87350-83-2; 2-chloroisophthalic acid, 13049-16-6; 1,4-dibromobutane, 110-52-1; 4-iodoaniline, 540-37-4; 1,5-dibromopentane, 111-24-0; morpholinobenzene, 92-53-5; 1,3,5-trinitrobenzene, 99-35-4; 4-iodonitrobenzene, 636-98-6.

Supplementary Material Available: Figure 5a–c with the bonding geometry of **3a** (selected bond distances, bond angles, and dihedral angles), tabulated calculated and observed structure factors, and Table VIII, listing the results of the PPP calculations for 4-(dialkylamino)-4'-nitrobiphenyl and for the (dialkylamino)nitrobiphenyls **3a**, **e**, **g**, **h** and **5a** [excitation energies ($\tilde{\nu}$, λ), oscillatory strengths, and polarizations (μ_x, μ_y, μ_z) are given for the individual electronic transitions] (95 pages). Ordering information is given on any current masthead page.

A Lewis Acid Catalyzed 1,2 Aryl Shift in α-Haloalkyl Aryl Acetals: A Convenient Route to α-Arylalkanoic Acids

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A new method for the synthesis of α-arylalkanoic acids is given, based on Lewis acid promoted rearrangement of acetals of primary and secondary α-haloalkyl aryl ketones (halo = Br, Cl) in hydrocarbon solvents. The reaction is selective, providing the esters of α-arylalkanoic acids in almost quantitative yields. The ability of "soft and borderline" Lewis acids in activating the carbon–halogen bond is compared with that of silver salts. The reaction mechanism is discussed. The present synthesis has been applied to some α-arylpropionic acids well-known as antiinflammatory drugs.

Introduction

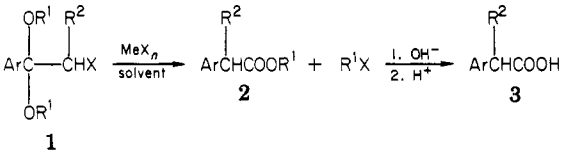
The importance of α-arylalkanoic acids in the pharmaceutical industry is well-known:[1] some of them, like 2-(4-isobutylphenyl)propionic acid and 2-(6-methoxy-2-naphthyl)propionic acid, show potent antiinflammatory and analgesic activities. This class of compounds has thus attracted the attention of many research groups and many papers[2] and several patents[3] have been published. Most of the syntheses of α-arylalkanoic acids start from aromatic acyl derivatives,[1] which can be prepared in high yields by selective electrophilic acylation and converted, by many different approaches, into α-arylalkanoic acids. Recently, we reported a synthesis of α-arylalkanoic acids starting from alkyl aryl ketones via halogenation, acetalization, and silver salts promoted rearrangement.[2a,b] The reaction occurs smoothly in almost quantitative yield. However, the use of at least a stoichiometric amount of a silver salt makes the method less attractive for large-scale preparations and certainly not convenient for industrial manufacturing. This prompted us to seek ways of overcoming the synthetic limits related to the massive use of silver catalysts. The role of silver salts is that of polarizing the carbon–halogen bond of the α-haloalkyl aryl acetal without exerting a strong interaction on the carbon–oxygen bond of the acetal moiety, thus avoiding the conversion of the acetal into the corresponding ketone and/or enol ether. Consequently, the research was aimed at finding other catalysts that could exhibit a behavior similar to that of silver salts.

Results and Discussion

In light of the requirements stated above, attention was directed mainly toward the use of "soft and borderline"[4] Lewis acids.

Zinc, tin, copper, mercury, palladium, cobalt, antimony, bismuth, and iron salts (MeX_n) were found to promote the conversion of alkyl acetals of α-haloalkyl aryl ketones into alkyl esters of α-arylalkanoic acids and into alkyl halides

Scheme I



(Table I, Scheme I). Hydrolysis of the esters **2** gives quantitatively the free acids **3**. The reaction takes place in several different solvents, and among them the ones generally used in Friedel–Craft reactions are preferred.

