spectively, and stored under nitrogen. 9,10-Dibromoanthracene (Aldrich) was recrystallized from xylenes before use. 9,10-Diphenylanthracene (Aldrich), methyldiphenylphosphine (Alfa), dimethylphenylphosphine (Aldrich), and triphenylphosphine (Aldrich) were used without further purification. Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a Varian 360L spectrometer. ^{31}P NMR spectra were recorded on a JEOL FX-60Q NMR spectrometer. IR spectra were recorded on a Perkin-Elmer Model 700 spectrometer.

Kinetics of Phosphorane Formation. For all phosphines, the following procedure was employed. A 10-fold or greater excess of the phosphine in benzene solution (prepared and stored under nitrogen, using benzene that was distilled over triphenylphosphine and under nitrogen) was added in the dark, via microsyringe with an 8-in. needle, directly into the bottom of the jacketed cell of a chemiluminescence apparatus containing 2.000 mL of benzene with $[1]_0 = 10^{-3}$ to 10^{-4} M. All runs contained 8×10^{-3} M 9,10-dibromoanthracene (DBA) as added fluorescer. Use of 9,10-diphenylanthracene as added fluorescer did not effect the rates of reaction. The reagents were rapidly mixed via magnetic stirring. The chemiluminescence intensity served as a measure of the instantaneous concentration of 1. The rate of thermal decomposition of 1 was negligibly slow compared to the rate of phosphorane formation. The decay of luminescence was monitored vs. time on a strip-chart recorder. Plots of the natural logarithm of the intensity vs. time were linear for at least 3 half-lives. The values of the pseudo-first-order rate constants were not effected by variations of the initial dioxetane concentration and varied linearly with the initial phosphine concentrations. The second-order rate constants were obtained by dividing the pseudo-first-order rate constants by the initial phosphine concentration.

Formation and Thermal Decomposition of Phosphoranes in C_6D_6. To 0.5 mL of a 5×10^{-2} M C_6D_6 solution of 1 was added an equal molar amount of phosphine. After the yields of the phosphorane were determined by ^{1}H NMR, the phosphoranes were heated at 60 °C in tightly capped NMR tubes until the NMR spectra showed no remaining phosphoranes. The products were tetramethylethylene oxide and the corresponding phosphine oxide as determined by integration of the NMR spectrum in each case. Tetramethyloxirane was identified by GC analysis. After the solvent and volatile components were removed, the solid residues were recrystallized from CCl_4/petroleum ether and identified as the phosphine oxides, on the basis of melting points and spectral data (IR, ^{1}H NMR, ^{31}P NMR). The data are summarized in Table VI.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, to NIH (RR 09210), the Camille and Henry Dreyfus Foundation, and to the Georgia State Research Fund.

Registry No. 1, 35856-82-7; **1d**, 88635-83-0; **2a**, 1486-28-8; **2b**, 3947-90-8; **2c**, 672-66-2; **2d**, 88635-84-1; **2e**, 603-35-0; **3a**, 88635-85-2; **3b**, 88635-86-3; **3c**, 88635-87-4; **3d**, 88635-88-5; **3e**, 49595-63-3; **4a**, 2129-89-7; **4b**, 3947-89-5; **4c**, 10311-08-7; **4d**, 88635-89-6; D_2, 7782-39-0.

α-Chloro Ketoximes as Precursors of Nitrosoalkenes: Preparation, Stereochemistry, and Conformation

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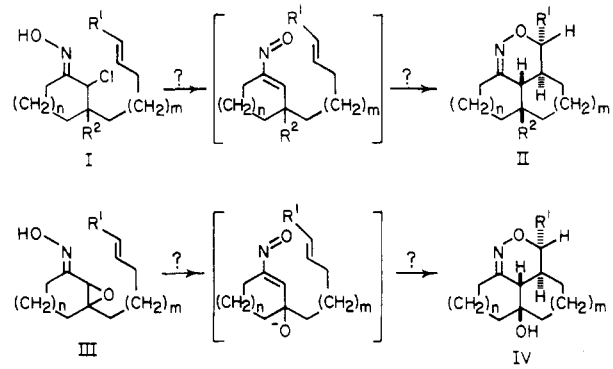
The ability of α-chloro and α,β-epoxy ketoximes and silyloximes of substituted cyclohexanones to serve as precursors for nitrosoalkenes has been investigated. α-Chloro ketoximes produced nitrosoalkenes efficiently with triethylamine regardless of oxime geometry or disposition of the chlorine atom. α-Chloro silyloximes were less efficient in production of nitrosoalkenes with tetrabutylammonium fluoride and led to a faster decay of reactive species. Nitrosoalkenes that cannot tautomerize are extremely stable and efficiently generated even from silyloximes. α,β-Epoxy ketoximes were shown to be incapable of generating nitrosoalkenes in detectable amounts under several conditions. A striking dependence of oxime geometry on oximation conditions was discovered. (*tert*-Butyldimethyl)silyloxime (*E*)-*trans*-**12** showed an unusual preference for the conformation in which both substituents assume axial orientations.

The transient existence of nitrosoalkenes has been known to organic chemists since the turn of the century. As early as 1898 nitrosoalkenes were postulated as intermediates in the reaction of α-halo oximes with nucleophilic bases.[1] Since then many groups have made good use of this method for the nucleophilic functionalization of carbons α to ketones with amines,[2] enamines,[3] alcoholates,[4] thiolates,[4] β-dicarbonyls,[2a,5] enolates,[6] phosphines,[7] sulfonium ylides,[8] and organomagnesium, [5a,9] -zinc,[9] and -lithium[10] reagents. Most of these nucleophiles are sufficiently

Scheme I



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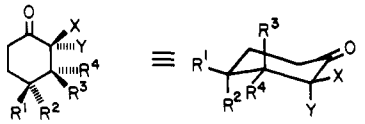
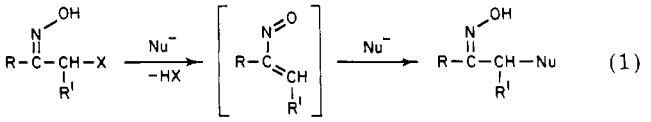
0022-3263/84/1949-0798$01.50/0

Chart I



1, $R^1 = R^2 = R^3 = R^4 = X = H$; $Y = Cl$
cis-2, $R^1 = t$-Bu; $R^2 = R^3 = R^4 = Y = H$; $X = Cl$
trans-2, $R^1 = t$-Bu; $R^2 = R^3 = R^4 = X = H$; $Y = Cl$
cis-3, $R^4 = Me$; $R^1 = R^2 = R^3 = X = H$; $Y = Cl$
trans-3, $R^4 = Me$; $R^1 = R^2 = R^3 = Y = H$; $X = Cl$
4, $R^3 = Me$; $R^4 = (E)$-4-hexenyl;
$R^1 = R^2 = H$, X or Y = Cl

basic to induce the 1,4-elimination of HX from the halo oxime (eq 1). The fleeting blue color reported in these



(1)

examples has been convincingly attributed to the intermediacy of nitrosoalkenes by independent isolation,[11] spectroscopic characterization[12] and kinetic and stereochemical studies.[13,14]

Recently, Gilchrist,[15] Viehe[12] and Iskander[16] have reported the interception of nitrosoalkenes as 4π components in [4 + 2] cycloaddition reactions.[17] General application of this potentially useful process is hampered by the following limitations: (1) only nucleophilic olefins (furans, dienes, enamines) give cycloadducts,[14] (2) electron-withdrawing substituents (phenyl, ester, ketone) on the nitrosoalkene are necessary for sufficient reactivity[12] (1-nitrosocyclohexene does not react with cyclopentadiene[15d]), and (3) a 5–20-fold excess of olefin is required. In addressing the limitations enumerated above we have initiated a program to investigate the feasibility of intramolecular nitrosoalkene olefin cycloadditions (INAOC) of the type shown in Scheme I. The viability of α,β-epoxy ketone oximes as precursors to nitrosoalkenes was first suggested by Corey et al.[18] who found that organocuprates react to give products formally resulting from epoxide opening at the α-carbon.[19] The actual intermediacy of nitrosoalkenes at any level of concentration was not proven.

