Notes

Stereochemistry of Room-Temperature Fluorination of Alkenes with Cesium Fluoroxysulfate

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Introduction of fluorine into organic molecules is important from the chemical and the pharmaceutical point of view, but the problem differs considerably from those concerning other halogen atoms.[1] There is only a limited number of reagents known that are able to introduce fluorine into organic molecules under mild conditions at room temperature. Of these, l.c. xenon difluoride is the easiest handled reagent known,[2-4] but its high price is a great disadvantage. Cesium fluoroxysulfate has also been found to react at room temperature with various organic molecules.[5-12]

We now report our investigations on the stereochemistry of fluorine introduction into various substituted alkenes with $CsSO_4F$ at room temperature.

Results and Discussion

Valuable information about the reactivity of a new fluorinating reagent can be obtained by studying its reactions with organic molecules that have already been investigated with other reagents. Many fluorinating agents have been tested on the 1,1-diphenylethene and (*E*)- and (*Z*)-stilbene, and all the reagents gave different products.[13-17]

In a typical experiment carried out in a polyethylene vessel, 1 mmol of alkene was dissolved in 4 mL of methylene chloride, then 1.5 mmol of hydrogen fluoride was introduced, and finally 1.3 mmol of cesium fluoroxysulfate was added. After the workup procedure, the crude reaction mixtures were analyzed by ^{19}F NMR spectroscopy and the products isolated by gas or thin-layer chromatography. Reactions in methanol were carried out in a similar way, except for the introduction of hydrogen fluoride. Reactions of (*E*)- and (*Z*)-stilbene with $CsSO_4F$, in the presence of hydrogen fluoride, gave in both cases two vicinal difluorides (**3a**, **4a**); the structures were determined on the basis of the spectroscopic data and their comparison with the independently synthesized compounds[13] (Scheme I). (*E*)-Stilbene gave predominantly syn adduct, while nonstereospecific addition was observed in the case of (*Z*)-stilbene. Room-temperature reactions of **1** or **2** in methanol gave in each case two vicinal methoxy fluorides **3b** and **4b**; the products were separated by preparative TLC and their structures determined on the basis of the spectroscopic data, which were in agreement with the literature.[14] The syn addition predominated again in the case of alkene **1**, and the nonstereospecific course was established for alkene **2**. In Table I, the effect of the reagent and reaction conditions on the structures of the products formed and the stereochemistry of fluorine introduction into (*E*)- and (*Z*)-stilbene are presented. It is evident that the syn/anti stereoselectivity strongly depends

Scheme I

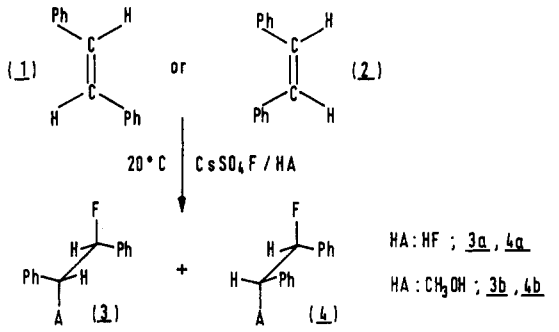
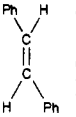
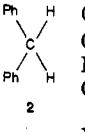


Table I. Stereochemistry of Fluorine Induction into (*E*)- and (*Z*)-Stilbene

alkene	reagent	solvent/ temp, °C	A	syn:anti adduct: 4:3	ref
 1	$CsSO_4F$	CH_2Cl_2/ HF/20	F	65:35	
	$CsSO_4F$	CH_3OH/20	OCH_3	70:30	
	XeF_2	CH_2Cl_2/ HF/20	F	38:68	13
	CF_3OF	CH_3OH/ −78	OCH_3	30:15	14
	CH_3COOF	$CFCl_3$/−78	$OCOCH_3$	54:7	15
	CF_3COOF	$CFCl_3$/−78	$OCOCF_3$	100:0	16