The reaction temperature (20–200 °C) depends strongly on the catalyst and on the starting acetal. Among the "soft and borderline" Lewis acids, the halides of the abovementioned metals have shown to be the catalysts of choice. In particular, zinc halides are among the most effective. For this reason, most of forthcoming considerations are relative to experiments with zinc halides in toluene. "Hard" Lewis acids are able to catalyze the rearrangement, but they are less attractive since, in some cases, the con-

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Table I.[a] Conversion of Alkyl Acetals of α-Haloalkyl Aryl Ketones 1 into α-Arylalkanoic Acids 3 (Scheme I)

entry	aryl group	R^2	R^1	X	catalyst (mol %)	solvent[b]	rctn temp, °C	rctn time, h	% yield of acids[c]
a	4-methoxyphenyl	H	CH_3	Br	$ZnBr_2$ (10)	Tol	115	1	95
b	4-methylphenyl	H	CH_3	Br	$ZnBr_2$	Tol	115	8	80
c	phenyl	H	CH_3	Br	$ZnBr_2$ (50)	Tol	115	24	81
d	4-chlorophenyl	H	CH_3	Br	$ZnBr_2$ (50)	Tol	115	24	*d*
e	4-methoxyphenyl	CH_3	CH_3	Br	$ZnBr_2$ (10)	Tol	115	0.5	98
f	4-methylphenyl	CH_3	CH_3	Br	$ZnBr_2$	Tol	115	1.5	96
g	phenyl	CH_3	CH_3	Br	$ZnBr_2$	Tol	115	5	80
h	4-chlorophenyl	CH_3	CH_3	Br	$ZnBr_2$	Tol	115	24	78
i	6-methoxy-2-naphthyl	CH_3	CH_3	Br	$ZnBr_2$	Tol	115	0.5	98[e]
j	4-isobutylphenyl	CH_3	CH_3	Cl	$ZnBr_2$	Tol	115	4	94[f]
k	4-methoxyphenyl	CH_3	CH_3	Cl	$ZnCl_2$ (10)	Tol	115	1	97
l	4-methoxyphenyl	CH_3	C_2H_5	Br	$ZnBr_2$ (10)	Tol	115	1	98
m	4-methoxyphenyl	CH_3	CH_3	Br	$SnCl_2$ (30)	Tol	115	1	94[g]
n	4-methoxyphenyl	CH_3	CH_3	Br	$CoCl_2$ (30)	sTCE	115	1	97[g]
o	4-methoxyphenyl	CH_3	CH_3	Br	Hg_2Cl_2 (15)	sDCE	80	20	98[g]
p	4-methoxyphenyl	CH_3	CH_3	Br	$PdCl_2$ (30)	sDCE	80	20	98[g]
q	4-methoxyphenyl	CH_3	CH_3	Br	Cu_2Br_2 (15)	sTCE	135	20	98[g]
r	4-methoxyphenyl	CH_3	CH_3	Br	$CaBr_2$ (30)	sTCE	146	3	25[h]

[a] Unless otherwise noted, the reaction conditions for the rearrangements are as given in the Experimental Section. [b] Tol = toluene; sTCE = 1,1,2,2-tetrachloroethane; sDCE = 1,2-dichloroethane. [c] Yields of α-arylalkanoic acids, based on introduced α-haloalkyl aryl acetals, are referred to crude products (obtained by hydrolysis of the reaction crudes) having a purity higher than 95%. [d] Less than 0.2% if any. [e] The (+) enantiomer (Naproxen) is well-known as a commercial anti-inflammatory drug. [f] The acid (Ibuprofen) is on the market as an antiinflammatory drug. [g] Yields are of methyl esters and are based on the introduced methyl acetal of α-haloalkyl aryl ketones. Yields are calculated on the basis of NMR and GLC analyses carried out on crude reaction products. [h] The reaction was stopped when no acetal could be detected, by NMR analysis, in the reaction mixture.

version of the α-halo acetals into the corresponding α-halo ketones and/or enol ethers competes with the rearrangement. So, useful catalysts are those having a higher affinity toward the halogen than toward the oxygens of the acetal group.

