A New Method for Introducing Iodo and Bromo Fluorides into Organic Molecules Using Elemental Fluorine

Shlomo Rozen* and Michael Brand

Department of Chemistry, Tel-Aviv University, 69978 Tel-Aviv, Israel

Received December 28, 1984

A new method for introducing IF and BrF into organic compounds is developed. These reagents have been prepared by the direct action of elemental fluorine on the two respective halogens at low temperatures. The reactions of these interhalogen compounds with isolated double bonds are fast even at −75 °C. They were found to be stereospecific (anti mode addition) and in most cases regiospecific too. With conjugated enones the reactions were considerably slower. In this case an easy HF elimination takes place, producing eventually α-halo enones. Since the benzylic C–I bond is very weak, the reaction of IF with stilbenes leads to the 1,2-difluoro adducts through a secondary attack of the nucleophilic fluorine on the iodine, either through S_N2 or through the rare S_Ni mechanism. Bromine fluoride on the other hand gave the expected BrF adducts. The BrF reactions are much more forceful than the parallel IF ones, and a proton donor has to be present in order to tame this reagent. The halogen fluoride adducts can serve as an entry for synthesis of other fluorine-containing compounds that are difficult to prepare. Thus both the CF_2 group and the rare β-fluoro ether moiety were easily obtained from various olefins.

The importance of selectively monofluorinated molecules with distinctive and highly interesting biological activity is continually reflected in the literature.[1] This situation creates, of course, a need for developing new fluorinating methods either for introducing this halogen in sites that were previously inaccessible or for producing better and more attractive alternatives to old procedures that suffer from considerable limitations.

We have recently demonstrated that F_2 can serve as a source of electrophilic fluorine for regio- and stereospecific monofluorinations in a direct[2] or an indirect[3] mode. Lagow and others have shown that under different conditions, F_2 will perfluorinate organic compounds through a radical pathway.[4] The picture would be completed if this same element were also able to serve as a source of nucleophilic fluorine in organic reactions in a way that would require no isolation or purification of the in situ formed reagents.

Adding the elements of a halogen and fluorine across double bonds is a procedure known for more than three decades.[5] It is surprising, however, to note that most of the chemistry of this category is presently performed by the two available old methods and their variations: (a) mixing an olefin with a source of positive halogen such as NBS or CH_3OCl together with anhydrous HF,[5a] BF_3·OEt_2,[5b] or the Py·HF complex;[6] (b) reacting the olefin with AgF and iodine or bromine.[7] Both procedures are limited either by the presence of the strong acidic media or by the somewhat difficult to prepare and quite expensive AgF. Moreover, neither method uses a unified reagent consisting of the two halogens but employs two consecutive reactions each using a separate reagent. Such reactions are indicated by the somewhat unique notation [XF], meaning that these elements are eventually added across a double bond but not necesarily through the employment of the XF molecule itself. Of the three fluorine interhalogens IF, BrF, and ClF only the last one is a stable compound that can be relatively easily isolated and purified. As a result, its chemistry has been explored and several publications by DesMarteau, Christe, and others are well-known.[8] The situation, however, is different with the other two monofluoro interhalogens. IF has been described in only a few publications, most of them dealing with its thermal stability in the gas phase[9] or with its strong tendency to disproportionate to IF_3 and IF_5 in solution.[10]

$$IF \rightleftharpoons I_2 + IF_3 \rightleftharpoons I_2 + IF_5$$

Reactions of IF with organic compounds, however, have practically not been performed.[11] Even less is known about BrF, since this molecule has never been isolated or fully characterized despite many efforts. It was concluded that it exists at low temperature and its complex with pyridine can be isolated.[12] We describe here for the first time the in situ synthesis of IF and BrF from the respective elements and some of their chemistry with various alkenes.[13]

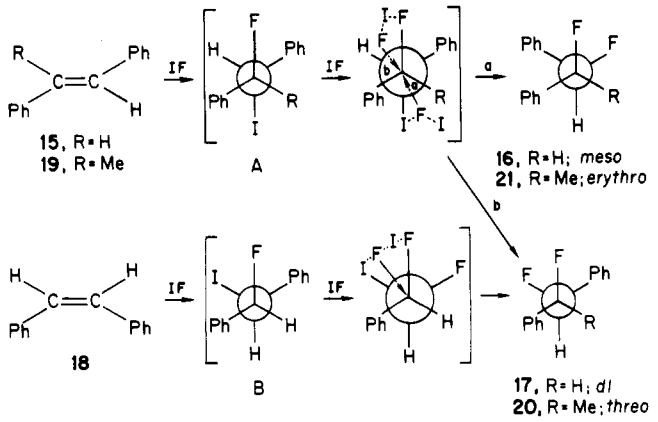
When nitrogen-diluted fluorine was passed through a cold (−75 °C) suspension of I_2 or Br_2 in $CFCl_3$ the original color of the reaction mixture changed to a brown suspension in the case of I_2 and to a pale yellow one in the case of bromine. As is evident from the following chemistry and from that described in the literature,[10,12] the main reactive species resulting from these reactions are IF and BrF. These two reagents are much more reactive than either I_2 or Br_2 and react with π systems at −75 °C in the dark in a matter of seconds.

The addition of IF across a double bond was found to be a fully regiospecific process in the Markovnikov sense,

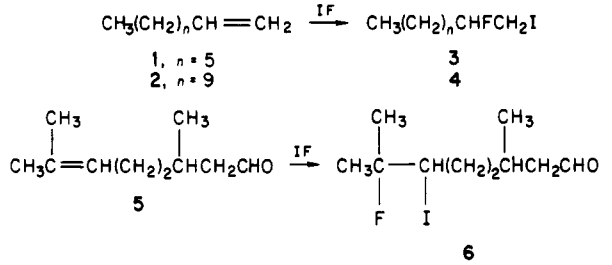
(1) Filler, R., Kobayashi, Y., Ed. "Biomedicinal Aspects of Fluorine Chemistry"; Elsevier Biomedical Press: Amsterdam, 1982.
(2) Rozen, S.; Gal, C.; Faust, Y. *J. Am. Chem. Soc.* **1980**, *102*, 6860. Gal, C.; Rozen, S. *Tetrahedron Letters* **1984**, *25*, 449.
(3) (a) Lerman, O.; Rozen, S. *J. Org. Chem.* **1980**, *45*, 4122. (b) Rozen, S.; Lerman, O. *J. Org. Chem.* **1980**, *45*, 672. (c) Lerman, O.; Tor, Y.; Hebel, D.; Rozen, S. *J. Org. Chem.* **1984**, *49*, 806.
(4) (a) Aikman, R. E.; Lagow, R. J. *J. Org. Chem.* **1982**, *47*, 2789 and references therein. (b) Adcock, J. L.; Robin, M. L. *J. Org. Chem.* **1983**, *48*, 2437 and references therein.
(5) See, for example: (a) Djerassi, C., Ed. "Steroid Reactions"; Holden-Day: San Francisco, 1963. (b) Heasley, V. L.; Gipe, R. K.; Martin, J. L.; Wiese, H. C.; Oakes, M. L.; Shellhamer, D. F. *J. Org. Chem.* **1983**, *48*, 3195.
(6) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 780.
(7) Hall, L. D.; Jones, D. L. *Can. J. Chem.* **1973**, *51*, 2902.
(8) (a) Katsuhara, Y.; DesMarteau, D. *J. Am. Chem. Soc.* **1980**, *102*, 2681. (b) Schack, C. J.; Christe, K. O. *J. Fluorine Chem.* **1978**, *12*, 325. (c) Naumann, D.; Herberg, S. *J. Fluorine Chem.* **1982**, *19*, 205. (d) Boguslavskaya, L. S.; Ternovskoi, L. A. *Zh. Org. Khim.* **1983**, *19*, 1881.
(9) Nair, K. P. R.; Hoeft, J.; Tiemann, E. *Chem. Phys. Lett.* **1979**, *60*, 253.
(10) Schmeisser, M.; Sartoi, P.; Naumann, D. *Chem. Ber.* **1970**, *103*, 880.
(11) See, however, the addition of IF, prepared from IF_5 + I_2, to perhalo olefins: Hauptschein, M.; Braid, M. *J. Am. Chem. Soc.* **1961**, *83*, 2383.
(12) Naumann, D.; Lehmann, E. *J. Fluorine Chem.* **1975**, *5*, 307.
(13) For a preliminary communications, see: Rozen, S.; Brand, M. *Tetrahedron Lett.* **1980**, *21*, 4543. Brand, M.; Rozen, S. *J. Fluorine Chem.* **1982**, *20*, 419.