alkene	reagent	solvent/ temp, °C	A	syn:anti adduct: 3:4	ref
 2	CF_3COOF	$CFCl_3$/−78	$OCOCF_3$	100:0	16
	CH_3COOF	$CFCl_3$/−78	$OCOCH_3$	55:11	15
	F_2	$CFCl_3$/−78	F	84:16	17
	CF_3OF	CH_3OH/ −78	OCH_3	46:22	14
	XeF_2	CH_2Cl_2/ HF/25	F	53:47	13
	$CsSO_4F$	CH_3OH/20	OCH_3	53:47	
	$CsSO_4F$	CH_2Cl_2/ HF/20	F	51:49	

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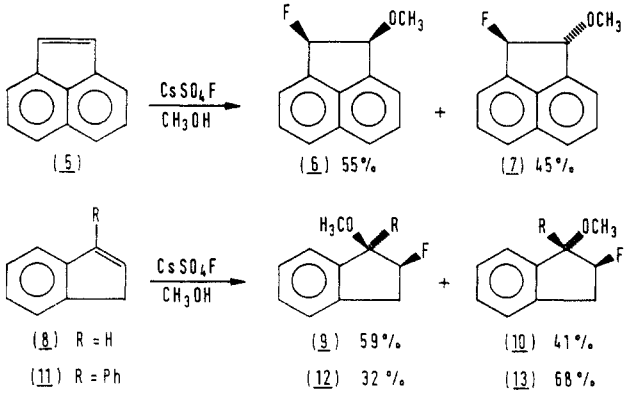
Scheme II



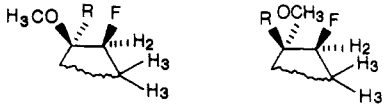
on the structure of the fluorination agent. Trifluoroacetyl hypofluorite[16] is the most syn stereoselective, while in the fluorination with xenon difluoride predominant anti addition was observed.[13] The syn to anti ratio of vicinal methoxy fluorides, observed by the reaction with $CsSO_4F$, is very similar to that observed in the reaction with fluoroxytrifluoromethane,[14] but in this case the methoxy fluorides were also accompanied by two vicinal difluorides and two vicinal trifluoromethoxy fluorides.

We extended our room-temperature fluorination to cycloalkenes, so as to eliminate the complexity that exists in the acyclic systems in which there is the possibility of rotation about the newly formed carbon–carbon single bond in the carbonium ion or radical intermediate, depending on its lifetime and on the energy barrier for the rotation.

Fluorination of acenaphthylene (**5**; Scheme II) at −78 °C with fluorine proceeded mainly as syn addition[18] (syn:anti = 35:11), vicinal difluorides were accompanied also by 1,1,2-trifluoroacenaphthene. On the other hand, room-temperature fluorination with xenon difluoride proceeded preferentially anti (anti:syn = 84:16).[19] Room-temperature fluorination of acenaphthylene with $CsSO_4F$ in methanol gave the crude reaction mixture that showed in its ^{19}F NMR two doublet of doublet signals in the relative ratio 55:45. The products were isolated by TLC, and on the basis of spectroscopic data we found that the syn selectivity was diminished.