Two important criteria must be met to successfully realize the reactions proposed: (1) the efficient, in situ generation of stable nitrosoalkenes and (2) selection of a dienophilic appendage with sufficient reactivity and proximity. We report herein the results of an initial study that defines the structural, stereochemical, and experimental parameters necessary to satisfy the first criterion.

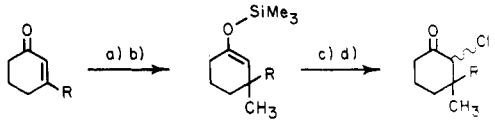
Table I. Selected Spectroscopic Data for α-Chloro Ketones

α chloro ketone	δ H-C(2)	$J_{2-3(cis)}$, Hz	$J_{2-3(trans)}$, Hz	$\nu_{C=O}$, cm^{-1}
cis-2	4.54	6.04	12.33	1725
trans-2	4.25	0	0	1715
cis-3	4.13	3.0		1715
trans-3	4.07		9.8	1727
4	4.03/ 4.14			1720

Results

A. α-Chloro Ketoximes. The 1,4-elimination of α-halo oximes is by far the most common method of generation of nitrosoalkenes.[14] Since systems such as I (Scheme I) will contain conformation-fixing groups, we anticipated the need to determine the effect on nitrosoalkene generation of (1) orientation of the chlorine atom, (2) geometry of the oxime, and (3) the number of β-hydrogens. The third parameter is significant since it provides a nonproductive pathway for consumption of nitrosoalkene by tautomerization.[2c,20]

1. Synthesis of α-Chloro Ketones. The α-chloro oximes[21] used in this study were all prepared by oximation of the α-chloro ketones in Chart I. A mixture of *cis*- and *trans*-2 was prepared according to Thorpe and Warkentin[22] and was easily separated by flash chromatography. *cis*- and *trans*-3 were prepared as a 1:2 mixture (66% overall) in two steps from 2-cyclohexenone (**6a**) as shown in eq 2.



(2)

6a 5 (89%) 3 (74%) R = H
6b 7 (87%) 4 (92%) R = (*E*)-4-hexenyl

(a) R = H, $CH_3MgBr/CuI/Et_2O/-30$ °C; R = (*E*)-4-hexenyl. $Li(CH_3)_2Cu/Et_2O/-60$ °C. (b) $Me_3SiCl/Et_3N/HMPA/-60$ °C → RT; (c) $CH_3Li/THF/RT$; (d) *N*-chlorosuccinimide/−70 °C

They were similarly obtained isomerically pure by flash chromatography. The β-disubstituted ketone **4** was prepared in an analogous fashion from 3-((*E*)-4-hexenyl)-2-cyclohexen-1-one,[23] **6b**, eq 3. The 1:1 mixture of diastereomers of **4** could not be separated easily by chroma-

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Table II. Preparation of α-Chloro Ketoximes

entry	α-chloro ketone	method[a]	product	yield, %	E/Z[b] ratio
1	*cis*-2	A	*cis*-9	34	>95/<5
2	*cis*-2	B	*cis*-9	82	>95/<5
3	*cis*-2	C	*cis*-11	92	>95/<5
4	*trans*-2	A	*trans*-9	63	<5/>95
5	*trans*-2	B	*trans*-9	89	83/17
6	*cis*-3	A	*cis*-10	71	18/82
7	*cis*-3	B	*cis*-10	82	80/20
8	*cis*-3	C	*cis*-12	91	50/50
9	*trans*-3	B	*trans*-10	53	>95/<5
10	*trans*-3	C	*trans*-12	85	>95/<5
11	4	C	13	82	>95/<5
12	1	B	8	56	81/19

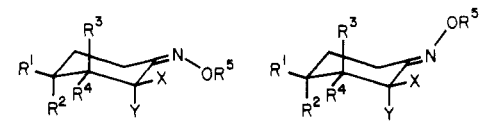
[a] See text. [b] Determined by integration of H-C(2) in ^{1}H NMR.

tography and was used as such. However, we suspected (vide infra) that in both isomers the chlorine atom assumes a single orientation. Chlorination of ketone enolates[24] with *N*-chlorosuccinimide is an excellent reaction, giving high yields even in the presence of enol ethers.[25]

The assignment of stereochemistry and conformation in 1-4 was made by a combination of ^{1}H NMR and IR spectroscopy, relying on well-established trends in vicinal interproton coupling[26] and carbonyl stretching frequencies.[27] Table I summarizes the data that is diagnostic for these compounds.[28] An axially oriented chlorine atom (*trans*-2 and *cis*-3) shows a higher IR stretch and its geminal equatorially oriented proton shows smaller vicinal couplings and vice versa. Observation of a single carbonyl IR stretch for 4 suggests a single orientation of the α-chlorine, but assignment is difficult.

2. Oximation and Silyloximation. The rate of oxime formation from ketones exhibits a pronounced dependence on the pH of the medium.[29] The lability of the products under basic conditions precluded reaction above pH 8. Extensive and now classic studies[30] have demonstrated a rate maximum around pH 5, and we accordingly subjected the chloro ketones to oximation with hydroxylamine hydrochloride and sodium acetate in methanol (method A). The results of various oximation reactions are compiled in Table II. When the chlorine atom is rigidly held in the equatorial position, entry 1, reaction under these conditions gives the *E* oxime in poor yield (Chart II). If, however, the chlorine atom is axial (entries 4 and 6), the oximation is more efficient and produces predominantly the *Z* isomer! We therefore sought a more efficient, generally applicable procedure and performed oximations under acidic conditions with potassium acetate in acetic acid, method B. Entries 2, 5, 7, 9, and 12 demonstrate that this method is more widely useful and gives better yields than method A. Also, quite surprisingly, the *E* oxime is formed selectively even when the chlorine is axial (entries 5 and 7) (see Discussion). The assignment of geometry of the oxime was

Chart II



8, $R^1 = R^2 = R^3 = R^4 = R^5 = X = H$; Y = Cl
cis-9, R^1 = *t*-Bu; $R^2 = R^3 = R^4 = R^5 = Y = H$; X = Cl
trans-9, R^1 = *t*-Bu; $R^2 = R^3 = R^4 = R^5 = X = H$; Y = Cl
cis-10, R^4 = Me; $R^1 = R^2 = R^3 = R^5 = X = H$; Y = Cl
trans-10, R^4 = Me; $R^1 = R^2 = R^3 = R^5 = Y = H$; X = Cl
cis-11, R^1 = *t*-Bu; $R^2 = R^3 = R^4 = Y = H$; R^5 = *t*-BuMe$_2$Si; X = Cl
cis-12, R^4 = Me; $R^1 = R^2 = R^3 = X = H$; R^5 = *t*-BuMe$_2$Si; Y = Cl
trans-12, R^3 = Me; $R^1 = R^2 = R^3 = X = H$; R^5 = *t*-BuMe$_2$Si; Y = Cl
13, R^3 = Me; R^4 = (*E*)-4-hexenyl; $R^1 = R^2 = X = H$; R^5 = *t*-BuMe$_2$Si; Y = Cl