0022-3263/85/1950-3342$01.50/0

Scheme I

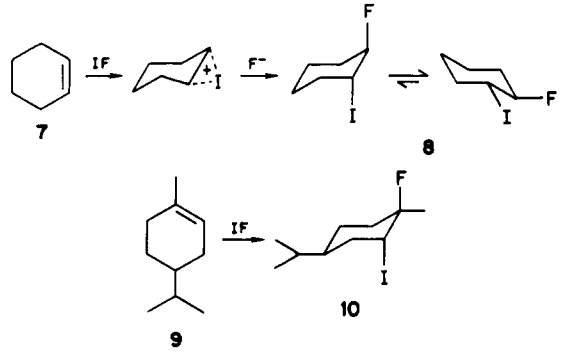


excluding any radical mechanism pathway. Aliphatic olefins such as 1-octene (1) and 1-dodecene (2) react with IF to give 1-iodo-2-fluoro derivatives 3 and 4, respectively, in 70% yield. Despite its high reactivity, an aldehyde



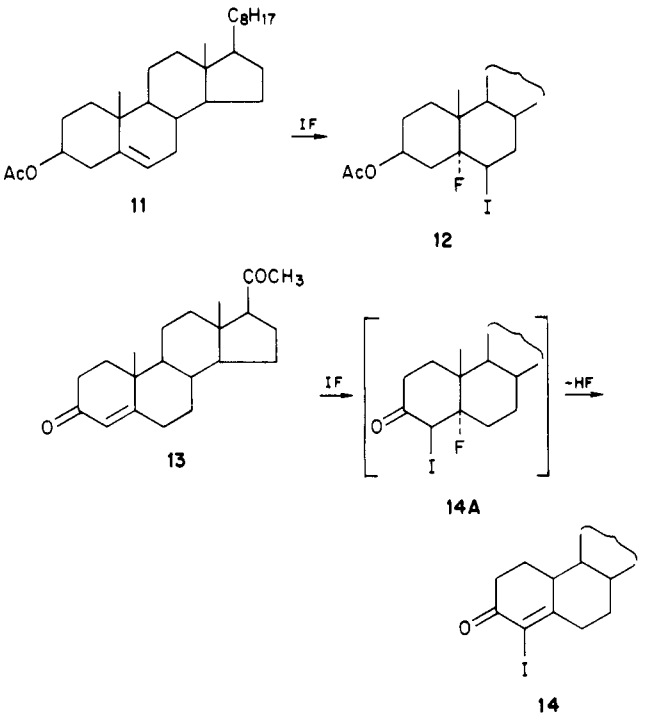
function may be present, since unlike IF_3 and IF_5, IF itself is not a strong oxidizer. Thus citronellal (5) forms only one regiospecific adduct, 3,7-dimethyl-7-fluoro-6-iodo-1-octanal (6) in good yield.

The reaction of iodine fluoride with an olefin is not only a regiospecific but also a stereospecific process. Cyclohexene (7) produces exclusively *trans*-1-fluoro-2-iodocyclohexane (8). The more hindered trisubstituted cy-



clohexene derivative 1-*p*-menthane (9) also gives the trans isomer of 1-fluoro-2-iodomenthane (10), although in somewhat lower yield. This type of addition emphasizes the difference between IF and other reagents made in situ from elemental fluorine. The latter reagents such as CF_3CF_2OF, CF_3COOF or CH_3COOF[3] possess an electrophilic fluorine that is eventually responsible for a dominantly syn addition. The trans addition of IF, however, indicates that here the elemental fluorine is transformed into a nucleophilic species which attacks the resulting bulky cyclic iodonium ion in an anti mode, on the ring carbon which corresponds to the more stable carbocation.

The in situ prepared IF also reacts quite efficiently with steroidal olefins. Thus 5α-fluoro-6β-iodocholesterol acetate (12) was produced in good yield in less than 5 min from cholesterol acetate (11).[14] Enones, like progesterone (13),

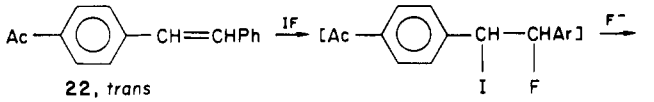


are much less reactive than regular olefins, which prolongs the reaction time. It was possible to detect in the crude mixture the IF adduct **14A**, but since the proton at C-4 is quite acidic, a fast elimination of HF took place, either on a chromatography column or during attempted crystallization, so that only the 4-iodoprogesterone (14) could be obtained with analytical purity.

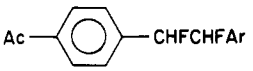
Stilbenes present an interesting case when reacted with IF. We were not able to trace any iodo fluoro adducts, but instead only the 1,2-difluoro derivatives were obtained in very good yields. The hypothetical possibility that fluorine itself might have reacted with the substrates was ruled out, since this halogen has very low solubility in $CFCl_3$[3a] and the stereochemistry of the adduct is different.[15] Reacting *trans*-stilbene (15) with IF gives a greater than 90% yield a 1:1 mixture of *meso*- and *dl*-1,2-difluoro-1,2-diphenylethane (16 and 17, respectively).[16] The reaction of *cis*-stilbene (18), however, although giving a similar yield, is much more stereocontrolled and the ratio of *dl*:*meso* (17:16) is higher than 4:1. We believe these results represent two consecutive reactions, the first one being the expected anti addition of IF, producing the intermediates with the most stable conformations A (from 15) and B (from 18) (Scheme I). The weak benzylic C–I bond is more susceptable to attack by nucleophilic F^- than any other C–I bond presented in this paper. It has been established that fluoro–iodo compounds are capable of forming I···F···I bridges,[17] so an extra molecule of IF may be complexed around the benzylic fluorine and iodine atoms in A and B. Configuration A presents an equal

(14) Barnes, C. S.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 1962.
(15) We have reacted some stilbenes with F_2 and always obtained a pure syn addition. See, also: Barton, D. H. R.; Hesse, R. H.; James, J. L.; Pechet, M. M.; Rozen, S. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 1105 and references therein.
(16) Barton, D. H. R.; Hesse, R. H.; Jackman, G. P.; Ogunkoya, L.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 739. For every case that we have examined in the literature or in our laboratories the fluorine atom in the *meso* or the *erythro* isomers resonates in the ^{19}F NMR at higher field than in the corresponding *dl* or *threo* isomers.
(17) Lehmann, E.; Naumann, D.; Schmeisser, M. *J. Fluorine Chem.* **1976**, *7*, 135.