The study of halogenation of indene enables, besides the exclusion of the possibility of the rotation about the newly formed C–C single bond, also the determination of the regioselectivity of the reaction. Room-temperature fluorination of indene (**8**) with xenon difluoride proceeded predominantly anti (70:30),[13] while low-temperature reaction with fluorine proceeded syn.[18,13] The reaction of indene with $CsSO_4F$ in methanol at room temperature resulted in the formation of two products, with the syn addition slightly predominating (59:41), while the nucleophile entering followed Markovnikov's type of regioselectivity. Vicinal methoxy fluorides were also observed recently by the fluorination of indene with xenon difluoride in methanol and in the presence of hydrogen fluoride, and nonstereospecific addition was established (syn:anti = 52:46, the presence of 2% of vicinal difluorides was also found).[20] ^1H NMR data of vicinal methoxy fluorides **9** and **10** are in excellent agreement with the published,[20] while ^{19}F NMR and mass spectral data were not given. In order to study the effect of an additional stabilization of the intermediate, formed during the course of the fluorine introduction to the alkene with $CsSO_4F$, we further studied the reaction with 1-phenylind-1-ene (**11**; Scheme II). The reaction resulted in a crude reaction mixture showing in its ^{19}F NMR two signals with a very similar chemical shift, as those observed for *cis*- and *trans*-1-methoxy-2-fluoroindane (**9**, **10**), but their ratio differed strongly from that observed by the fluorination of indene. The products were isolated by preparative TLC; the NMR data of various vicinal methoxy fluorides of cycloalkanes (**6**, **9**, **12**, **7**, **10**, **13**) are presented in Table II; and, on the basis of the spectroscopic data, it is evident that anti addition took place predominantly by the fluorination of 1-phenylind-1-ene with $CsSO_4F$.

Table II. NMR Data for Vicinal Methoxy Fluorides



	6	9	12	7	10	13
δ(F)	−186.7	−203.8	−200.8	−173.2	−183.5	−182.2
δ(H_2)	6.1	5.31	5.0	6.20	5.22	5.0
$^3J_{FR}$[a]	12	14		21	18	
$^3J_{RH_2}$	5	5		<1	3	
$^3J_{FH_3}$		27	15		24	36
		24	6		18	25.5
$^3J_{H_2H_3}$		5	7		5	<1
		5	7		3	4

[a] In hertz.

Cesium fluoroxysulfate represents the unique example of a potential anionic electrophile possessing two potential electrophilic centers, which become more pronounced after the formation of a hydrogen bond between hydrogen fluoride or methanol, while the nature of the reaction with organic molecules depends on their structure. Direct oxidation was mainly observed with sulfides and triphenylphosphine,[11] while in all other cases mainly fluoro-substituted products were established.[7-12] Reaction of alkene with $CsSO_4F$ can result in the formation of an ion radical, a β-fluoro carbonium ion or a β-fluoro-substituted radical. The entering of the nucleophile according to Markovnikov's type of regioselectivity suggests that the main intermediate involved in the reactions in the presence of hydrogen fluoride or methanol is of a carbonium ion nature.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 727 B spectrometer and ^1H and ^{19}F NMR spectra by a Jeol JNM-PS 100, with Me_4Si or CCl_3F as internal references. Mass spectra and high-resolution measurements were taken on a CEC-21-110 spectrometer. Gas–liquid partition chromatography was carried out on Varian Aerograph Models 2700 and 3700 and TLC on Merck-PSC-Fertigplatten silica gel F-254.

Fluorination of (*E*)- and (*Z*)-Stilbene in the Presence of Hydrogen Fluoride. A 1-mmol sample of alkene (**1**, **2**) was dissolved in 4 mL of methylene chloride, 1–1.5 mmol of hydrogen fluoride was introduced, and under stirring 1.3 mmol of $CsSO_4F$ was added. The reaction mixture was slightly exothermic; the reaction mixture was then stirred at room temperature for 1 h. After the usual workup procedure the reaction mixtures were analyzed by ^{19}F NMR and GLC. The pure products were isolated according to the literature,[13] and the spectroscopic data were in agreement with the data of the independently synthesized compounds.[13]

Fluorination of Alkenes in Methanol. A 1-mmol sample of alkene (**1**, **2**, **5**, **8**, **11**) was dissolved in 2 mL (for **1**, **2**, **8**, and **11**) or in 4 mL (for **5**) of dry methanol, and under stirring in a

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nitrogen atmosphere at room temperature, 1.3 mmol of $CsSO_4F$ was slowly added over a peroid of 5 min. The reaction mixture was then stirred at room temperature for an additional 1 h; the reaction was slightly exothermic. Methylene chloride (20 mL) was added, the insoluble precipitate filtered off, the filtrate washed with water, the organic layer dried over anhydrous Na_2SO_4, and the solvent evaporated in vacuo. The crude reaction mixture was analyzed by ^{19}F NMR and GLC. The product distributions stated in Table I and Scheme II represent the average of at least three experiments. Pure products were isolated by gas or thin-layer chromatography.