Analysis of the data reported in Table I shows that the reaction is catalytic as far as the metal halide is concerned, since less than a stoichiometric amount of metal halide is required to completely convert the substrates into products. At the end of the reaction, the catalyst is found either unchanged or as a mixture of metal halides (i.e., $ZnBr_2$, $ZnCl_2$, and ZnClBr), if the halogen of the substrate differs from that of the catalyst. In this last case, a mixture of alkyl halides (Scheme I: i.e., R^1Br and R^1Cl) is obtained.

It is worth noting that no halogen scrambling was observed between the substrate and the catalyst: starting from α-bromo acetals, no α-chloro acetals, which are less reactive (see below), were detected during the reaction. This implies that the breaking of the carbon–halogen bond of the acetal is irreversible, and no equilibrium exists between the substrate and the catalyst.

The data reported in Table I, although relative to heterogeneous conditions (generally the catalyst is only slightly soluble in the reaction medium), suggest that the reaction rate is enhanced by the presence of electron-donating substituents on the aromatic ring and decreased by electron-withdrawing groups and that this effect is more pronounced for primary α-halo acetals.

This trend has been confirmed by competitive experiments carried out in the presence of zinc bromide among primary and secondary α-bromo acetals, respectively (Table II, runs 1–4).

The strong polar effect of the substituents on the aryl group indicates that a positive center is developed in the transition state (Scheme II).

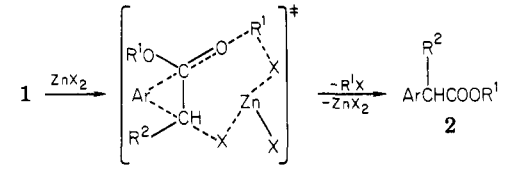
Secondary α-bromo acetals are more reactive than primary ones as shown by runs 5–7 of Table II. This difference in reactivity is more marked when electron-withdrawing groups are present as substituents on the aromatic ring. The difference in reactivity between secondary and primary α-bromo acetals can be related to the energy of

Table II.[a] Competitive Experiments between Methyl Acetals of α-Haloalkyl Aryl Ketones

run	aryl group	R^2	X	rctn time, min	% conversion
1	4-methoxyphenyl	CH_3	Br	6	30
	4-methylphenyl	CH_3	Br		6
2	4-methylphenyl	CH_3	Br	9	30
	4-chlorophenyl	CH_3	Br		5
3	4-methoxyphenyl	H	Br	120	30
	4-methylphenyl	H	Br		2
4	4-methylphenyl	H	Br	300	30
	4-chlorophenyl	H	Br		*b*
5	4-methoxyphenyl	CH_3	Br	4	30
	4-methoxyphenyl	H	Br		6
6	4-methylphenyl	CH_3	Br	18	30
	4-methylphenyl	H	Br		1
7	4-chlorophenyl	CH_3	Br	540	30
	4-chlorophenyl	H	Br		*b*
8	4-methoxyphenyl	CH_3	Br	5	30
	4-methoxyphenyl	CH_3	Cl		4

[a] The reaction conditions are as given in the Experimental Section: the two starting α-halo acetals (equimolar amount of each, 5 mmol), zinc bromide (1 mmol) in toluene (20 mL) at 80 °C. [b] Less than 0.2%, if any.

Scheme II



carbon–bromine bond and to the stabilization of the positive reactive center (Scheme II).

The greater polar effect observed for primary derivatives reflects the reactivity–selectivity principle,[5] the assistance of the aromatic ring becoming more important when the

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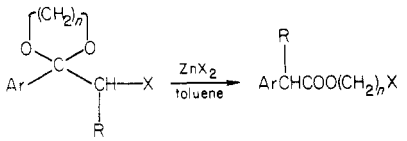
Scheme III



n = 2, 3

reactivity of the carbon–bromine bond decreases.

As far as the nature of the halogen of the α-halo acetal is concerned, the order of reactivity is bromine > chlorine (Table II, run 8). This order of reactivity suggests that the carbon–halogen bond[6] is broken in the rate-determining step. From our findings it is clear that the role of "soft and borderline" Lewis acids in promoting the rearrangement parallels that shown by silver catalysts.[2a,b] A reasonable mechanism for the rearrangement is depicted in Scheme II.