opportunity for an IF molecule to be complexed around either the benzylic fluorine or the benzylic iodine. In either case a nucleophilic fluoride is brought into a position suitable for replacing the iodine, but while route a, a rare example of a S_Ni reaction, leads to the *meso* isomer **16**, route b, forms the *dl* isomer **17** via the normal S_N2 mechanism. In the case of configuration B an additional molecule of IF can attach itself only between the benzylic fluorine and iodine, forming a single favorable pathway for a S_Ni attack by the fluoride on the C–I bond, resulting in the formation of the *dl* difluoro isomer **17**. The relatively small amount of the *meso* derivative **16** may originate from an accidental S_N2 reaction of an uncomplexed IF on the benzylic carbon bonded to the iodine. Scheme I is also supported by the results with other stilbenes which we have examined. *trans*-α-Methylstilbene (**19**) reacts with IF in 90% yield, producing a mixture of *threo* (**20**) and *erythro* (**21**)-1-methyl-1,2-difluoro-1,2-diphenylethane in a ratio of 5:1 (**20**:**21**). Steric hindrance diminishes the prospects of route a but does not affect the complexation of IF with the benzylic fluorine atom leading to the dominant *threo* isomer **20** (route b). A different type of stereochemical control is exercised by the strong electron-withdrawing group in *trans*-4-acetylstilbene (**22**). Here



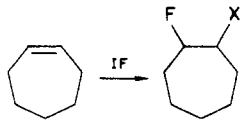
22, *trans* **23A**



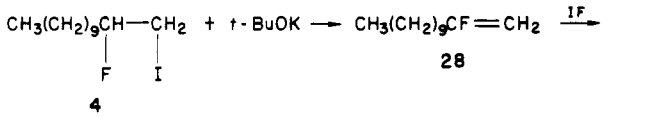
23, Ar = C_6H_4I, *erythro*
24, Ar = C_6H_4I, *threo*

the 1,2-difluoro adduct was obtained in 75% yield but in a ratio of *erythro*-1,2-difluoro-1-[4-acetylphenyl]-2-iodophenylethane (**23**) to the *threo* isomer (**24**) of 9:1. As outlined in Scheme I, the anti addition of IF to the double bond leads to the intermediate adduct **23A**, in which the benzylic iodine atom is highly polarized. This makes route a more favorable, resulting mainly in the formation of the *erythro* isomer **23**. In this particular case the acetyl group in **22** increases the activation energy required for the addition reactions across the double bond, enhancing the chance for the electrophilic iodine to react also with the relatively activated phenyl ring, most probably on the ortho position.

As already indicated, a nucleophile can react with the weak C–I bond. The oxygen of water is such a nucleophile, as demonstrated with cycloheptene (**25**). Upon reaction



25 **26**, X = I
27, X = OH



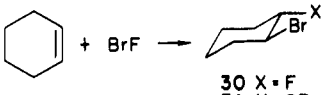
4 **28**

$CH_3(CH_2)_9CF_2CH_2I$

29

with IF, it forms the expected adduct **26**, but the iodine can be easily hydrolyzed, when the compound is absorbed on a silica gel column for 24 h, producing the fluorohydrin **27**. Using a stronger and more sterically hindered base than H_2O, as in the reaction of **4** with *t*-BuOK causes an elimination of HI, and 2-fluoro-1-dodecene (**28**) was formed in excellent yield. This could be reacted again with IF to produce the 1-iodo-2,2-difluorododecane (**29**) in good yield. The full regiospecificity of this reaction is based again on the fact that the positive charge of the iodo carbocation is stabilized on the fluorine-bonded carbon. *gem*-Difluoro compounds such as **29**, with a nearby iodine atom, which can serve as a substrate for further chemical transformations, are not easy to prepare and have potential importance in enzymatic studies, since most biochemical degradations will probably be disturbed by the CF_2 moiety.

With solvents consisting only of $CFCl_3$, $CFCl_3/CHCl_3$ (EtOH free), or $CFCl_3$/dry CH_3CN, the reaction of BrF with olefins proved to be too uncontrollable and unselective even at −75 °C, and only bromine and fluorine containing tars were obtained. When, however, a proton donor was added to the reaction mixture prior to the addition of the olefin, a surprising taming effect on the BrF was observed. The magnitude of this effect is a function of the solubility of the donor in the cold reaction mixture. The proton donors of limited solubility such as succinimide, AcOH, or *t*-BuOH did not entirely eliminate tar production, but formation of the desired bromo–fluoro adducts was already made possible although in moderate yields. Using the more soluble EtOH or *i*-PrOH raised the yield of the adducts into the range of 70–80%. The moderating effect of these proton donors on the reactions of BrF can operate through either one or both of the following mechanisms: (a) BrF reacts with the donor to produce HF and the hypobromite—ROBr;[5b,18] (b) hydrogen bonds formed between the proton and the fluorine enhance the polarizability of the BrF, making it more susceptible to gentle ionic reactions.[19] In the case of IF no such help is needed, since this molecule is already highly polarized. Bromine fluoride, like IF, adds across double bonds in an anti mode, indicating the formation of a cyclic bromonium ion. The use of an alcohol as a proton donor, however, has a certain drawback as is evident from the reaction with **7**, where the

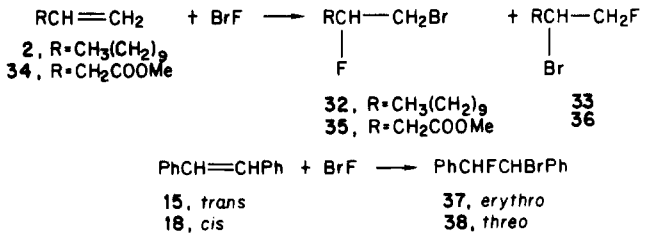


7 **30** X = F
31 X = OR

desired main product **30** might be accompanied by up to 10% of a bromoether of type **31**. Such oxygenated byproducts result from the competition of the nucleophilic alcohol for the positive charge in the bromonium ion.

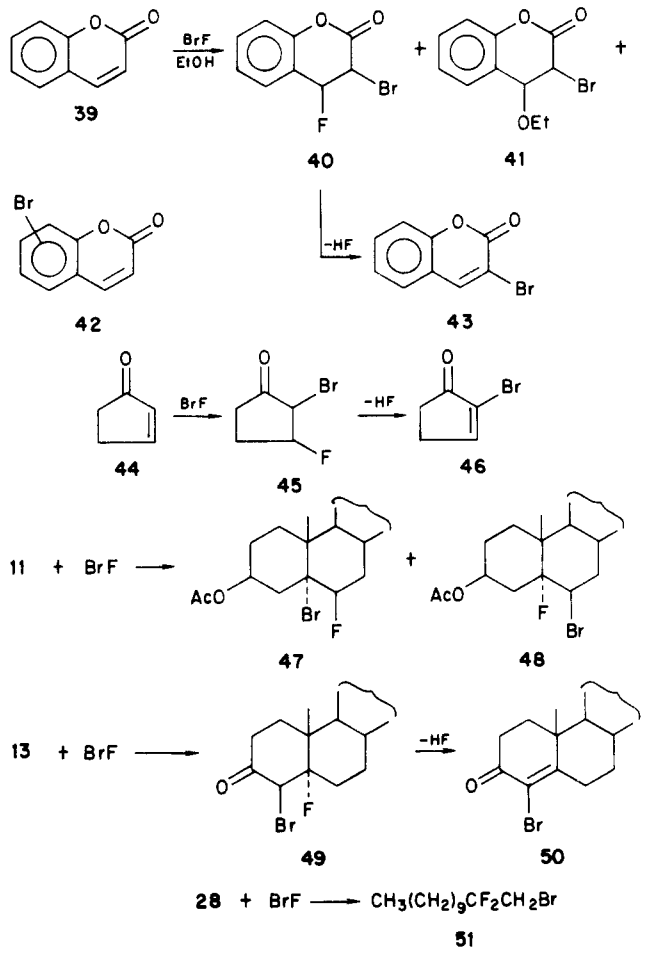
Besides the reactivity, there are some additional differences between the reactions of BrF and IF. While the main product of 1-dodecene (**2**) was the expected 1-bromo-2-fluorododecane (**32**), we have also isolated a minor anti-Markovnikov adduct, 1-fluoro-2-bromododecane (**33**) in a ratio of 4:1 (**32**:**33**). Less than a full regiospecific addition can also be found in other terminal olefins, such as methyl 3-butenoate (**34**). The ratio of the Markovnikov adduct **35** to the anti-Markovnikov one **36** was 5:3, respectively. The lack of absolute regiocontrol can be explained by the fact that in BrF the F^- is a stronger nucleophile than the fluoride in IF because of the aggregated form of the latter. This enhances the S_N2 reaction, which is subject to steric influences, leading to the formation of