Table III. Selected Spectroscopic Data for α-Chloro Ketoximes

compound	δ H-C(2)	δ H-C(6) equatorial	$J_{2-3(cis)}$, Hz	$J_{2-3(trans)}$, Hz
(*E*)-*cis*-9	4.70	3.24	5.1	10.3
(*E*)-*cis*-11	4.46	3.37	5.4	10.2
(*E*)-*trans*-9	4.79	3.27	0	0
(*Z*)-*trans*-9	5.64	2.35	0	0
(*E*)-*cis*-10	4.55	3.18	2.1	
(*Z*)-*cis*-10	5.45	2.25	2.3	
(*E*)-*cis*-12	4.56	3.25	0	
(*Z*)-*cis*-12	5.49	2.27	0	
(*E*)-*trans*-10	4.26	2.65[a]		5
(*E*)-*trans*-12	4.34	3.11		2.4
(*E*)-13	3.99	3.26		

[a] Both axial and equatorial protons in this resonance.

simple due to the strong anisotropic deshielding by the oxime oxygen on the equatorial protons[31] at C(2) or C(6), (ca. ~0.9 ppm). The relevant chemical shifts and vicinal coupling constants (vide infra) for these protons are collected in Table III.

We then turned our attention to the preparation of silyloximes,[32] which were expected to offer several advantages. Primarily, we were interested in generating nitrosoalkenes under neutral conditions to suppress unwanted

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side reactions. Secondly, it was essential that we develop an oximation method for α-chloro ketones possessing acid-labile functional groups. Given the limitations on pH mentioned above and the unsatisfactory results in buffered, protic media, silyloximes offered a novel solution.

Thus, treatment of α-chloro ketones in chloroform solution with 2 equiv of O-*tert*-butyldimethylsilyl hydroxylamine[33,34] and activated 4-Å molecular sieves (method C) produced the silyloximes in excellent yield (Table II, entries 3, 8, 10, and 11). The progress of the reactions could be monitored by IR or TLC, and the products were stable to silica gel chromatography and distillation. This procedure can thus be recommended for oximation of acid- or base-sensitive carbonyl compounds, since desilylation can be effected with tetra-*n*-butylammonium fluoride (TBAF).

The spectroscopic identification of silyloximes was analogous to their protic counterparts with one remarkable exception (Table III). For α-chloro ketone *cis*-**2** and its derivatives (*E*)-*cis*-**9** and (*E*)-*cis*-**11**, the diequatorial nature of both *tert*-butyl and chlorine moieties is assured by the large, diaxial, vicinal-proton coupling constants (10.2–12.3 Hz). Similarly, *trans*-**3** exhibits such a coupling (9.8 Hz) as expected, but its derivatives (*E*)-*trans*-**10** and (*e*)-*trans*-**12** display a marked diminution in magnitude for this data. We suggest that in these derivatives the equilibrium concentration of the ring-flipped conformer with both groups axial becomes significant or dominant. We term this the *vinylogous anomeric effect* and will address its origin and implications in the Discussion section.

3. Generation of Nitrosoalkenes. The eventual success of INAOC reactions relies on the ability to efficiently generate solutions of stable nitrosoalkenes. We chose to evaluate efficiency and stability by generating nitrosoalkenes in a UV–vis spectrometer. Efficiency was measured in terms of a pseudoextinction coefficient (ϵ) from the usual Beer's law equation ($A = \epsilon cl$) for the n–π* absorption at 700–720 nm. This absorption is relatively weak, (ϵ = 20–56 for nitrosoalkenes,[12] ϵ = 10–60 for nitrosoalkanes,[35a] ϵ = 40–70 for nitrosoarenes[35b]) and since extinction coefficients for pure nitrosocyclohexenes are not known,[36] concentrations cannot be measured. By substituting the initial concentration of α-chloro oxime, ϵ reflects the fraction of α-chloro oxime (invisible at 720 nm) that was converted to nitrosoalkene. The stability of nitrosoalkenes was evaluated by measuring the rate of decay of the n-π* absorption at room temperature.

Thus, a solution of the substrate in a Pyrex cuvette was treated with either triethylamine[37] (oximes) or TBAF (silyloximes) and the spectrum was recorded. The results are compiled in Table IV. With the exception of entry 4, the generation of nitrosoalkene was instantaneous. Entries 1–6 for α-chloro oximes are grossly similar, suggesting little dependence of reaction efficiency on oxime geometry or disposition of the α-chlorine atom (axial vs. equatorial). The ϵ were indicative of a reasonably efficient reaction. Half-lives were consistent with the expected lability of nitrosoalkenes and provide a lower limit to INAOC cyclization rates for synthetically useful purposes.

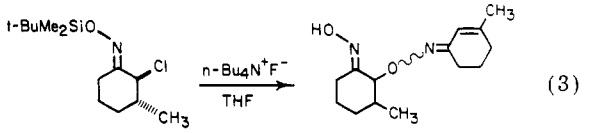
Table IV. Generation of Nitrosoalkenes[a]

entry	substrate	concn, M	λ_{max},[b] nm	ϵ	$t_{1/2}$, min
1	**8**	0.050	716	19	2
2	(*E*)-*cis*-**9**	0.049	716	26.0	10
3	(*E*)-*trans*-**9**	0.050	716	27.6	9
4	(*Z*)-*trans*-**9**	0.049	716	20.6	15[c]
5	(*E*)-*trans*-**10**	0.052	716	28.4	10
6	(*E*)-*cis*-**10**	0.050	710	22.0	12
7	(*E*)-*cis*-**11**	0.052	700	9.1	30
8[d]	(*E*)-*cis*-**11**	0.053	720	14.0	3
9[e]	(*E*)-*cis*-**11**	0.061	706	7.6	*f*
10[g]	(*E*)-*cis*-**11**	0.047	707	9.8	120[h]
11	(*E*)-*cis*-**12**	0.049	716	11.8	2
12[e]	(*E*)-*cis*-**12**	0.064	707	11.0	12
13[e]	(*E*)-*trans*-**12**	0.061	710	13.0	10
14	**13**	0.044	716	40.9	450[h]
15	**13**	0.040	710	43.1	900[h]

[a] All experiments were performed in a 1-cm Pyrex cuvette in CH_3CN unless otherwise specified. Triethylamine was used with oximes **8–10**, TBAF with silyloximes **11–13**. [b] ±2 nm. [c] Maximum absorbance was reached after 2 min. [d] Reaction performed in THF. [e] 0.5 equiv of TBAF was used. [f] Very slow decay. [g] TBAF trihydrate was used in this experiment without azeotropic drying. [h] $t_{1/2}$ was extrapolated from slow decay.