The interaction of the substrate with the catalyst causes a progressive polarization of the carbon–halogen bond with the concomitant shift of the aryl group. The evolution of the transition state toward the products is possibly either a synchronous or a two-step process, through a dioxonium ion.[2b]

In agreement with the first hypothesis, the reaction of cyclic haloacetals with zinc halides in toluene gave ω-haloalkyl esters in almost quantitative yields. No isomeric ester or byproduct coming from an elimination process was found (Scheme III; see Experimental Section).

Conclusions

"Soft and borderline" Lewis acids have been shown to be good alternatives to silver catalysts for the activation of carbon–halogen bonds. The possibility is open for these catalysts to replace silver salts in other reactions where a carbon–halogen bond is broken.

Furthermore, since under the present reaction conditions, no rearrangement is found with α-halo ketones, the method provides an additional and significant example of changing (masking) the normal nature of a functional group in planning a synthetic strategy.[7]

The present method, constituting a very advantageous synthesis of α-arylalkanoic acids, has been applied to the industrial preparation of important α-arylpropionic acids.[3d,e]

Experimental Section

^{1}H NMR spectra were taken at 60 MHz for solutions in deuteriochloroform. The chemical shifts are expressed in ppm and are relative to internal Me_4Si. IR spectra were taken in Nujol mulls. GLC analyses were performed on a Carlo Erba 4200 instrument using a glass column (2 m × 2 mm) containing OV-1 3% on Supelcoport, 80–100 mesh. Analytical TLC were performed on precoated silica gel with a fluorescent indicator. Visualization was accomplished under UV light. Melting points, measured on a Köfler apparatus, and boiling points are not corrected. Elemental analyses were carried out on a Hewlett-Packard instrument (C, ±0.2%; H, ±0.2%). Satisfactory analytical data were obtained for all compounds investigated.

Preparation of Alkyl Acetals of α-Haloalkyl Aryl Ketones. Most of the α-haloalkyl aryl acetals were obtained from appropriate α-haloalkyl aryl ketones by the previously reported methods.[2a] For the others, their preparations are described below.

2-Bromo-1,1-dimethoxy-1-(4-methoxyphenyl)ethane: mp 56–58 °C (methanol) (lit.[2a] mp 56–58 °C); ^{1}H NMR δ 3.20 (s, 6 H), 3.60 (s, 2 H), 3.79 (s, 3 H), 6.70–7.50 (m, 4 H).

2-Bromo-1,1-dimethoxy-1-(4-methylphenyl)ethane: ^{1}H NMR δ 2.36 (s, 3 H), 3.23 (s, 6 H), 3.63 (s, 2 H), 7.16–7.53 (m, 4 H).

2-Bromo-1,1-dimethoxy-1-phenylethane: mp 46–47 °C (methanol) (lit.[8] mp 46–46.9 °C); ^{1}H NMR δ 3.18 (s, 6 H), 3.58 (s, 2 H), 7.30 (m, 5 H).

2-Bromo-1,1-dimethoxy-1-(4-chlorophenyl)ethane: mp 52–53 °C (hexane); ^{1}H NMR δ 3.23 (s, 6 H), 3.60 (s, 2 H), 7.28–7.66 (m, 4 H).

2-Bromo-1,1-diethoxy-1-(4-methoxyphenyl)ethane: mp 55–56 °C (methanol) (lit.[2a] mp 55–56 °C); ^{1}H NMR δ 1.13 (t, 6 H, J = 7 Hz), 3.47 (q, 4 H, J = 7 Hz), 3.57 (s, 2 H), 3.80 (s, 3 H), 6.70–7.50 (m, 4 H).

2-Bromo-1,1-dimethoxy-1-(6-methoxy-2-naphthyl)propane: mp 87–89 °C (methanol) (lit.[2a] mp 87–89 °C); ^{1}H NMR δ 1.53 (d, 3 H, J = 7 Hz), 3.26 (s, 3 H), 3.43 (s, 3 H), 3.90 (s, 3 H), 4.50 (q, 1 H, J = 7 Hz), 7.00–8.00 (m, 6 H).