(18) For a similar reaction of acetyl hypobromite with ROH, see: Roscher, N. M.; Liebermann, J. Jr. *J. Org. Chem.* **1982**, *47*, 3559.
(19) We have found a similar reaction pattern in the direct substitution reactions of tertiary unactivated hydrogens by elemental fluorine.[2]



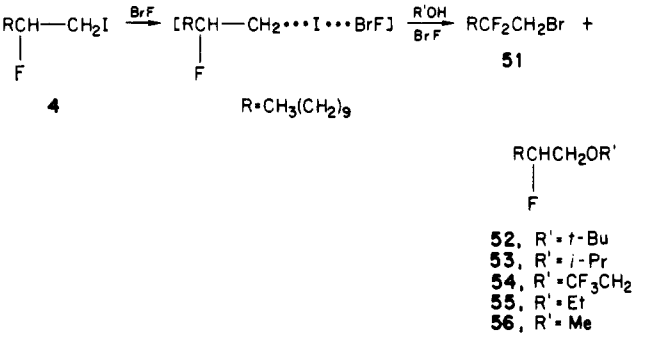
33. In the case of 34 additional inductive effects from the electronegative carbomethoxy group encourage the formation of the anti-Markovnikov adduct **36** even more. While in some cases the regiospecificity might not be complete, the anti mode stereospecificity of the BrF addition is. Thus only *erythro*-1,2-diphenyl-1-bromo-2-fluoroethane (**37**) was obtained from **15** and the *threo* isomer **38** from **18**. Since the C–Br bond is stronger than the C–I one, no difluoro compounds like **16** or **17** were formed, as with the parallel reaction of IF.

Enones such as **13**, **39**, and **44** reacted wth BrF with full regiospecificity but usually much more slowly than with the other olefins. The corresponding adducts **40**, **45**, and **49**, which have been detected, possess an acidic hydrogen



vicinal to the carbonyl and the fluorine atom, a fact that encourages an easy elimination of HF. Attempts to purify these compounds by crystallization or chromatography caused a quantitative transformation to the corresponding α-bromo enones **43**, **46**, and **50**. In the case of coumarin (**39**), additional byproducts **41** and **42** were also identified, since the slow reaction increased the chances of BrF to react with some other potential reactive centers. With other steroidal olefins, e.g., cholesterol acetate (**11**), BrF gave the two expected adducts **47** and **48** in a ratio of 4:1, respectively.

Bromine fluoride added in a full regiospecific mode to vinylfluorides, producing the potentially important 1-bromo-2,2-difluoro moiety in the same way IF did. As an example, 2-fluoro-1-dodecene (**28**) produces 1-bromo-2,2-difluorododecane (**51**) in good yield. Compound **51** can



also be obtained directly from the fluoro–iodo adduct **4** when treated at –75 °C with a mixture of BrF and *t*-BuOH. This reaction however produces also 30% 2-fluorododecyl *t*-butyl ether (**52**). Since *t*-BuOH does not react with **4** even under reflux, it is obvious that the electrophilic bromine becomes attached to the bulky iodine atom, weakening further the labile C–I bond to the point where even the weak nucleophilic *t*-BuOH can react with it to form the β-fluoro ether **52**. Since, however, the oxygen in *t*-BuOH is highly hindered, the main result of the bromine complexation with the iodine is eventual HI elimination with a consequent attack of BrF on the newly formed double bond, producing the *gem*-difluoro compound **51**. When other less hindered alcohols were involved, more of the rare fluoro ethers could be readily synthesized. Thus the isopropyl (**53**), β,β,β-trifluoroethyl (**54**), ethyl (**55**), and methyl (**56**) ethers were obtained in yields higher than for the *tert*-butyl ether (**52**) and understandably without the formation of the difluoro derivative **51**. Since the C–Br bond is stronger than the C–I one, BrF does not have the same effect on bromo compounds, which remain largely unreacted under parallel conditions employed for the iodo derivatives. It should be noted that the simpler β-fluoro ethers such as **55** can also be prepared directly from **4** under prolonged treatment with NaOEt in boiling EtOH. When, however, the NaOEt was replaced with a more hindered alkoxide like *i*-PrONa, elimination of HI, producing **28**, is the main reaction course and only a minor amount of the β-fluoro ether **53** is obtained. With *t*-BuOK no traces of the fluoroether **52** were detected and only elimination forming **28** took place in higher than 90% yield.

In conclusion, this work presents the first attempt to use F_2 as a direct source for nucleophilic fluorine, showing thus the versatility of this element which can also be used directly as a source for radical and electrophilic fluorine. The described method also has the advantage of using neutral conditions, thus broadening the spectrum of the olefins that can be used. The products are also of general importance, since one can perform many reactions on the iodine and the bromine without affecting the fluorine atom, thus eventually placing this halogen in specially selected positions where no other method is able to do so. Last, but not least, is the great potentials these reactions have for preparation of ^{18}F-containing derivatives for use in the rapidly developing Positron Emitting Transaxial Tomography (PETT),[20] since the starting reagent $^{18}F_2$ is relatively easy to make and since the reaction times of the halo

(20) For an interesting review on PETT and the role of ^{18}F in this field, see: Degani, R. *Chem. Eng. News* 1981, *59*, 30.

fluorides with olefins are very short—a "must", when preparation of ^{18}F-containing compounds is considered.

Experimental Section

^1H NMR spectra were recorded with a Bruker WH-90 spectrometer at 90 MHz with $CDCl_3$ as the solvent and Me_4Si as an internal standard, while ^{19}F spectra were measured at 84.67 MHz and are reported in parts per million upfield from $CFCl_3$, which also served as the internal standard. Mass spectra were measured with a Du Pont 21-491B spectrometer. IR spectra were recorded on a Perkin-Elmer 177 spectrometer.

General Fluorination Procedure. A description of the setup and the procedures for working with elemental fluorine has previously been described.[3a,b] It should, however, be remembered that the reactions described should be conducted with care since F_2 is a strong oxidizer and not much is known about IF and BrF. The work should be conducted in a well-ventilated area or in an efficient hood. If elementary precautions are taken, however, the work with fluorine and its derivatives is safe and relatively simple. In the past we have never had any accidents while working with F_2.

Preparation of IF and Its Reactions with Olefins. A suspension of 25 g of I_2 (100 mmol) in 450 mL of $CFCl_3$ was cooled to −75 °C. Nitrogen-diluted (10%) fluorine (total of 50 mmol of F_2) is bubbled into the mixture during a period of about 10 h. Upon completion of the F_2/N_2 addition, a brown suspension of a mixture of IF and I_2 results, ^{19}F NMR −161 ppm. A cold 20-mL $CHCl_3$ solution of 10–20 mmol of the olefin is added in one portion to the IF mixture at −75 °C. After a few minutes at that temperature, the reaction mixture was "worked up as usual", a term describing the stopping of the reaction by pouring it into 500 mL of dilute thiosulfate solution, washing with water until neutral, drying over $MgSO_4$, and evaporating. The crude product was usually purified by chromatography on a short silica gel column and, if needed, also by high-pressure liquid chromatography (LiChrosorb si 60, Merck). Unless a melting point is given, the products are liquids.

Only unpublished physical data for the fluorine-containing compounds are given in this section. Microanalyses also confirm the correct composition of the new fluorinated compounds.

