an additional 1 h at 15 °C, trichloroacetaldehyde (1.48 g, 10 mmol) in toluene (10 mL) was added dropwise with stirring. The reaction solution was stirred for 4 h at 15 °C and then quenched with an excess of an aqueous ammonium chloride solution and extracted with diethyl ether (3 × 50 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure and **4b** was separated from the residue by chromatography on silica gel using hexane–ethyl acetate (9:1): yield 2.48 g (97%; 98% based on unrecovered phenol).

Compounds **4a–j** listed in Table II were prepared in a similar way. Analytical, IR, UV, and ^{1}H NMR data for all prepared compounds are collected in the Supplementary Material.

(1*R*)-1-(2-Hydroxyphenyl)-2,2,2-trichloroethyl (1*S*)-Camphanate (5Aa). To a solution of (–)-**4a** (0.63 g, 2.6 mmol) in 4.0 mL of dry pyridine (1*S*)-camphanoyl chloride (0.61 g, 2.8 mmol) was added under stirring at 0 °C, and the mixture was allowed to react overnight at room temperature. The mixture was quenched with a 2 N aqueous HCl solution, and the organic layer was successively washed with aqueous $NaHCO_3$ solution and water. After drying (Na_2SO_4) the solvent was removed in vacuo giving a solid residue. The title compound was isolated by chromatography on silica gel by using ca. 9:1 hexane/ethyl acetate and further purified by recrystallization from 1:2 cyclohexane/CH_2Cl_2: 0.50 g (46%), colorless prismatic crystals, mp 196–197 °C; $[\alpha]_{589}$ –27.9° (*c* 0.2, 95% ethanol); IR (KBr) 3323, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$/200 MHz) δ 1.02 (s, 3 H, CH_3), 1.14 (s, 6 H, CH_3), 1.6–2.6 (m, 4 H, CH_2), 5.62 (s, 1 H, CH), 6.83 (d, J = 8 Hz, 1 H, H-3), 6.97 (t, J = 8 Hz, 1 H, H-5), 6.95 (s, 1 H, OH), 7.31 (t, J

(6) Yamaguchi, S. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol 1, Chapter 7.

(7) The chemical shift difference of C_4–CH_3 protons between **5A** and **5B** is 0.03–0.05 ppm in $CDCl_3$.

(8) This study also confirmed, within ± 3%, the enantiomeric composition of **4** in Table II.

(9) For a recent application of this methodology see: Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G.; Soncini, P.; Gasparri Fava, G.; Ferrari Belicchi, M. *Tetrahedron Lett.* **1985**, *26*, 2021.

(10) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

(11) Gerlach, H. *Helv. Chim. Acta* **1968**, *51*, 1587.

= 8 Hz, 1 H, H-4), 7.65 (d, J = 8 Hz, 1 H, H-6).

Anal. Calcd for $C_{18}H_{19}Cl_3O_5$: C, 51.26; H, 4.54; Cl, 25.23. Found: C, 51.33; H, 4.69; Cl, 25.41.

(1*R*)-1-(2-Hydroxy-3-methylphenyl)-2,2,2-trichloroethyl (1*S*)-Camphanate (5Ae). The title compound was prepared following the above procedure. Recrystallization from 8:2 petroleum ether/CH_2Cl_2 afforded 0.79 g (70%) of **5Ae** as colorless needles: mp 152-153 °C; $[\alpha]_{589}$ -12.8 (c 0.3, 95% ethanol); IR (KBr) 3360, 1756 cm^{-1}; ^{1}H NMR ($CDCl_3$/200 MHz) δ 1.01 (s, 3 H, CH_3), 1.13 (s, 6 H, CH_3), 1.6-2.6 (m, 4 H, CH_2), 2.28 (s, 3 H, CH_3), 5.40 (s, 1 H, CH), 6.90 (t, J = 8 Hz, 1 H, H-5), 6.98 (s, 1 H, OH), 7.20 (d, J = 8 Hz, 1 H, H-4), 7.50 (d, J = 8 Hz, 1 H, H-6).

Anal. Calcd for $C_{19}H_{21}Cl_3O_5$: C, 52.37; H, 4.86; Cl, 24.41. Found: C, 52.33; H, 4.97; Cl, 24.62.

Crystal Structure Determination of Compounds 5Aa and 5Ae. Crystal data for **5Aa**: $C_{18}H_{19}Cl_3O_5$, M_r = 421.7, trigonal space group $P3_2$ (from systematic absences and structural analysis), cell dimensions, $a = b$ = 11.635 (2) Å, c = 12.662 (2) Å, V = 1484.5 (4) Å^3, Z = 3, Cu Kα λ = 1.54178 Å, μ = 4.503 mm^{-1}, D_c = 1.415 g cm^{-3}, 3016 reflection measured, 1745 with $I > 2\sigma(I)$ used in refinement of 235 parameters, $(\Delta\rho)_{max}$ = 0.10, $(\Delta\rho)_{min}$ = -0.09, max 2θ = 140°.

Crystal data for **5Ae**: $C_{19}H_{21}Cl_3O_5$, M_r = 435.7, elongated prisms, monoclinic space group $P2_12_12_1$ (from systematic absences and structural analysis), cell dimension, a = 21.491 (3) Å, b = 15.277 (2) Å, c = 6.476 (1) Å, V = 2126.2 (5) Å^3, Z = 4, Cu Kα λ = 1.54178 Å, μ = 4.208 mm^{-1}, D_c = 1.361 g cm^{-3}, 2361 reflections measured, 1431 with $I > 2\sigma(I)$ used in refinement of 244 parameters, $(\Delta\rho)_{max}$ = 0.16, $(\Delta\rho)_{min}$ = -0.13, max 2θ = 140°.