2-Chloro-1,1-dimethoxy-1-(4-isobutylphenyl)propane: ^{1}H NMR δ 0.90 (d, 6 H, J = 6 Hz), 1.28 (d, 3 H, J = 7 Hz), 1.80 (m, 1 H), 2.46 (d, 2 H, J = 6 Hz), 3.16 (s, 3 H), 3.33 (s, 3 H), 4.33 (q, 1 H, J = 7 Hz), 6.70–7.60 (m, 4 H).

2-Bromo-1,1-dimethoxy-1-(4-methoxyphenyl)propane: ^{1}H NMR δ 1.53 (d, 3 H, J = 7 Hz), 3.16 (s, 3 H), 3.33 (s, 3 H), 3.80 (s, 3 H), 4.50 (q, 1 H, J = 7 Hz), 6.80–7.56 (m, 4 H).

2-Chloro-1,1-dimethoxy-1-(4-methoxyphenyl)propane: ^{1}H NMR δ 1.33 (d, 3 H, J = 7 Hz), 3.23 (s, 3 H), 3.36 (s, 3 H), 3.83 (s, 3 H), 4.41 (q, 1 H, J = 7 Hz), 6.86–7.60 (m, 4 H).

2-Bromo-1,1-dimethoxy-1-(4-methylphenyl)propane: ^{1}H NMR δ 1.53 (d, 3 H, J = 7 Hz), 2.33 (s, 3 H), 3.20 (s, 3 H), 3.36 (s, 3 H), 4.50 (q, 1 H, J = 7 Hz), 7.12–7.56 (m, 4 H).

Preparation of 2-Bromo-1,1-dimethoxy-1-phenylpropane. A mixture of 2-bromo-1-phenylpropan-1-one (21.3 g, 0.1 mol), trimethyl orthoformate (30 mL, 0.3 mol), methanesulfonic acid (0.98 g, 0.01 mol), and methanol (100 mL) was heated at reflux for 24 h. It was then poured, with vigorous stirring, into a saturated aqueous sodium carbonate solution and extracted with diethyl ether (3 × 80 mL). The combined organic extracts were washed with 2% aqueous sodium hydrogen carbonate and dried (sodium sulfate). Evaporation of the solvent under reduced pressure gave a mixture of α-bromo ketone and α-bromo acetal. The residue, trimethyl orthoformate (30 mL, 0.3 mol), methanesulfonic acid (0.98 g, 0.01 mol), and methanol (100 mL), was heated at reflux for 24 h. The reaction mixture was worked up as described above. (If the conversion of the α-halo ketone into the corresponding α-halo acetal was not complete, the reaction was carried out again.) 2-Bromo-1,1-dimethoxy-1-phenylpropane: ^{1}H NMR δ 1.56 (d, 3 H, J = 7 Hz), 3.23 (s, 3 H), 3.43 (s, 3 H), 4.56 (q, 1 H, J = 7 Hz), 7.53 (m, 5 H).

In an analogous way, **2-bromo-1,1-dimethoxy-1-(4-chlorophenyl)propane** was prepared: ^{1}H NMR δ 1.53 (d, 3 H, J = 7 Hz), 3.23 (s, 3 H), 3.36 (s, 3 H), 7.43–7.76 (m, 4 H).

Preparation of 2-(Bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane. A mixture of 2-bromo-1-(4-methoxyphenyl)ethanone (4.60 g, 20 mmol), 1,3-propanediol (15 mL), trimethyl orthoformate (5 mL), and methanesulfonic acid (0.02 g, 0.2 mmol) was heated at 35 °C for 2 h. The reaction mixture was added dropwise to a well-stirred saturated sodium carbonate solution, dried on sodium sulfate, and filtered. The solvent was evaporated under reduced pressure to give crude 2-(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (5.74 g). Crystallization from methanol gave the analytically pure product (5 g, 17.4 mmol; yield 87%): mp 80–81 °C; ^{1}H NMR δ 1.26 (m, 2 H), 3.34 (s, 2 H), 3.86 (s, 3 H), 3.88 (m, 4 H), 6.86–7.47 (m, 4 H).