Preparation of BrF and Its Reaction with Olefins. A suspension of 0.5 mL of Br_2 (about 10 mmol) in 250 mL of $CFCl_3$ was prepared. Nitrogen-diluted (10%) fluorine was bubbled through the suspension until the red color of Br_2 disappeared and was replaced by a pale yellow suspension of BrF, ^{19}F NMR −158 ppm. About 200 mL of precooled $CHCl_3$ (containing the appropriate alcohol—usually EtOH unless otherwise stated) was added and stirred for 15 min during which time a solution is obtained. Subsequently a cold (−78 °C) solution of 10 mmol of olefin in $CHCl_3$ was added, allowed to react for a few minutes unless otherwise stated, and worked up as usual.

1-Iodo-2-fluorooctane (3). A cold $CHCl_3$ solution of 15 mmol (1.68 g) of 1-octene (**1**) was added in one portion to the IF suspension, obtained as described above. The reaction was stopped after 2 min and worked up as usual. The crude product was purified by chromatography using petroleum ether as the eluent on a short silica gel column to afford 2.7 g (70%) of **3** as an oil: ^1H NMR δ 4.68 (CHF, 1 H, d quint, J_{HF} = 48 Hz, J_{HH} = 6 Hz), 3.50 (CH_2I, 2 H, dd, J_{HF} = 20 Hz, J_{HH} = 6 Hz), 0.82–1.89 (13 H, m); ^{19}F NMR −171 ppm (m); MS, m/e 258 (M^+), 131 [$(M - I)^+$], 173 [$(CHFCH_2I)^+$]. Anal. Calcd for $C_8H_{16}FI$: C, 37.21; H, 6.20. Found: C, 37.61; H, 6.42.

1-Iodo-2-fluorododecane (4). This compound was obtained from **2** in the same manner as **3** in 70% yield as an oil, which solidifies at 5 °C: ^1H NMR δ 4.46 (CHF, 1 H, d quint, J_{HF} = 48 Hz, J_{HH} = 6 Hz), 3.30 (CH_2I, 2 H, dd, J_{HF} = 20 Hz, J_{HH} = 6 Hz), 0.81–1.83 (21 H, m); ^{19}F NMR −171 ppm (m); MS, m/e = 314 (M^+), 187 [$(M - I)^+$], 173 [$(CHFCH_2I)^+$]. Anal. Calcd for $C_{12}H_{24}FI$: C, 45.86; H, 7.64. Found: C, 45.59; H, 7.69.

3,7-Dimethyl-7-fluoro-6-iodo-1-octanal (6). A cold (−75 °C) $CHCl_3$ solution of 15 mmol of citronellal (**5**) was added to the IF suspension and allowed to react for 1–2 min. After the usual workup and after chromatography using 10% EtOAc in petroleum ether as eluent, **6** was obtained in 50% yield as an oil: IR (neat) 1720 cm^{-1}; ^1H NMR δ 9.5 (CHO, 1 H, t), 4.30 (CHI, 1 H, m), 1.45 (CH_3CF, 3 H, d, J_{HF} = 22 Hz), 1.40 (CH_3CF, 3 H, d, J_{HF} = 22 Hz), 0.87 (CH_3, 3 H, d, J_{HH} = 6 Hz); ^{19}F NMR −134 ppm (m). Compound **6** decomposes slowly in the air due to both oxidation and dehydrofluorination.

***trans*-1-Fluoro-2-iodocyclohexane (8).** **8** was prepared in a similar way as the above compounds. It was obtained in 64% yield as an oil with the same physical and spectral properties as reported in the literature.[6,7]

***trans*-1-Fluoro-2-iodomenthane (10).** A cold $CHCl_3$ solution of 1.38 g of **9** was allowed to react with IF for 5 min and then worked up as usual. Purification by chromatography using petroleum ether as the eluant gave 1.28 g of **10** (45% yield) as an oil: ^1H NMR δ 4.47 (CHI, 1 H, dt, J_{HH} = 2.5 Hz, $J_{HF(vic)}$ = 9 Hz), 1.59 (CH_3CF, 3 H, d, J = 22 Hz), 0.89 (CH_3, 6 H, d); ^{19}F NMR −145 ppm (m); MS, m/e 284 (M^+), 264 [$(M - HF)^+$]. Anal. Calcd. for $C_{10}H_{18}FI$: C, 42.25; H, 6.34. Found: C, 42.65; H, 6.46.

5α-Fluoro-6β-iodocholesterol Acetate (12). A cold $CHCl_3$ solution of 2.14 g of **11** was allowed to react with IF for 5 min and then worked up as usual. Chromatography with 5% EtOAc in petroleum ether as eluent afforded 1.86 g of **12** (65% yield): mp 132 °C (from IPA); IR 1710 cm^{-1}; ^1H NMR δ 4.55–4.88 (H at C3, 1 H, m), 4.3 (H at C6, 1 H, dt, J_{HF} = 11 Hz, J_{HH} = 2.5 Hz), 2.02 (CH_3CO, 3 H, s), 0.93 (Me-19, 3 H, s), 0.71 (Me-18, 3 H, s); ^{19}F NMR −145 ppm ($J_{F_{ax}H_{ax}}$ = 37 Hz); MS, m/e 574 (M^+), 447 [$(M - I)^+$], 388 [$(M - I - OAc)^+$], 368 [$(M - I - HF - OAc)^+$]. Anal. Calcd for $C_{29}H_{48}FIO_2$: C, 60.63; H, 8.36. Found: C, 60.38; H, 8.34.

4-Iodoprogesterone (14). The reaction of **13** (1.56 g) with IF was continued for 10 h at −75 °C in order to achieve a full conversion. After the usual workup the crude mixture was chromatograhed using 10% EtOAc in petroleum ether as eluent, yielding 1.53 g of **14** (70% yield): mp 132 °C (from MeOH); IR 1710, 1720 cm^{-1}; ^1H NMR δ 2.13 (Ac, 3 H, s), 1.23 (Me-19, 3 H, s), 0.68 (Me-18, 3 H, s); MS, m/e 440 (M^+), 312 [$(M - HI)^+$]. Anal. Calcd for $C_{21}H_{29}IO_2$: C, 57.27; H, 6.59. Found: C, 57.30; H, 6.69.

Reaction of *trans*- and *cis*-Stilbene (15 and 18) with IF. A cold solution of **15** (1.8 g) was reacted with IF for 5 min. The reaction was worked up as usual and chromatographed with 5% EtOAc in petroleum ether serving as eluent. The two difluoro isomers **16** and **17** were thus obtained, in 42% yield each. Their physical and spectral properties matched those reported in the literature.[16] In a parallel reaction *cis*-stilbene (**18**) gave the same two products, but the major isomer **17** was obtained in 65% yield while the minor one **16** was formed in 15% yield.

Reaction of *trans*-α-Methylstilbene (19) with IF. **19** (1.94 g) was allowed to react with IF for 5 min at the same conditions as described before. After the usual workup the GC and the spectral data indicated that the two isomers **20** and **21** were obtained. The minor *erythro* isomer (**21**), about 15% yield, was not fully purified. The major *threo* isomer (**20**) was crystallized from petroleum ether: mp 70 °C; yield 75%; ^1H NMR δ 7.00–7.34 (Ar, 10 H, m), 5.49 (CHF, 1 H, dd, J_{HF} = 45 Hz, J_{HF} = 17 Hz), 1.78 (CH_3, 3 H, dd, $^3J_{HF}$ = 23 Hz, $^4J_{HF}$ = 2.1 Hz); ^{19}F NMR −187 (CHF, dd, $^2J_{HF}$ = 45 Hz, $^3J_{FF}$ = 10 Hz), −159 ppm ($CFCH_3$, m); MS, m/e 232 (M^+), 123 [$(C_6H_5CFMe)^+$]. Anal. Calcd for $C_{15}H_{14}F_2$: C, 77.59; H, 6.03. Found: C, 77.07; H, 6.01.