Reaction with (*E*)- and (*Z*)-Stilbene (1, 2). The following products were isolated by preparative TLC (SiO_2, petroleum ether:CH_2Cl_2 = 9:1). ***d,l-erythro*-1-Fluoro-2-methoxy-1,2-diphenylethane (3b)**: 19.5%; mp 51–52 °C (lit.[14] mp 52–54 °C); NMR $\delta(F) = -186$ (dd, $^2J_{FH_1} = 49.5$ Hz, $^3J_{FH_2} = 15$ Hz), $\delta(H_1) = 5.5$ (dd, $^3J_{H_1H_2} = 5.5$ Hz, 1 H), $\delta(H_2)$ 4.38 (dd, 1 H), $\delta(OCH_3) = 3.25$ (s, 3 H), $\delta(H) = 7.25$ (m, 10 H); mass spectrum, *m/e* 230 (M^+, 0.5%), 210 (0.5), 122 (11), 121 (100), 109 (5), 105 (5), 91 (6), 77 (30), 51 (3). ***d,l-threo*-1-Fluoro-2-methoxy-1,2-diphenylethane (4b)**: 46.5%; oily; NMR $\delta(F) = -181.5$ (dd, $^2J_{FH_1} = 49.5$ Hz, $^3J_{FH_2} = 13$ Hz), $\delta(H_1) = 5.4$ (dd, $^3J_{H_1H_2} = 8$ Hz, 1 H), $\delta(H_2) = 4.45$ (dd, 1 H), $\delta(OCH_3) = 3.35$ (s, 3 H), $\delta(H) = 7.2$ (m, 10 H); mass spectrum, *m/e* 230 (M^+, 0.5%), 210 (0.5), 122 (11), 121 (100), 109 (5), 105 (10), 91 (5), 77 (20), 51 (3).

Reaction with Acenaphthylene (5). The following products were isolated by preparative TLC (SiO_2, petroleum ether:$CHCl_3$ = 1:1). ***cis*-1-Fluoro-2-methoxyacenaphthene (6)**: 44.5%; mp 39–39.5 °C; NMR $\delta(F) = -186.7$ (dd, $^2J_{FH_1} = 54$ Hz, $^3J_{FH_2} = 12$ Hz), $\delta(H_1) = 6.1$ (dd, $^3J_{H_1H_2} = 5$ Hz, 1 H), $\delta(H_2) = 5.1$ (dd, 1 H), $\delta(OCH_3) = 3.6$ (s, 3 H), $\delta(H) = 7.4$–7.8 (m, 6 H); mass spectrum $C_{13}H_{11}OF$, calcd *m/e* 202.0794, found *m/e* 202.0799, *m/e* 203 (M^+ + 1, 14%), 202 (M^+, 100), 201 (14), 188 (10), 187 (68), 186 (12), 172 (14), 171 (70), 170 (31), 159 (52), 158 (20), 157 (21), 139 (15), 133 (20). ***trans*-1-Fluoro-2-methoxyacenaphthene (7)**: 42%; oily; NMR $\delta(F) = -173.2$ (dd, $^2J_{FH_1} = 56$ Hz, $^3J_{FH_2} = 21$ Hz), $\delta(H_1) = 6.2$ (d, 1 H), $\delta(H_2) = 5.25$ (d, 1 H), $\delta(OCH_3) = 3.55$ (s, 3 H), $\delta(H) = 7.4$–7.8 (m, 6 H); mass spectrum for $C_{13}H_{11}OF$, calcd *m/e* 202.0794, found *m/e* 202.0790, *m/e* 203 (M^+ + 1, 14 %), 202 (M^+, 100), 201 (10), 188 (9), 187 (65), 186 (12), 172 (11), 171 (60), 170 (30), 159 (40), 158 (7), 157 (12), 139 (9), 133 (16).