Preparation of 2-(Bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxolane. A mixture of 2-bromo-1-(4-methoxyphenyl)-ethanone (4.60 g, 20 mmol), ethylene glycol (15 mL), triethyl orthoformate (5 mL), and methanesulfonic acid (0.02 g, 0.2 mmol) was heated at 35 °C for 2 h. The reaction mixture was worked up as described above. Crystallization from methanol gave analytically pure 2-(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxolane (4.40 g, 16 mmol, yield 80%): mp 78–79 °C (lit.[9] mp 71–72

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°C); ^{1}H NMR δ 3.67 (s, 2 H), 3.83 (s, 3 H), 3.90 (m, 2 H), 4.13 (m, 2 H), 6.80–7.53 (m, 4 H).

Preparation of α-Arylalkanoic Acids from α-Haloalkyl Aryl Ketals. General Procedure. A mixture of anhydrous catalyst (amount given in Table I), α-haloalkyl aryl acetal (10 mmol), and the solvent (10 mL) was heated at reflux, under nitrogen, and kept under these conditions for the time given in Table I.

After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the crude ester, which was dissolved in a solution of 30% aqueous sodium hydroxide (15 mL) in methanol (50 mL) and heated at reflux, under stirring, for 4 h. The reaction mixture was poured into water and extracted with diethyl ether (2 × 50 mL). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (3 × 80 mL). The organic extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the crude α-arylalkanoic acid. Purity, determined by GLC on the corresponding methyl ester (obtained by treatment with diazomethane), was found to be higher than 95%. The results are given in Table I.

Physical data of α-arylalkanoic acids of Table I: 2-(4-methoxyphenyl)acetic acid, mp 87–88 °C (water) (lit.[2a] mp 83–84 °C); 2-(4-methylphenyl)acetic acid, mp 94 °C (benzene) (lit.[2a] mp 91 °C); phenylacetic acid, mp 76–77 °C (hexane) (lit.[2a] mp 77 °C); 2-(4-methoxyphenyl)propionic acid, mp 57 °C (hexane) (lit.[2a] mp 56–57 °C); 2-(4-methylphenyl)propionic acid, mp 38–39 °C (hexane) (lit.[2h] mp 36–37 °C); 2-phenylpropionic acid, mp 16 °C (hexane) (lit.[2a] mp 16 °C); 2-(4-chlorophenyl)propionic acid, mp 57 °C (hexane) (lit.[10] mp 57–58 °C); 2-(6-methoxy-2-naphthyl)-propionic acid, mp 154–155 °C (acetone–hexane) (lit.[2a] mp 150–151 °C); 2-(4-isobutylphenyl)propionic acid, mp 76 °C (hexane) (lit.[2a] mp 75–77 °C).

Reaction between 2-(Bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane and Zinc Bromide. A mixture of anhydrous zinc bromide (0.67 g, 3 mmol), 2-(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (2.87 g, 10 mmol), and toluene (10 mL) was heated at reflux, under nitrogen, for 3 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with water and dried (Na_2SO_4).

Evaporation of the solvent under reduced pressure gave the 3-bromopropyl ester of 2-(4-methoxyphenyl)acetic acid (2.81 g, 9.8 mmol; yield 98%) as an oil: ^{1}H NMR δ 2.10 (m, 2 H, J = 6 Hz), 3.36 (t, 2 H, J = 6 Hz), 3.51 (s, 2 H), 3.73 (s, 3 H), 4.17 (t, 2 H, J = 6 Hz), 6.75–7.33 (m, 4 H); IR (stretching C=O) 1735 cm^{-1}.

Reaction of 2-(Bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxolane with Zinc Bromide. Anhydrous zinc bromide (0.67 g, 3 mmol) and 2-(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxolane (2.73 g, 10 mmol) were reacted under the experimental conditions described above. The 2-bromoethyl ester of 2-(4-methoxyphenyl)acetic acid (2.67 g, 9.8 mmol; yield 98%) was obtained as an oil: ^{1}H NMR δ 3.47 (t, 2 H, J = 6 Hz), 3.60 (s, 2 H), 3.73 (s, 3 H), 4.37 (t, 2 H, J = 6 Hz), 6.80–7.30 (m, 4 H); IR (stretching C=O) 1735 cm^{-1}.