Of the various plausible fates for nitrosoalkenes, we considered tautomerization to be significant (vide infra) and sensitive to experimental conditions. Thus we examined the generation of nitrosoalkenes under "neutral conditions" from α-chloro silyloximes with TBAF. Entries 7, 8, and 10 are representative of many experiments. In general, the efficiency of nitrosoalkene generation was 2–3 times lower and the half-lives 3–5 times shorter than with simple oximes.[38] Entries 9, 12, and 13 are experiments performed with 0.5 equiv of TBAF on the basis of silyloxime (ϵ was calculated based on TBAF). The efficiency of generation and stability of resulting solutions improved marginally. Further, use of TBAF without azeotropic removal of crystal water[39] (entry 10) improved stability but not efficiency. These results suggested that an impurity, not F^-, was responsible for the decomposition of nitrosoalkenes.

This suspicion was supported by the results of a preparative experiment with (*E*)-*trans*-**12** and also entry 14. The principle source of decay of nitrosoalkene was shown to be tautomerization by isolation in ca. 80% yield of dimeric oxime **14**, eq 3. Further, when tautomerization



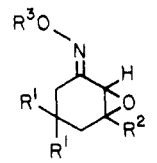
(*E*)-*trans*-**12** **14** (3)

was blocked, as in **13** (entry 14), the nitrosoalkene was very efficiently generated (ϵ = 43) and remarkably stable.

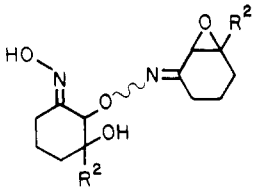
B. α,β-Epoxy Ketoximes. The ability of α,β-epoxy ketone oximes to serve as nitrosoalkene precursors has never been unambiguously established. Preliminary experiments failed to manifest the reaction in Scheme I using substrates **15** and **16** prepared by epoxidation[40] (70–93%)

(33) West, R.; Boudjouk, P. *J. Am. Chem. Soc.* **1973**, *95*, 3983.
(34) Prepared by adaptation of the procedure of Duboudin: Duboudin, F.; Frainnet, E.; Vinion, G.; Dabescat, F. *J. Organomet. Chem.* **1974**, *82*, 41. See supplementary material.
(35) (a) Rao, C. N. R.; Bhaskar, K. R. In "Chemistry of the Nitro and Nitroso Groups"; Feuer, H., Ed.; Interscience: New York, 1969; Part 1; pp 147–152. (b) Tanaka, M.; Tanaka, J.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 766.
(36) Ciattoni[11a] measured the λ_{max} of 1-nitrosocyclohexene but not the extinction coefficient.
(37) DBU gave a voluminous precipitate and pyridine reacted only slowly.
(38) Preliminary experiments with the (trimethylsilyl)oxime of (*E*)-*cis*-**2** were promising (λ_{max} 710 (25), $t_{1/2}$ = 60 min) but very difficult to reproduce. The variable quality of TBAF was suspected, but neither changing the supplier nor recrystallization improved the outcome.
(39) It has been recently suggested that attempted removal of the waters of hydration results in decomposition to bifluoride, butene, and tri-*n*-butylamine: Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112.

and oximation (method A, 79–92%) of the corresponding ketones.[23] Under no conditions (K_2CO_3/CH_3CN, KH/THF, *n*-BuLi, THF) was a blue color observed. With potassium bases several new products were formed which were identified as diastereomeric dimers **20** and **21**.



15, $R^1 = R^3$; R^2 = 4-pentenyl
16, $R^1 = R^3 = H$; R^2 = (*E*)-4-hexenyl
17, $R^1 = R^2 = CH_3$; $R^3 = H$
18, $R^1 = R^2 = CH_3$; R^3 = *t*-BuMe$_2$Si

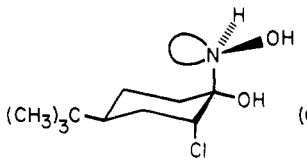


20, R^2 = 4-pentenyl
21, R^2 = (*E*)-4-hexenyl

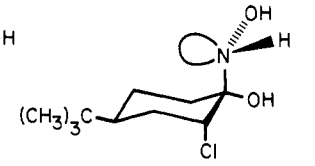
UV-vis experiments with simpler α,β-epoxy ketoximes **17** and **18** under a variety of conditions (**17**: Et_3N, DBU; **18**: *n*-$Bu_4N^+F^-$, Me_3SiOTf, Me_3SiI) failed to show any absorption >700 nm.

Discussion

A. α-Chloro Ketoximes. 1. Geometry. The divergent stereochemical behavior of α-chloro ketones under different oximation conditions is noteworthy. At neutral pH (method A) *trans*-**2** and *cis*-**3** (axial Cl) gave predominantly the *Z* oximes and *cis*-**2** (equatorial Cl) reacted very slowly to give (*E*)-*cis*-**9**. Jencks[30b] has convincingly shown that under these conditions the addition of hydroxylamine is fast and the rate-determining step is the acid-catalyzed dehydration of the carbinolamine intermediate. A priori one may consider species i and ii[41] (for *trans*-**2**) as the



i



ii

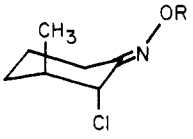
limiting reactive intermediates. Collapse of i and ii leads directly to the conjugate acids of (*Z*)-*trans*-**9** and (*E*)-*trans*-**9** by elimination of water assisted by the nitrogen lone pair. Since i and ii are formed in a fast, preequilibrium step, the predominance of *Z* oximes may arise from (1) a faster rate of collapse at i, (2) comparable rates of collapse but predominance of i at equilibrium, or (3) an ex post facto equilibration of oximes that favors *Z*.

Subjection of oxime mixtures enriched in the *E* isomer to the reaction conditions of method A led to partial or complete destruction of the *E* isomer selectively. Thus, if a kinetic preference for the production of *Z* isomer exists, it is difficult to factor out from the inherent instability of the *E* isomer under the reaction conditions. The source of instability is apparently a greater tendency to undergo substitution at C(2) as judged by the incorporation of methanol and acetate in the reaction products. This may arise from either a greater acidity of the *E* isomer[42] or a greater susceptibility to nucleophilic attack.

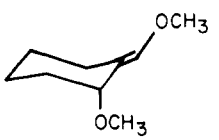
Under acidic conditions (method B), *E* oximes predominated and rates were qualitatively independent of the disposition of the chlorine atom. The well-known, bell-shaped pH-rate curve for oximation[29] has been interpreted as a change in rate-determining step. at low pH, dehydration becomes rapid and less free hydroxylamine is present. Thus, the explanations for predominance of *E* oximes are limited to either (1) a faster rate of formation of i or (2) ex post facto equilibration that favors *E*. Subjection of (*Z*)-*trans*-**9** (>95% *Z*) to the conditions of method B resulted in the partial isomerization to a 62:38 *E*/*Z* mixture of *trans*-**9**.[43] Since isomerization of oximes at low pH is well documented,[44] this is not surprising; the preference for *E* geometry, however, merits comment.