Reaction of *trans*-4-Acetylstilbene (22) with IF. This reaction, carried out as described above, gave two difluoro adducts. The minor *threo* isomer **24** was obtained in less than 8% yield was not fully purified although its spectral properties including the fluorine signal at −176 ppm strongly support the structure. The major isomer was crystallized from MeOH and proved to be the *erythro*-**23**: mp 118 °C; IR 1680 cm^{-1}; ^1H NMR δ 6.83–8.01 (Ar, 9 H, m), 5.63 (CHF, 2 H, dm, J_{HF} = 49 Hz), 2.606 (Ac, 3 H, s); ^{19}F NMR −187 ppm (m); MS, m/e 386 (M^+), 235 [$(IC_6H_4CHF)^+$]. Anal. Calcd for $C_{16}H_{13}F_2IO$: C, 49.74; H, 3.37. Found: C, 48.95; H, 3.33.

1-Fluoro-2-iodocycloheptane (26). **26** obtained as an oil in 45% yield from **25** in its reaction with IF and purified by chromatography using petroleum ether as eluent: ^1H NMR δ 4.23–5.15 (CHICHF, 2 H, dm), 1.42–2.55 (10 H, m); ^{19}F NMR −154 ppm (m); MS, m/e 223 [$(M - F)^+$], 115 [$(M - I)^+$], 96 [$(M - IF)^+$]. Anal. Calcd for $C_7H_{12}FI$: C, 34.71; H, 4.96. Found: C, 34.93; H, 5.34.

1-Iodo-2,2-difluorododecane (29). The IF adduct **4** (2 g) was refluxed with 1.1 g of *t*-BuOK in 100 mL of *t*-BuOH for 16 h. After the usual workup and chromatography using petroleum ether as eluent, the oily fluoro olefin **28** was obtained in 90% yield: ^1H NMR δ 4.6 (vinyl H, cis to F, 1 H, br s), 4.05 (vinyl H, trans to

F, 1 H, dd, J_{HF} = 30 Hz, $^4J_{HH}$ = 2 Hz), 0.80–2.50 (21 H, m); ^{19}F NMR −95 ppm (m). Anal. Calcd for $C_{12}H_{23}F$: C, 77.42; H, 12.37. Found: C, 77.37; H, 12.10. Compound **28** was then allowed to react with IF for about 5 min and worked up as usual. Chromatography of the crude product using petroleum ether as eluent gave a solid, mp 30 °C (from petroleum ether), which proved to be **29** (75% yield): ^{1}H NMR δ 3.4 (CH_2I, 2 H, t, J = 14 Hz), 0.88–1.83 (21 H, m); ^{19}F NMR −95 ppm (quint, J = 14 Hz); MS, m/e 332 (M^+). Anal. Calcd for $C_{12}H_{23}F_2I$: C, 43.37; H, 6.93. Found: C, 43.15; H, 7.04.

Reaction of Cyclohexene (7) with BrF. A cold solution of **7** (2 g) in $CHCl_3$ containing 2% EtOH was allowed to react with BrF for 5 min. The reaction mixture was then worked up as usual and chromatographed with petroleum ether as eluent. The BrF adduct **30** was thus isolated as an oil in 61% yield. This compound is identical with the one described in the literature.[6] Along with **30**, about 8–10% of the bromoether **31** was also obtained.[21]

Reaction of 1-Dodecene (2) with BrF. 1-Dodecene reacted with BrF for 10 min and was worked up as usual and subjected to chromatography using petroleum ether as eluent. The two main compounds were separated. The major one proved to be 1-bromo-2-fluorododecane (**32**): oil; 66% yield, ^{1}H NMR δ 4.63 (CHF, 1 H, d quint, J_{HF} = 47 Hz, J_{HH} = 6 Hz), 3.46 (CH_2Br, 2 H, dd, J_{HF} = 20 Hz, J_{HH} = 6 Hz), 0.81–1.83 (21 H, m); ^{19}F NMR −178 ppm (m); MS, m/e 248, 246 [(M − HF)$^+$], 168 [(M − Br − F)$^+$]. Anal. Calcd for $C_{12}H_{24}BrF$: C, 53.93; H, 8.99. Found: C, 53.33; H, 9.63. The minor component was the isomer **33**: oil; 18% yield; ^{1}H NMR δ 4.53 (CH_2F, 2 H, dm, J_{HF} = 47 Hz), 4.23 (CHBr, 1 H, m), 0.81–1.83 (21 H, m); ^{19}F NMR −210 ppm (dt, $^2J_{HF}$ = 47 Hz, $^3J_{HF}$ = 20 Hz); MS, m/e 268, 266 (M^+), 247 [(M − HF)]$^+$. Anal. Calcd for $C_{12}H_{24}BrF$: C, 53.93; H, 8.99. Found: C, 54.20; H, 9.10.

Reaction of Methyl 3-Butenoate (34) with BrF. The methyl ester **34** was reacted with BrF for 5 min, worked up as usual, and chromatographed using 5% EtOAc in petroleum ether as eluent. The major product isolated was **35** in 50% yield, as an oil: IR (neat) 1750 cm^{-1}; ^{1}H NMR δ 5.15 (CHF, 1 H, dm, J_{HF} = 46 Hz), 3.80 (CH_3, 3 H, s), 3.70 (CH_2Br, 2 H, dd, J_{HF} = 24 Hz, J_{HH} = 5 Hz), 2.81 (CH_2CO, 2 H, dd, J_{HF} = 17 Hz, J_{HH} = 6 Hz); ^{19}F NMR −178 ppm (m); MS, m/e 169, 167 [(M − OCH_3)]$^+$, 141, 139 [(M − CO)]$^+$. Anal. Calcd for $C_5H_8BrFO_2$: C, 30.15; H, 4.02. Found: C, 29.95; H, 3.98. The minor isomer **36** was obtained in 30% yield as an oil: IR (neat) 1750 cm^{-1}; ^{1}H NMR δ 4.45 (CH_2F, 2 H, dm, J_{HF} = 43 Hz), 4.30 (CHBr, 1 H, m), 3.80 (CH_3, 3 H, s), 3.00 (CH_2CO, 2 H, dd, $^4J_{HF}$ = 4 Hz, J_{HH} = 6 Hz); ^{19}F NMR −212 ppm (dt, $^2J_{HF}$ = 43 Hz, $^3J_{HF}$ = 14 Hz); MS, m/e 169, 167 [(M − OCH_3)$^+$], 141, 139 [(M − $COOCH_3$)$^+$], 119 [(M − Br)$^+$]. Anal. Calcd for $C_5H_8BrFO_2$: C, 30.15; H, 4.02. Found: C, 29.80; H, 3.85.

Reaction of *trans*- and *cis*-Stilbene (15 and 18) with BrF. A cold chloroform solution of **15** was reacted with BrF for 5 min and then worked up as usual. Chromatography using 5% EtOAc in petroleum ether as eluent gives pure *erythro*-1,2-diphenyl-1-bromo-2-fluoroethane (**37**) in 84% yield, mp 120 °C (from petroleum ether), identical with the same compound described previously.[22] In a parallel reaction, *cis*-stilbene (**18**) produced the *threo* isomer **38** in 65% yield, mp 65 °C (from petroleum ether).[22]