Reaction with Indene (8). The following products were separated by preparative TLC (SiO_2, petroleum ether:$CHCl_3$ = 1:1). ***cis*-1-Methoxy-2-fluoroindane (9)**: 42%; mp 37–37.5 °C; NMR $\delta(F) = -203$ (dddd, $^2J_{FH_2} = 54$ Hz, $^3J_{FH_3} = 27$ Hz, 24 Hz, $^3J_{FH_1} = 14$ Hz), $\delta(H_1) = 4.6$ (dd, $^3J_{H_1H_2} = 5$ Hz, 1 H), $\delta(H_2) = 5.4$ (dddd, $^3J_{H_2H_3} = 5$ Hz, 5 Hz, 1 H), $\delta(H_3) = 3.25$ (m, 2 H), $\delta(OCH_3) = 3.57$ (s, 3 H), $\delta(H) = 7.25$ (m, 4 H); mass spectrum for $C_{10}H_{11}OF$, calcd *m/e* 166.0794, found *m/e* 166.0795, *m/e* 167 (M^+ + 1, 10 %), 166 (M^+, 80), 165 (54), 136 (12), 135 (10), 134 (22), 133 (32), 131 (31), 115 (42), 103 (38). ***trans*-1-Methoxy-2-fluoroindane (10)**: 39%; oily NMR $\delta(F) = -183.5$ (dddd, $^2J_{FH_2} = 54$ Hz, $^3J_{FH_3} = 24$ Hz, 18 Hz, $^3J_{FH_1} = 18$ Hz), $\delta(H_1) = 4.8$ (dd, $^3J_{H_1H_2} = 3$ Hz, 1 H), $\delta(H_2) = 5.22$ (dddd, $^3J_{H_2H_3} = 5$ Hz, 3 Hz, 1 H), $\delta(H^3) = 3.12$ (m, 2 H), $\delta(OCH_3) = 3.54$ (s, 3 H), $\delta(H) = 7.2$ (m, 4 H); mass spectrum for $C_{10}H_{11}OF$, calcd *m/e* 166.0794, found *m/e* 166.0790, *m/e* 167 (M^+ + 1, 8%), 166 (M^+, 72), 165 (42), 136 (10), 135 (100), 134 (18), 133 (32), 131 (30), 115 (45), 103 (45).

Reaction with 1-Phenylind-1-ene (11). The following products were isolated by preparative TLC (SiO_2, petroleum ether:$CHCl_3$ = 1:1). ***r*-1-Phenyl-1-methoxy-*t*-2-fluoroindane (12)**: 25%; oily; NMR $\delta(F) = -200.8$ (ddd, $^2J_{FH_2} = 54$ Hz, $^3J_{FH_3} = 15$ Hz, 6 Hz), $\delta(H_2) = 5.0$ (ddd, $^3J_{H_2H_3} = 7$ Hz, 1 H), $\delta(H_3) = 3.2$ (m, 2 H), $\delta(OCH_3) = 3.18$ (s, 3 H), $\delta(H) = 7.3$ (m, 9 H); mass spectrum for $C_{16}H_{15}OF$, calcd *m/e* 242.1107, found *m/e* 242.1109, *m/e* 243 (M^+ + 1, 12%), 242 (M^+, 72), 212 (20), 211 (100), 210 (46), 209 (32), 207 (21), 192 (9), 191 (35), 189 (15), 183 (11), 179 (22), 178 (31), 165 (61), 133 (32), 105 (10), 77 (23). ***r*-1-Phenyl-1-methoxy-*c*-2-fluoroindane (13)**: 51.6%; mp 102–103 °C; NMR $\delta(F) = -182.2$ (ddd, $^2J_{FH_2} = 54$ Hz, $^3J_{FH_3} = 36$ Hz, 25.5 Hz), $\delta(H_2) = 5.0$ (dd, $^3J_{H_2H_3} = 4$ Hz, 1 H), $\delta(H_3) = 3.3$ (m, 2 H), $\delta(OCH_3) = 3.0$ (s, 3 H), $\delta(H) = 7.3$ (m, 9 H); mass spectrum for $C_{16}H_{15}OF$, calcd *m/e* 242.1107, found *m/e* 242.1102, *m/e* 243 (M^+ + 1, 10 %), 242 (M^+, 60), 212 (16), 211 (100), 210 (25), 209 (21), 207 (16), 192 (7), 191 (27), 189 (11), 179 (17), 178 (25), 165 (48), 133 (26), 105 (8), 77 (18).