One might have anticipated that the *Z* isomer would predominate at equilibrium since it enjoys an additional anomeric stabilization[45] of the nitrogen sp^2 lone pair by the $\sigma^*_{C(2)-C(1)}$ bond.[46,47] Indeed, such effects have been documented for imidates[49a] and hydroximidoyl chlorides,[49b] but are not general.[50] We suggest that minimization of net dipole moment is the dominant factor governing these equilibria.[51]

2. Conformation. The conformation of rigid and flexible alicyclic ketoximes has been investigated in detail by ^1H and ^{13}C NMR[31,52] spectroscopy. In general the ketoximes assume the same conformation as the parent ketones except when the α- and α′-carbons are sterically encumbered. The conformation of α-halo ketoximes has not been studied systematically. We have found that for either oxime of *cis*-**9**, **-10**, **-11**, or **-12** and *trans*-**9**, the conformations are similar to the parent ketones as reflected in the vicinal J_{2-3} coupling constants. In (*E*)-*trans*-**10** and **-12**, however, the coupling constant drops markedly from 9.8 Hz (*trans*-**3**) to 5–2.4 Hz, respectively. This trend is explained by an increasing equilibrium proportion of the ring-flipped conformer with both substituents axial. This



E-*trans*-**9**: R = H
E-*trans*-**11**: R = *t*-BuMe$_2$Si



22

phenomenon is termed the *vinylogous anomeric effect* since its origin can be seen as the n–σ* interaction of the oxygen lone-pair electrons transmitted through the $\pi^*_{C=N}$.

(40) Wasson, R. L.; House, H. O. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. 4, p 552.
(41) The products of axial attack are shown, but identical arguments can be made for the adducts from equatorial attack.
(42) No blue color was detected, only the rapid precipitation of sodium chloride.
(43) Isomerization also occurred on silica gel or during distillation.
(44) Metzger, H. In "Methoden der Organischen Chemie"; Mueller, E., Ed.; George Theime Verlag: Stuttgart, 1968; Band X/4; pp 282–294.
(45) For an excellent, recent discourse, see: Kirby, A. J. "The Anomeric Effect and Related Stereochemical Effects at Oxygen"; Springer-Verlag: Berlin, 1983.
(46) Baldwin has recently described the kinetic consequences of such an interaction in the reactions of quinone monooxime ethers: Baldwin J. E.; Norris, R. K. *J. Org. Chem.* **1981**, *46*, 697.
(47) This assumes that $\sigma^*_{C(2)-C(1)}$ is a better acceptor bond[48] than $\sigma^*_{C(a)-C(1)}$ by virtue of the chlorine atom. The effect, therefore, is expected to be weak.
(48) (a) Epiotis, N. D.; Yates, R. L.; Larson, J. R.; Kirmaier, C. R.; Bernardi, F. *J. Am. Chem. Soc.* **1977**, *99*, 8379. (b) Reference 45, pp 75–77.
(49) (a) Fodor, G.; Phillips, B. A. In "The chemistry of Amidines and Imidates"; Patai, S., Ed.; Wiley: New York, 1975; p 132. (b) Johnson, J. E.; Silk, N. M.; Nalley, E. A.; Arfan, M. *J. Org. Chem.* **1981**, *46*, 546.
(50) (a) McCarthy, D. G.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1080, 1085. (b) Meese, C. O.; Walter, W.; Berger, M. *J. Am. Chem. Soc.* **1974**, *96*, 2259.
(51) For a systematic study on the effects of remote substituents on quinone monooxime geometry, see: Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1966**, *19*, 841; **1969**, *22*, 935; **1971**, *24*, 1449; **1972**, *25*, 1907.
(52) (a) Geneste, P.; Durand, R.; Kamenka, J. M.; Beierbeck, H.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1978**, *56*, 1940. (b) Fraser, R. R.; Dhawan, K. L.; Taymaz, K. *Org. Magn. Reson.* **1978**, *11*, 269.

Lessard[53] has observed a similar effect operating in enol ether **22** in which ΔG_0 (axial − equatorial) is >−1.0 kcal. The difference in magnitude of the effect between (*E*)-*trans*-**10** and -**12** may arise from the superior donor property of silicon compared to hydrogen.[54] Further evidence for the existence of (*E*)-*trans*-**10** as an equally balanced mixture of conformers comes from the observation of a *two-proton* multiplet at δ 2.65 corresponding to the C(6) methylene group. In all other *E* oximes (including (*E*)-*trans*-**12**) the equatorial H-C(6) is unique at ca. δ 3.28. Further exploration of the magnitude, generality, and synthetic utility of this effect is underway.

3. Nitrosoalkenes. The lack of dependence of nitrosoalkene generation on oxime geometry or chlorine orientation allows considerable latitude in the preparation of precursors. At the same time the viability of "equatorially fixed" α-chloro ketoximes is surprising. In light of the preceding discussion it may be expected that deprotonation of the oxime also increases the equilibrium proportion of reactive conformers (twist-boat?).

The efficiency of generation and stability of nitrosoalkenes clearly depended upon substrate structure and reaction conditions. As a qualitative guide we consider ε of ca. 30 to indicate highly efficient conversion to nitrosoalkene. This standard was approached by most substrates upon reaction with Et_3N, but the $t_{1/2}$ for the resulting solutions was ca. 10 min. The situation was worse with silyloximes, which produced nitrosoalkenes with poorer efficiency (ε = 7–14) and shorter lifetimes ($t_{1/2}$ = 3–10 min). Thus, in order for INAOC reactions to be synthetically useful, cycloaddition must be very fast ($t_{1/2}$ < 10 min at 20 °C). This sets severe limitations on the nature of the dienophilic group. However, Gilchrist[14] has pointed out that the optimum conditions for intermolecular [4 + 2] cycloadditions of nitrosoalkenes employ the slow release (heterogeneous, weak base) of reactive heterodiene to suppress nonproductive bimolecular processes. While this will be particularly true for *intramolecular* reactions, our results suggest that the principle decomposition pathway for nitrosoalkenes is a unimolecular process that may be subject to catalysis. Alternatively, *nitrosoalkenes that are incapable of tautomerization are very stable* and can be generated with excellent efficiency, even from silyloximes. Thus, the reported instability of 1-nitrosocyclohexene[11a] results, most likely, from tautomerization, not dimer- and polymerization as suggested. These substrates are the logical first choices for the examination of INAOC cycloadditions. The stability of the nitrosoalkene from **13** suggests that either more strenuous conditions or more reactive dienophiles are needed.

The failure of α,β-epoxy oximes to produce measurable amounts of nitrosoalkenes suggests that their use in INAOC reactions may be limited (vide supra). At present we are exploring the potential for α,β-epoxy nitrones to serve as precursors in intramolecular nitrosonium ion–olefin cycloadditions.[55] These results, as well as the successful INAOC reactions, will be reported elsewhere.

Experimental Section

General Methods. Proton NMR spectra were recorded on either Varian Model EM-390 (90 MHz), Varian Model HA-220 (220 MHz), Varian Model XL-200 (200 MHz) or Nicolet Model NT-360 spectrometers in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in δ with respect to tetramethylsilane (δ 0.0) or chloroform (δ 7.27) as internal standards, multiplicities are indicated by s (singlet), d (doublet), t (triplet), qa (quadruplet), m (multiplet) and br (broadened). Data are given as follows: chemical shift (multiplicity, coupling constant, integrated intensity, assignment). Infrared (IR) spectra were obtained on either a Perkin Elmer Model 237B or a Nicolet Model 7199C FT IR spectrometer in chloroform solutions. Peaks are reported in cm^{-1} with the following intensities s (strong, 66–100%), m (medium, 33–66%), weak (0–33%), and sh (shoulder). Mass spectra were obtained on a Varian MAT CH-5 spectrometer with ionization voltages of 10 and 70 eV. Data are reported for *m/z* (intensity relative to base = 100). High-resolution and fast atom bombardment spectra were obtained on Varian MAT-731 or MAT-311A spectrometers. UV-vis spectra were recorded on a Perkin Elmer Model 551 spectrophotometer.