Intensity data were collected at room temperature using Ni-filtered Cu Kα radiation and ω-2θ scan technique. In both types of data collection, the intensity of a standard reflections was measured every 20 reflections to check the stability of the crystal and the electronics. No correction for absorption was applied.

For both compounds the structure was solved by direct methods with Multan[12,13] and refined by full-matrix least-squares cycles using the SHELX-76[14] system of computer programs with initially isotropic and then anisotropic thermal parameters. For both compounds all the hydrogen atoms were located from a difference Fourier synthesis. The final conventional R_f index was 0.0406 for **5Aa** and 0.0562 for **5Ae** (observed reflections only). Scattering factors for Cl, C, H, and O were taken from ref 15, and both the real and imaginary components of anomalous dispersion were included.[15]

The molecular structures and numbering schemes of the two compounds are shown in Figure 1. Bond distances and angles are within normal ranges (see supplementary material). The geometry of camphanic groups well agree with previous X-ray works.[16,17]

An interesting aspect concerning the structure of the compounds **5Aa** and **5Ae** is their different conformation, emphasized from the following torsion angles: O(4)-C(10)-C(9)-O(3) = -147.7(6), O(4)-C(10)-C(9)-O(2) = 36.5 (6)° for **5Aa**; O(4)-C(11)-C(10)-O(3) = -20.4(1.3), O(4)-C(11)-C(10)-O(2) = 160.5 (6)° for **5Ae**. This behavior is probably determined by the steric hindrance of the phenolic o-methyl group in **5Ae**, which, favoring the formation of intramolecular H-bonds, prevents the intermolecular association.

In fact as shown in Figure 3 (in supplementary material) in **5Ae** an intramolecular hydrogen bond between O(1) and Cl(1) (O(1)...Cl(1) = 3.260 (7) Å) is formed determining a monomeric structure, while in **5Aa** an intermolecular H-bond, involving O(1)-H as donor and carbonyl O(5) ($x - 1, y - 1, z$) as acceptor (2.802 (4) Å) forms infinite chains of head-to-tail H-bonds. These chains run along three directions, [100], [010], and [110], at level z, $^2/_3 + z$, $^1/_3 + z$, respectively, due to the presence of the 3-fold screw axis.

The carbonyl groups have short intermolecular contacts: in **5Aa**, O(5) with C(5) ($x + 1, y + 1, z$) at 3.379 (6) Å; in **5Ae**, O(5) with C(9) ($x - {}^1/_2, {}^3/_2 - y, -z$) at 3.304 (12) Å. These weak interactions determine the connection of the chains in **5Aa** and the formation of chains running along the [100] direction in **5Ae**.

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Supplementary Material Available: Bond distances and angles, final coordinates of the atoms and thermal parameters with their estimated standard deviation for the crystal structure determination of compounds **5Aa** and **5Ae**, tables of analytical and spectral data for compounds **4a-j**, and Figure 3, showing molecular packing of **5Aa,e** (11 pages) (the observed and calculated structure factors can be obtained from G.G.F. on request). Ordering information is given on any current masthead page.

(12) Germain, G.; Main, P. T.; Woolfson, M. M. *Acta Crystallogr.* **1971**, *A27*, 368.
(13) Declercq, J. P.; Germain, G.; Main, P. T.; Woolfson, M. M. *Acta Crystallogr.* **1973**, *A29*, 231.
(14) Sheldrick, G. M. "SHELX-76", Program for Crystal Structure Determination, University of Cambridge: England, 1976.
(15) "International Tables for X-ray Crystallography"; Kynoch Press: Birmingham, 1974; Vol. IV, pp 99, 149.
(16) Dwivedi, G. L.; Srivastava, R. C. *Acta Crystallogr.* **1972**, *B28*, 2567.
(17) Gani, D.; Hitchcock, P. B.; Young, D. W. *J. Chem. Soc., Chem. Commun.* **1983**, 898.

The Oxidation of Acetophenones to Arylglyoxals with Aqueous Hydrobromic Acid in Dimethyl Sulfoxide

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The reaction of acetophenones with aqueous hydrobromic acid (HBr) in dimethyl sulfoxide (Me_2SO) leads to the formation of arylglyoxals in good yield. Evidence has been obtained which suggests that this oxidation is mediated by a low concentration of molecular bromine, with the consecutive intermediacy of the α-bromo- and α-hydroxyacetophenones. The reaction of α-bromoacetophenone **2** with Me_2SO alone provides the arylglyoxal **4** with the glyoxylic acid **6** as the major products. The α-hydroxyacetophenone **3** and thiol ester **5** are intermediates leading to **4** and **6**, respectively, and may be isolated as minor products. The presence of water in the medium suppresses the formation of **5** and **6** and results in a cleaner conversion to **4**. Treatment of aryl aldehyde **13** with **14** followed by reaction of the resulting **15** with aqueous HBr in Me_2SO gave arylglyoxal **4** in good yield.

The oxidation of acetophenones to arylglyoxals or their corresponding hydrates (e.g., **1** → **4**; See Scheme I) is usually carried out with selenium dioxide (selenious acid). This method has a wide scope and provides the aryl-

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