Reaction of Coumarin (39) with BrF. A cold solution of **39** in $CHCl_3$ containing 2% EtOH was reacted with BrF for 16 h in order to achieve a full conversion. After the usual work up, the crude mixture was subjected to a quick chromatography using 10% EtOAc in petroleum ether serving as eluent. The main compound isolated was the BrF adduct **40**, although not in analytical purity: yield 50%; oil; IR (neat) 1750 cm^{-1}; ^{1}H NMR δ 6.96–7.46 (Ar, 4 H, m), 5.56 (CHF, 1 H, dd, J_{HF} = 49 Hz, J_{HH} = 3.2 Hz), 4.66 (CHBr, 1 H, dd, J_{HF} = 8 Hz, J_{HH} = 3.2 Hz); ^{19}F NMR −147.5 ppm (dd, $^2J_{HF}$ = 49 Hz, $^3J_{HF}$ = 8 Hz); MS, m/e = 244, 246 (M^+), 224, 226 [(M − HF)$^+$]. In addition to **40** two other minor compounds were isolated and identified. One proved to be **42**: 25% yield; mp 150 °C (from IPA); IR 1715 cm^{-1}; ^{1}H NMR δ 7.17–7.78 (Ar and benzylic, 4 H, m), 6.40 (CHCO, 1 H, d, J = 9 Hz); MS, m/e 226, 224 (M^+), 198, 196 [(M − CO)$^+$]. Anal. Calcd for $C_9H_5BrO_2$: C, 48.00; H, 2.22; Br, 35.56. Found: C, 48.03; H, 2.48; Br, 35.58. The other compound was identified as the ethyl ether **41**: yield 15%, mp 125 °C (from IPA); IR 1750 cm^{-1}; ^{1}H NMR δ 7.20–7.80 (Ar, 4 H, m), 4.35 (CHX, 2 H, m), 3.35 (CH_2, 2 H, q, J = 6 Hz), 1.02 (CH_3, 3 H, t, J = 6 Hz); MS, m/e 270, 272 (M^+), 224, 226 [(M − C_2H_5OH)$^+$]. Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.71; H, 4.06. Found: C, 49.50; H, 4.25. Prolonged chromatography converts **40** to **43** in quantitative yield.[23]

Reaction of Cyclopentenone (44) with BrF. A cold (−75 °C) solution of **44** (2 g) in $CHCl_3$ was mixed with the BrF suspension for 16 h in order to achieve a full conversion. After the usual workup the crude reaction mixture was subjected to fast chromatography using 10% EtOAc in petroleum ether as eluent. The BrF adduct **45** was obtained in 90% yield, although not in analytical purity, as an oil: IR 1750 cm^{-1}; ^{1}H NMR δ 5.55 (CHF, 1 H, dm, J_{HF} = 48 Hz), 4.45 (CHBr, 1 H, dd, J_{HF} = 12 Hz, J_{HH} = 2 Hz), 2.5–3.2 (4 H, m); ^{19}F NMR −171 ppm (m); MS, m/e 182, 180 (M^+), 162, 160 [(M − HF)$^+$]. An attempt to further purify **45** resulted in HF elimination quantitatively producing **46**, mp 39 °C.[24]

Reaction of Cholesterol Acetate (11) with BrF. The steroidal olefin was reacted with BrF for 5–10 minutes and the reaction mixture worked up as usual and chromatographed using 5% EtOAc in petroleum ether as eluent. The two isomers[25] **47** and **48** were obtained in 55% and 15% yield, respectively, with their physical and spectral properties matching those in the literature.

Reaction of Progesterone (13) with BrF. With an enone system the reaction took nearly 16 h to achieve full conversion. After the usual workup the crude product was chromatographed quickly with 25% EtOAc in petroleum ether as eluent. The BrF adduct **49** was thus obtained in higher than 90% purity: yield 60%; mp 150–152 °C; IR 1745, 1720 cm^{-1}; ^{1}H NMR δ 4.60 (CHBr, 1 H, d, J_{HF} = 20 Hz), 2.12 (Ac, 3 H, s), 1.10 (Me-19, 3 H, d, $^4J_{CH}$ = 3 Hz), 0.64 (Me-18, 3 H, s); ^{19}F NMR −124 ppm (br signal); MS, m/e 394, 392 [(M − HF)$^+$], 314 [(M − BrF)$^+$]. Attempts to purify this compound either by chromatography or by repeated crystallization led quantitatively to the bromo olefin **50** via HF elimination: mp 167 °C (from EtOAc); IR 1710, 1720 cm^{-1}; ^{1}H NMR δ 2.13 (Ac, 3 H, s), 1.24 (Me-19, 3 H, s), 0.68 (Me-18, 3 H, s); MS, m/e 394, 392 (M^+), 313 [(M − Br)$^+$]. Anal. Calcd for $C_{21}H_{29}BrO_2$: C, 64.12; H, 7.38; Br, 20.36. Found: C, 64.40; H, 6.94; Br, 20.20.

1-Bromo-2,2-difluorododecane (51). This compound was obtained in 70% yield as an oil from 2-fluoro-1-dodecene (**28**) and BrF. It was purified by chromatography using petroleum ether as eluent: ^{1}H NMR δ 3.51 (CH_2Br, 2 H, t, J_{HF} = 14 Hz), 0.88–1.80 (21 H, m); ^{19}F NMR −99 ppm (quint, J = 14 Hz); MS, m/e 286, 284 (M^+). Anal. Calcd for $C_{12}H_{23}BrF_2$: C, 50.53; H, 8.07. Found: C, 50.54; H, 7.97.

Reactions of 1-Iodo-2-fluorododecane (4) with BrF in the Presence of Various Alcohols. **4** (2 g) was dissolved in Freon-11 (50 mL) cooled to −75 °C and added to the BrF suspension containing the desired alcohol (2–4%). The reaction was well vibrated for 16 h at that temperature, worked up as usual, and chromatographed. With *t*-BuOH as the alcohol two products were obtained, which were separated by chromatography eluting first with petroleum ether followed by 5% EtOAc in petroleum ether. The two products were identified as the 1-bromo-2,2-difluorododecane (**51**) in 40% yield along with β-fluorododecyl *tert*-butyl ether (**52**) in 25% yield as an oil: ^{1}H NMR δ 4.65 (CHF, 1 H, d quint, J_{HF} = 46 Hz, J_{HH} = 6 Hz), 3.42–3.90 (H's α to the O, 2 H, m), 1.26 (t-Bu, 9 H, s), 0.88 (CH_3, 3 H, t, J = 6 Hz); ^{19}F NMR −186.5 ppm (m); MS, m/e 173 [(M − CH_2O − *t*-Bu)$^+$]. No difluoro derivative as **51** was obtained when the alcohol was replaced by *i*-PrOH, maintaining the similar conditions as in the previous experiment. Chromatography with 5% EtOAc in petroleum ether as eluent produced the oily β-fluorododecyl isopropyl ether in 60% yield, although in only 60% conversion: ^{1}H NMR δ 4.59 (CHF, 1 H, d quint, J_{HF} = 48 Hz, J_{HH} = 6 Hz), 3.36–3.75 (H's α to the O, 3 H, m), 1.172 (*i*-Pr, 6 H, d, J = 6 Hz), 0.88 (CH_3, 3 H, t, J

(21) Dauphin, G.; Kergomard, A.; Scorset, A. *Bull. Soc. Chim. Fr.* **1976**, 862.
(22) Zupan, M.; Polak, A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 971.
(23) Cussans, N. J.; Huckerby, T. N. *Tetrahedron* **1975**, *31*, 2587.
(24) Dunn, G. L.; DiPasquo, V. J.; Hoover, R. E. *Tetrahedron Lett.* **1966**, 3737.
(25) Kobayashi, Y.; Kumadaki, I.; Ohsawa, A.; Honda, M.; Hanzawa, Y. *Chem. Pharm. Bull.* **1975**, *23*, 196.