Registry No. 1, 103-30-0; 2, 645-49-8; 3a, 14090-31-4; (±)-3b, 52795-54-7; (±)-4a, 52855-20-6; (±)-4b, 52776-26-8; 5, 208-96-8; (±)-6, 106268-81-9; (±)-7, 106295-73-2; 8, 95-13-6; (±)-9, 106268-82-0; (±)-10, 106268-83-1; 11, 1961-97-3; (±)-12, 106268-84-2; (±)-13, 106268-85-3; HF, 7664-39-3; $CsSO_4F$, 70806-67-6.

HZSM-5-Catalyzed Dihydroxybenzene Equilibration†

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The equilibrations of disubstituted benzenes are important reactions for both practical and theoretical reasons. Billions of pounds of xylenes are equilibrated each year to provide the para isomer for polyester manufacture.[1] While not as important commercially, other disubstituted benzenes have been equilibrated by a variety of techniques.

Olah used $AlCl_3/H_2O$ to equilibrate $C_6H_4X_2$ with X = Cl[2a] and Br[2b] in liquid-phase reactions. Xylenes undergo both isomerization and disproportionation with $AlCl_3$, and the relative rate constants for the isomerization were determined.[3] Difluorobenzenes do not equilibrate with acid catalysts,[2a] but they do thermally scramble above 1000 °C.[4] The three-component equilibrium has not been experimentally achieved. Terphenyls have been equilibrated, but the analytical methods of the day were not able to quantitatively analyze all three components.[5]

Substituted benzenes with two different substituents, one of which is OH, have also been equilibrated. Cresols and xylenols probably equilibrate by CH_3 and not by OH migration;[6] hydroxybiphenyls probably equilibrate by phenyl migration.[7]

There are two competing mechanisms in methylbenzene exchange. HZSM-5 catalyzes both the intermolecular methyl exchange which disproportionates toluene to benzene and *p*-xylene and also the intramolecular exchange which equilibrates the three xylene isomers with essentially no disproportionation.

In our initial experiments looking for OH exchange, we sought to maximize our possibility for success by assuming that either mechanism might occur. Thus mixtures of dihydroxybenzene, phenol, and catalyst were studied. Phenol was introduced as a benzene solution for ease of handling.

We have now found that the zeolite[8] H-ZSM5 catalyzes the equilibration of dihydroxybenzenes. Figure 1 shows a composition diagram of the paths taken by each pure isomer toward equilibrium. When we initially found the ortho–para exchange, which is usually characteristic of an intermolecular process, we continued to leave phenol in the reaction recipe. Only toward the end of this study was the control run without phenol. The results were independent of the presence of phenol which suggests an intramolecular process for the OH exchange.

The reaction is so slow that equilibrium could not be achieved in convenient times starting from each pure component. Therefore mixtures of 1,2- and 1,4-dihydroxybenzenes were treated with HZSM-5. Each new product composition was used as the starting point for the next experiment—converging on the equilibrium of 6%

† Contribution No. 3891.

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