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are corrected. Bulb-to-bulb distillations were done on a Büchi GKR-50 Kugelrohr apparatus, boiling points refer to air-bath temperatures and are uncorrected. Analytical TLC was performed on precoated Merck silica gel 60 plates with QF-254 indicator. Solvent mixtures are usually hexane/ethyl acetate (H–EA) blends. Column chromatography was performed by the method of Still[56] using Woelm 32–63-μm silica gel. Analytical gas chromatography was performed on a Varian Model 3700 chromatograph fitted with a flame ionization detector, column 11% QF-1 on 60–80 Chromosorb G (6 ft × $^1/_8$ in.). Elemental combustion analyses were performed by the University of Illinois Microanalytical Service Laboratory.

"Dry" solvents were distilled freshly before use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Benzene, acetonitrile, triethylamine, and hexamethylphosphoramide (HMPA) were distilled from powdered calcium hydride. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride and filtered through basic alumina Activity I prior to use. Chloroform was passed through neutral alumina Activity I prior to use. Acetonitrile used in UV–vis experiments was Aldrich Gold Label. Methyllithium was purchased from Aldrich and titrated by double titration. *N*-Chlorosuccinimide was recrystallized from benzene. Copper(I) iodide was purified according to Kauffman.[57] Tetrabutylammonium fluoride trihydrate was purchased from both Aldrich and Fluka and was recrystallized under nitrogen from THF/Et_2O at −40 °C. All other reagents were used as received or distilled as necessary. All air- or moisture-sensitive reactions were conducted in oven (140 °C) or flame-dried glassware under at atmosphere of dry nitrogen. Brine refers to saturated aqueous sodium chloride solution.

3-Methyl-1-(trimethylsiloxy)-1-cyclohexane (5). A stirred solution of 41.4 mL of methyl magnesium bromide (2.9 M in Et_2O, 120 mmol) in a 500-mL Morton flask was diluted with 100 mL of dry THF and treated with 1.52 g (8.0 mmol) of copper(I) iodide in one portion at room temperature and immediately cooled to −30 °C. The resulting mixture was treated dropwise with a solution of 7.69 g (80.0 mmol) of 2-cyclohexen-1-one in 20 mL of dry THF such that the temperature never rose above −30 °C. After being stirred for 30 min at −40 to −50 °C, the mixture was cooled to −60 °C whereupon 15.3 mL (15.8 g, 88 mmol) of HMPA, 22.3 mL (16.2 g, 160 mmol) of triethylamine, and 20.2 mL (17.4 g, 160 mmol) of chlorotrimethylsilane were added. The mixture was stirred at −70 °C for 1 h and allowed to warm to 20 °C over 1 h (GC analysis showed complete silylation of the enolate). The reaction mixture was poured onto 300 mL of saturated aqueous $NaHCO_3$ solution and was extracted with pentane (3 × 400 mL). The individual organic extracts were washed in series, 100-mL each of saturated aqueous $NaHCO_3$ solution and brine. The combined extracts were dried (K_2CO_3) and concentrated by rotary evaporation, and the residue was distilled at aspirator vacuum to afford 13.08 g (89%) of silyl enol ether **5**: bp 94–96 °C (35 torr); ^1H NMR (90 MHz) δ 4.77 (doublettoid, *J* = 1 Hz, 1 H, H-C(2)), 2.4–1.5 (7 H), 1.07 (d, *J* = 7 Hz, CH_3-C(3)), 0.32 (s, 9 H, $(CH_3)_3Si$);

(53) (a) Lessard, J.; Viet, M. T. P.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 1015. (b) Viet, M. T. P.; Lessard, J.; Saunders, J. K. *Tetrahedron Lett.* **1979**, 317. See also: (c) Zefirov, H. S.; Baranenkov, I. V. *Tetrahedron* **1983**, *39*, 1765.

(54) Pauling electronegativity: Si, 1.8; H, 2.1.

(55) (a) Schatzmiller, S.; Gygax, P.; Hall, D.; Eschenmoser, A. *Helv. Chim. Acta* **1973**, *56*, 2961 and references therein. (b) Riediker, M.; Graf, W. *Ibid.* **1979**, *62*, 205, 1586, 2053.

(56) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(57) Kauffman, G. B.; Pinnell, R. P. *Inorg. Synth.* **1960**, *6*, 3.

IR 2910 (s), 2840 (m), 1660 (s), 1450 (m), 1355 (m), 1250 (s), 1175 (s), 1040 (m), 985 (m), 960 (m), 890 (s), 850 (s).

***cis*- and *trans*-2-Chloro-3-methylcyclohexan-1-one (*cis*-3 and *trans*-3).** To a cold (0 °C) magnetically stirred, solution of 2.50 g (13.6 mmol) of **5** in 20 mL of dry THF was added 10.1 mL of methyllithium (1.48 M in Et_2O, 14.9 mmol) via syringe. The solution was allowed to warm to room temperature and after stirring for 1 h was transferred via cannula to a slurry of 2.16 g (16.22 mmol) of *N*-chlorosuccinimide in 40 mL of THF at such a rate that the temperature never rose above −50 °C. The reaction was quenched after stirring for 40 min at −70 °C by the addition of 30 mL of saturated aqueous $NaHCO_3$ solution. The mixture was warmed to room temperature, poured onto 30 mL of water, and extracted with pentane (3 × 75 mL). The individual extracts were washed in series with water (2 × 75 mL) and brine (75 mL). The combined extracts were dried ($MgSO_4$) and concentrated by rotary evaporation to leave 2.12 g of crude chloro ketones. Purification by silica gel column chromatography with benzene yielded 498 mg of *cis*-**3** and 982 mg of *trans*-**3** (total yield 1.480 g, 74%). Analytical data was obtained from a distilled (Kugelrohr) sample.

***cis*-3**: bp 70 °C (4 torr); ^{1}H NMR (200 MHz) δ 4.20 (d, *J* = 3.0 Hz, 1 H, H-C(2)), 2.90–2.80 (m, 1 H, axial H-C(6)), 2.32–2.18 (m, 2 H), 2.05–1.84 (m, 1 H), 1.80–1.57 (m, 3 H), 1.09 (d, *J* = 6.7 Hz, 3 H, CH_3-C(3)); IR 3019 (m), 2971 (m), 2940 (m), 2870 (m), 1718 (s), 1460 (m), 1455 (m), 1447 (m), 1379 (w), 1329 (w), 1316 (m), 1258 (m), 1229 (m), 1212 (m), 1208 (m), 1131 (w), 1087 (w), 1043 (w), 957 (w), 949 (w), 932 (w); MS (70 eV), *m/z* (relative intensity) 148 (12), 146 (M^+, 37), 110 (12), 104 (29), 102 (100), 97 (14), 82 (53), 69 (16), 68 (44), 67 (17), 56 (17), 55 (79). Anal. Calcd for $C_7H_{11}OCl$: C, 57.34; H, 7.56; Cl, 24.18. Found: C, 57.22; H, 7.36; Cl, 24.31.