Reaction of 2-Bromo-1,1-dimethoxy-1-(4-methoxyphenyl)propane with a Stoichiometric Amount of Zinc Chloride: Determination of the Ratio between Methyl Chloride and Methyl Bromide. A mixture of anhydrous zinc chloride (1.36 g, 10 mmol), 2-bromo-1,1-dimethoxy-1-(4-methoxyphenyl)propane (2.88 g, 10 mmol), and toluene (10 mL) was stirred at reflux for 1 h. The gas, evolved during the reaction, was collected into cold (0 °C) chloroform. NMR analysis carried out on the chloroform solution revealed the presence of methyl bromide and methyl chloride in a 2:1 ratio. In a parallel experiment, aliquots (0.5 mL) were removed at suitable intervals and diluted with toluene. 3-Phenyl-1-bromopropane was added as internal standard. The solutions were analyzed by GLC: 2-chloro-1,1-dimethoxy-1-(4-methoxyphenyl)propane was not detected (the GLC method shows the presence of less than 0.50% of α-chloro acetal in a mixture of α-chloro and α-bromo acetals).

Competitive Experiments (Table II). A mixture of anhydrous zinc bromide (1 mmol) and of two α-halo acetals (10 mmol, molar ratio 1:1) in toluene (20 mL) was stirred, under nitrogen, at 80 °C. Aliquots (0.5 mL) were removed at suitable times and diluted with toluene (4 mL). 3-Phenyl-1-bromopropane was added as internal standard. The amount of the two methyl esters and of the unreacted α-halo acetals were determined by GLC. The results are reported in Table II.

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Registry No. **1a**, 80336-70-5; **1b**, 84508-58-7; **1c**, 33604-54-5; **1d**, 84508-61-2; **1e**, 84508-65-6; **1f**, 87338-02-1; **1g**, 87338-03-2; **1h**, 87338-04-3; **1i**, 80336-55-6; **1j**, 84508-64-5; **1k**, 87338-05-4; **1l**, 87350-67-2; **3a**, 104-01-8; **3b**, 622-47-9; **3c**, 103-82-2; **3d**, 1878-66-6; **3e**, 942-54-1; **3f**, 938-94-3; **3g**, 492-37-5; **3h**, 938-95-4; **3i**, 23981-80-8; **3j**, 15687-27-1; $ZnBr_2$, 7699-45-8; $ZnCl_2$, 7646-85-7; $SnCl_2$, 7772-99-8; $CoCl_2$, 7646-79-9; HgCl, 7546-30-7; $PdCl_2$, 7647-10-1; CuBr, 7787-70-4; $CaBr_2$, 7789-41-5; 2-bromo-1-phenyl-1-propanone, 2114-00-3; 2-(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane, 80336-74-9; 3-bromopropyl 2-(4-methoxyphenyl)acetate, 80336-90-9; 2-(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxolane, 4366-28-3; 2-bromoethyl (4-methoxyphenyl)acetate, 80336-89-6; 2-bromo-1-(4-methoxyphenyl)ethanone, 2632-13-5.

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Synthesis of Carbon and Phosphorus Esters of α-Fluoro Alcohols

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Carbon and phosphorus esters of α-fluoro alcohols are promising functions for the construction of suicide substrates for esterases, phosphatases, and other enzymes. A route for the synthesis of substrates incorporating these hitherto inaccessible functionalities is reported here. The acetate, diethyl phosphate, and diphenyl phosphate esters of 1,1-difluoro alcohols have been prepared in low to moderate yields from 1,1-difluoro-1-alken-3-ols by allylic transposition of the esterified hydroxyl group. A general synthetic route to the required 1,1-difluoro-1-alken-3-ols, involving ketone trimethylsilylcyanation, reduction to trimethylsilylated α-hydroxy aldehydes, and difluoromethylene Wittig reaction, has been developed. The difluorinated olefins can be reduced to the monofluoro derivatives with $LiAlH_4$. The phosphate but not the carbon esters can be prepared from the *mono*fluorovinyl alcohols by the allylic transposition approach.

The hydrolysis of carboxylic and phosphate esters, a universal biological process, is catalyzed by a broad variety of distinct enzymes that differ in mechanism, substrate specificity, and cellular location. The diversity of hydro-

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