= 6 Hz); ^{19}F NMR -186.5 ppm (m); MS, *m/e* 173 [(M - CH_2O - *i*-Pr)$^+$]. Anal. Calcd for $C_{15}H_{31}FO$: C, 73.17; H, 12.60. Found: C, 73.05; H, 12.62. Similar results were obtained when trifluoroethanol was used, producing the β-fluorododecyl β,β,β-trifluoroethyl ether (**54**): oil; 55% yield (75% conversion); ^{1}H NMR δ 4.65 (CHF, 1 H, dm, J_{HF} = 49 Hz), 3.95 (OCH_2CF_3, 2 H, q, J_{HF} = 12 Hz), 3.5-4.0 (CH_2O, 2 H, m) 0.85-1.80 (21 H, m); ^{19}F NMR -75 (CH_3, 3 F, t, J_{HF} = 12 Hz), -186.5 ppm (CHF, 1 F, m); MS, *m/e* 173 [(M - $CH_2OCH_2CF_3$)$^+$]. Anal. Calcd for $C_{14}H_{26}F_4O$: C, 59.74; H, 9.09. Found: C, 60.43, H, 9.52. The ethyl ether **55** was also synthesized by this method in 60% yield (60% conversion): ^{1}H NMR δ 4.62 (CHF, 1 H, dm, J_{HF} = 49 Hz), 3.33-3.70 (CH_2O, 4 H, m), 0.81-1.65 (24 H, m); ^{19}F NMR -186.5 ppm (m); MS, *m/e* 173 [(M - CH_2OEt)$^+$]. Anal. Calcd for $C_{14}H_{29}FO$: C, 72.41; H, 12.50. Found: C, 71.60; H, 12.05. This compound could also be prepared by refluxing **4** and NaOEt for 16 h in 85% yield. The methyl ether **56** (oil) could also be prepared from **4** and BrF in similar conditions as described above in 70% yield: ^{1}H NMR δ 4.62 (CHF, 1 H, dm, J_{HF} = 48 Hz), 3.51 (CH_2O, 2 H, dd, $^3J_{HF}$ = 20 Hz, J_{HH} = 4.5 Hz), 3.4 (OCH_3, 3 H, s), 0.85-1.80 (21 H, m); ^{19}F NMR -186 ppm (m); MS, *m/e* 173 [(M - CH_2OCH_3)$^+$]. Anal. Calcd for $C_{13}H_{27}FO$: C, 71.56; H, 12.39. Found: C, 71.37; H, 12.79.

Acknowledgment. We thank the Fund for Basic Research, administrated by The Israel Academy of Science and Humanities, for supporting this research.

Registry No. **1**, 111-66-0; **2**, 112-41-4; *dl*-**3**, 97211-45-5; *dl*-**4**, 97211-46-6; *dl*-**5**, 26489-02-1; **6**, 97211-47-7; **7**, 110-83-8; *dl*-**8**, 97211-48-8; *dl*-**9**, 1195-31-9; *dl*-**10**, 97211-49-9; **11**, 604-35-3; **12**, 2560-88-5; **13**, 57-83-0; **14**, 97211-50-2; **15**, 103-30-0; *meso*-**16**, 14090-31-4; *dl*-**17**, 52795-54-7; **18**, 645-49-8; **19**, 833-81-8; *dl*-**20**, 97211-51-3; *dl*-**21**, 97211-52-4; **22**, 20488-42-0; *dl*-**23**, 97211-53-5; *dl*-**24**, 97234-64-5; **25**, 628-92-2; **26**, 77517-69-2; **27**, 97211-54-6; **28**, 97211-55-7; **29**, 97211-56-8; *dl*-**30**, 97211-57-9; *dl*-**31**, 60886-86-4; *dl*-**32**, 97211-58-0; *dl*-**33**, 97211-59-1; **34**, 3724-55-8; *dl*-**35**, 97211-60-4; *dl*-**36**, 97211-61-5; *dl*-**37**, 59982-09-1; *dl*-**38**, 59974-31-1; **39**, 91-64-5; **40**, 82470-30-2; **41**, 82470-31-3; **42**, 82451-75-0; **43**, 939-18-4; **44**, 930-30-3; **45**, 82470-32-4; **46**, 10481-34-2; **47**, 55106-05-3; **48**, 84983-52-8; **49**, 97211-62-6; **50**, 97211-63-7; **51**, 97211-64-8; *dl*-**52**, 97211-65-9; *dl*-**53**, 97211-66-0; *dl*-**54**, 97211-67-1; *dl*-**55**, 97234-65-6; *dl*-**56**, 97234-66-7; IF, 13873-84-2; I_2, 7553-56-2; F_2, 7782-41-4; BrF, 13863-59-7; Br_2, 7726-95-6; *t*-BuOH, 75-65-0; EtOH, 64-17-5; *i*-PrOH, 67-63-0; CF_3CF_2OH, 75-89-8; NaOEt, 141-52-6; MeOH, 67-56-1.

Mechanism of Amine and Amide Ion Substitution Reactions at the Carbon-Nitrogen Double Bond

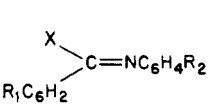
James Elver Johnson,* Abdolkarim Ghafouripour, Mohammad Arfan, Susan L. Todd, and Deborah A. Sitz

Department of Chemistry, Texas Woman's University, Denton, Texas 76204

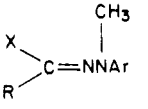
Received January 28, 1985

Reactions of the (*Z*)-hydroximoyl chlorides **3a-e** with secondary amines without solvent at 32 °C for 24 h give high yields of (*Z*)-benzamidoximes **7a-f**. Although the amidoximes **7a-f** do not isomerize under the reaction conditions, they isomerize to the *E* isomers (**8a-f**) by refluxing them in dioxane. Under the same reaction conditions, the (*E*)-hydroximoyl chlorides **4a** or **4b** give no detectable product with secondary amines even after 2 days at 32 °C. In benzene solution the reactions of pyrrolidine with (*Z*)-hydroximoyl chlorides **3a-d** contain both first- and second-order terms in amine. The amine-catalyzed process gives a Hammett correlation with σ with a ρ value of +1.06. The uncatalyzed process is insensitive to changes in para substituents in **3** ($\rho \simeq 0$). The reaction of pyrrolidine with the hydroximoyl bromide **3g** gives an element effect (k_{Br}/k_{Cl}) of 10.1 for the catalyzed process and 26.9 for the uncatalyzed pathway. Lithium pyrrolidide in a benzene-hexane solution reacts rapidly with both **3a** and **4a** (relative reaction rate of **3a**/**4a** = 6 at 21 °C). The reaction of **3a** gives only the (*Z*)-amidoxime **7a** whereas the (*E*)-hydroximoyl chloride **4a** gives a 57:43 mixture of the (*Z*)- and (*E*)-amidoximes (**7a** and **8a**). These results are consistent with a stereoelectronically controlled nucleophilic addition-elimination mechanism for the reaction of **3a** or **4a** with secondary amines and their conjugate bases.

Extensive studies have been carried out on the mechanisms of bimolecular nucleophilic reactions at the C=O and activated C=C bonds, but there are relatively few studies on bimolecular nucleophilic reactions at the C=N bond. A detailed kinetic study on bimolecular substitution at the C=N bond has been carried out by Ta-Shma and Rappoport[1-3] on the reactions of diaryl imidoyl chlorides (**1a**) with secondary amines in benzene[3] or acetonitrile.[2] Depending on the solvent and the nature of the substituents on the aromatic ring attached to carbon, they suggested a pathway involving a nitrilium ion intermediate or a nucleophilic addition-elimination mechanism. The stereochemistry of the imidoyl chloride reactions could not be determined because the *Z* and *E* isomers of these compounds and their substitution products are not known.



1a, X = Cl
b, X = CN



2a, X = Cl
b, X = Br
c, X = OCH_3
d, X = SAr
e, X = OAr

Besides our work,[5,6] two other full reports have appeared on the stereochemistry of bimolecular substitution at the

(1) Ta-Shma, R.; Rappoport, Z. *Tetrahedron Lett.* **1971**, 3813-3816.
(2) Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1976**, *98*, 8460-8467.
(3) Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1977**, *99*, 1845-1858.
(4) Ta-Shma, R.; Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* **1977**, 659-667.
(5) Johnson, J. E.; Nalley, E. A.; Weidig, C. *J. Am. Chem. Soc.* **1973**, *95*, 2051-2052.
(6) Johnson, J. E.; Nalley, E. A.; Weidig, C.; Arfan, M. *J. Org. Chem.* **1981**, *46*, 3623-3629.

0022-3263/85/1950-3348$01.50/0