***trans*-3**: bp 80 °C (6 torr); ^{1}H NMR (220 MHz) δ 4.12 (d, *J* = 10.2 Hz, 1 H, H-C(2)), 2.72–2.65 (m, 1 H), 2.47–2.28 (m, 1 H), 2.08–1.99 (m, 3 H), 1.80–1.56 (m, 2 H), 1.23 (d, *J* = 6.4 Hz, 3 H, CH_3-C(3)); IR 3025 (m), 2965 (s), 2935 (s), 2855 (m), 1729 (s), 1460 (m), 1454 (m), 1446 (m), 1429 (m), 1380 (m), 1353 (w), 1330 (w), 1313 (m), 1272 (m), 1260 (m), 1229 (w), 1212 (m), 1208 (m), 1180 (m), 1118 (w), 1098 (m), 1048 (m), 973 (m), 960 (w), 932 (m), 862 (m). MS (70 eV), *m/z* (relative intensity) 146 (M^+, 20), 104 (29), 102 (84), 97 (13), 82 (42), 76 (15), 69 (18), 68 (40), 67 (23), 56 (25), 55 (100), 53 (19), 42 (33), 41 (73). Anal. Calcd for $C_7H_{11}OCl$: C, 57.34; H, 7.56; Cl, 24.18. Found: C, 57.00; H, 7.72; Cl, 23.90.

3-(4-(*E*)-Hexenyl)-3-methyl-1-(trimethylsiloxy)-1-cyclohexene (7). To a cold (−40 °C) suspension of 9.61 g (50.5 mmol) of copper(I) iodide in 100 mL of dry Et_2O was added dropwise 63.9 mL (101 mmol) of methyllithium (1.58 M in Et_2O). The resulting clear, colorless solution was stirred at −40 °C for 10 min and then was cooled to −70 °C whereupon it was treated dropwise with a solution of 3.00 g (16.8 mmol) of **6** in 50 mL of dry Et_2O, keeping the reaction temperature below −60 °C. After stirring at −60 °C for 30 min, GC analysis indicated complete consumption of the enone, and the resulting enolate was quenched by consecutive addition of 3.22 mL (3.32 g, 18.51 mmol) of HMPA, 28.14 mL (20.43 g, 202 mmol) of triethylamine, and 25.64 mL (21.95 g, 202 mmol) of chlorotrimethylsilane. The reaction mixture was warmed to room temperature, stirred for 45 min, and then poured into 400 mL of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with pentane (3 × 500 mL), and the individual pentane extracts were washed in series with water (2 × 400 mL) and brine (400 mL). The combined organic extracts were dried (K_2CO_3), concentrated by rotary evaporation, and distilled in vacuo to yield 3.89 g (87%) of **7** (bp 102–105 °C (0.7 torr)). GC analysis showed this material to be ca. 85% pure, which was sufficient for subsequent reactions: ^{1}H NMR (90 MHz) δ 5.44 (m, 2 H, -C*H*=C*H*-), 4.68 (s, 1 H, H-C(2)), 2.15–1.25 (15 H), 1.03 (s, 3 H, CH_3-C(3)), 0.33 (s, 9 H, $(CH_3)_3Si$); IR 2900 (s), 1655 (m), 1450 (w), 1358 (w), 1249 (s), 1135 (m), 967 (s), 860 (s), 845 (s).

(2*R,3*R**)- and (2*R**,3*S**)-2-Chloro-3-(4-hexenyl)-3-methylcyclohexan-1-one (4).** To a cold (0 °C) stirred solution of 3.81 g (15.0 mmol) of **7** in 60 mL of dry THF was added dropwise 10.42 mL (16.46 mmol) of methyllithium (1.58 M in Et_2O). After being warmed to room temperature and stirred for 1 h, the resulting enolate solution was transferred via cannula to a −70 °C slurry of 2.38 g (18.0 mmol) of *N*-chlorosuccinimide in 20 mL of dry THF, keeping the reaction temperature less than −60 °C. The reaction was quenched after for 40 min of stirring at −70 °C by addition of 40 mL of saturated aqueous NH_4Cl solution. The mixture was warmed to room temperature, poured into 100 mL of water, and extracted with Et_2O (3 × 200 mL). The individual organic extracts were washed in series with water (2 × 200 mL) and brine (200 mL), combined, and dried ($MgSO_4$). Rotary evaporation of the solvent left 4.68 g of crude product, which was purified by column chromatography on silica gel with benzene to yield 2.68 g (92% based on 85% pure **7**) of a 53:47 mixture diastereomers of **4** (R_f 0.33, 0.38 (C_6H_6)): ^{1}H NMR (90 MHz) δ 5.40 (m, 2 H, -C*H*=C*H*-), 4.14 (s, 0.53 H, H-C(2)), 4.03 (s, 0.47 H, H-C(2)), 2.9–2.6 (m, 1 H, axial H-C(6)), 2.4–1.3 (14 H), 1.08 and 0.97 (2 s, 3 H, CH_3-C(3)); IR 2890 (s), 1720 (s), 1450 (m), 1375 (w), 970 (m).

General Oximation Procedures. Method A. To a cold (0 °C), stirred solution of the α-chloro ketone or α,β-epoxy ketone in methanol (ca. 0.5 M) were added 2.2 molar equiv of sodium acetate and 1.1 molar equiv of hydroxylamine hydrochloride. After 1 h the reaction mixture was poured onto water (4 mL/mL methanol) and extracted with three portions (each 1 mL/mL H_2O) of Et_2O. The individual Et_2O extracts were washed twice with water (4 mL/mL CH_3OH) and brine (4 mL/mL CH_3OH) and then combined and dried (Na_2SO_4). Rotary evaporation of the Et_2O left a crude product, which was purified by silica gel column chromatography (3:1 H–EA) and/or recrystallized as necessary.

Method B. To a stirred solution of the α-chloro ketone in glacial acetic acid (HOAc) (ca. 0.5 M) were added 1.5 molar equiv of potassium acetate and 1.5 molar equiv of hydroxylamine hydrochloride at room temperature. After 30 min–1.5 h (TLC) the reaction mixture was poured onto water (4 mL/mL HOAc) and worked up as described for method A.

Method C. To a stirred solution of the α-chloro ketone (α,β-epoxy ketone) in dry chloroform ($CHCl_3$) (ca. 0.33 M) was added 2.0 molar equiv of *O*-(*tert*-butyldimethylsilyl)hydroxylamine along with activated 4-Å molecular sieves (20–50 $^1/_8$-in. pellets). The reaction mixture was stirred under argon for 18–72 h (TLC), filtered, and concentrated on the Rotavap. The resulting crude product was purified by silica gel column chromatography (6:1 H–EA) and distilled (Kugelrohr) if necessary.

(*E*)-*cis*-4-*tert*-Butyl-2-chlorocyclohexan-1-one oxime ((*E*)-*cis*-9): method B, yield 82%, >95% *E*; mp 135.5–136 °C dec (from Et_2O); ^{1}H NMR (220 MHz, Me_2SO-d_6) δ 4.70 (d × d, *J* = 5.1, 10.3 Hz, 1 H, H-C(2)), 3.33 (s, 1 H, OH), 3.30–3.18 (m, 1 H, equatorial, H-C(6)), 2.40–2.30 (m, 1 H, axial H-C(6)), 1.96–1.62 (m, 2 H), 1.46–1.41 (m, 2 H), 0.86 (s, 9 H, $(CH_3)_3C$-C(4)); IR 3580 (w), 3280 (m), 2962 (s), 2870 (m), 1367 (w), 1220 (s), 1213 (s), 1209 (s); MS (70 eV), *m/z* (relative intensity) 203 (M^+, 1.9), 149 (11), 147 (33), 112 (55), 57 (100), 41 (32), 29 (14). Anal. Calcd for $C_{10}H_{18}NOCl$: C, 58.96; H, 8.91; N, 6.88; Cl, 17.40. Found: C, 58.77; H, 8.81; N, 6.86; Cl, 17.55.

(*E*)-*cis*-4-*tert*-Butyl-2-chlorocyclohexan-1-one (*tert*-butyldimethylsilyl)oxime ((*E*)-*cis*-11): method C, yield 92%, >95% *E*; R_f 0.6 (H–EA, 1:6); bp 110 °C (0.07 torr) (Kugelrohr); ^{1}H NMR (220 MHz) δ 4.46 (d × d, *J* = 10.2, 5.4 Hz, 1 H, H-C(2)), 3.41–3.34 (d × d, *J* = 15.1, 4.1 Hz, 1 H equatorial H-C(6)), 2.43–2.36 (m, 1 H, axial H-C(6)), 1.84–1.59 (m, 3 H), 1.30 (br d, *J* = 10 Hz, 2 H), 0.92 (s, 9 H, $(CH_3)_3C$-C(4)), 0.87 (s, 9 H, $(CH_3)_3C$-Si), 0.16 (s, 6 H, $((CH_3)_2Si)$; IR 3020 (w), 2960 (s), 2930 (s), 2859 (s), 1473 (m), 1463 (m), 1446 (w), 1438 (w), 1396 (w), 1390 (w), 1368 (m), 1252 (s), 1223 (m), 1213 (m), 1208 (m), 965 (m), 948 (m), 930 (s), 920 (m), 891 (m), 857 (s), 840 (s); MS (70 eV) , *m/z* (relative intensity) 262 (23), 261 (4), 260 (60), 204 (20), 109 (13), 108 (12), 94 (16), 75 (75), 73 (16), 69 (15), 67 (15), 57 (100), 55 (24). Anal. Calcd for $C_{16}H_{32}NOClSi$: C, 60.44; H, 10.14; N, 4.40; Cl, 11.15. Found: C, 60.29; H, 9.98; N, 4.62; Cl, 11.29.

(*Z*)-*trans*-4-*tert*-Butyl-2-chlorocyclohexan-1-one oxime ((*Z*)-*trans*-9): method A, yield 63%, >95% *Z*; mp 82–83.5 °C (pentane); ^{1}H NMR (220 MHz) δ 8.42 (s, 1 H, OH), 5.64 (s, 1 H, H-C(2)), 2.59 (d × t, *J* = 4.6, 14.1 Hz, 1 H, axial H-C(6)), 2.35 (d, *J* = 14.5 Hz, 1 H), 2.18 (d, *J* = 14.0 Hz, 1 H), 2.02–1.54 (m, 3 H), 1.29–1.09 (m, 1 H), 0.90 (s, 9 H, $(CH_3)_3C$-C(4)); IR 3583 (w), 3268 (m), 2960 (s), 2871 (m), 1479 (m), 1470 (m), 1367 (s), 1236 (m), 970 (s), 941 (m). MS (70 eV), *m/z* (relative intensity) 203 (M, 2), 147 (15), 112 (32), 57 (100), 55 (10). Anal. Calcd for $C_{10}H_{18}NOCl$: C, 58.96; H, 8.91; N, 6.88; Cl, 17.40. Found: C, 59.18; H, 8.91; N, 6.64; Cl, 17.71.

(*E*)-*trans*-4-*tert*-Butyl-2-chlorocyclohexan-1-one oxime ((*E*)-*trans*-9): method B, yield 89%, 90% *E*; mp 88–93 °C (pentane); ^{1}H NMR (360 MHz) δ 8.13 (br s, 1 H, OH), 5.65 (s, 0.1 H, H-C(2), *Z* isomer), 4.79 (s, 0.9 H, H-C(2), *E* isomer), 3.27 (d, *J* = 14.5 Hz, 0.9 H, equatorial H-C(6), *E* isomer), 2.26 (d × d, *J* = 2.2, 14.0 Hz, equatorial H-C(6), *E* isomer), 2.18 (d × t, *J* = 14.2, 5.4 Hz, axial H-C(6), *E* isomer), 1.99–1.03 (m, 4 H), 0.90 (s, 9 H, $(CH_3)_3$C-C(4)); IR 3580 (m), 3290 (m), 2962 (s), 2870 (w), 1480 (m), 1437 (m), 1367 (s), 1210 (m), 977 (m), 931 (m); MS (70 eV), *m*/*z* (relative intensity) 203 (M^+, 3), 147 (21), 112 (34), 57 (100); HRMS[58] calcd for $C_{10}H_{18}NOCl$ 203.1080, found 203.1058.

(*Z*)-*cis*-2-Chloro-3-methylcyclohexan-1-one oxime ((*Z*)-*cis*-10): method A, yield 71%, 82% *Z*; ^{1}H NMR (220 MHz) δ 5.45 (d, *J* = 2.3 Hz, 0.6 H, H-C(2) *Z* isomer); 4.53 (d, *J* = 2.3 Hz, 0.4 H, H-C(2) *E* isomer), 3.17 (br d, *J* = 14 Hz, 0.4 H, equatorial H-C(6) *E* isomer), 2.54 (d × t, *J* = 5.0, 13.7 Hz, 0.4H axial H-C(6) *E* isomer), 2.25 (d, *J* = 14.7 Hz, 0.6 H, equatorial H-C(6) *Z* isomer), 2.14 (d × t, *J* = 14.6, 5.6 Hz, 0.6 H, axial H-C(6), *Z* isomer), 1.94–1.83 (m, 2.3 H), 1.64–1.39 (m, 3.2 H), 1.08 (d, *J* = 6.5 Hz, 3 H, CH_3-C(3); IR 3580 (m, sh), 3300 (m, br), 3010 (m), 2970 (s), 2935 (s), 2865 (s), 1460 (s), 1453 (m), 1446 (m), 1378 (m), 1357(w), 1331 (w), 1322 (w), 1268 (m), 1235 (w), 1222 (m), 1121 (w), 1045 (w), 970 (m), 957 (s), 928 (m).

(*E*)-*cis*-2-Chloro-3-methylcyclohexan-1-one oxime ((*E*)-*cis*-10): method B, yield 82%, 80% *E*; bp 100 °C (0.5 torr); ^{1}H NMR (220 MHz) δ 7.8 (br s, 1 H, OH), 5.45 (d, *J* = 2.4 Hz, 0.2 H, H-C(2) *Z* isomer), 4.55 (d, *J* = 2.1 Hz, 0.8 H, H-C(2) *E* isomer), 3.18 (br d, *J* = 13 Hz, 0.8 H, equatorial H-C(6) *E* isomer), 2.77–2.47 (m, 0.8 H), 2.22–2.07 (m, 1.5 H), 2.02–1.79 (m, 1.7 H), 1.76–1.31 (m, 3 H), 1.08 (d, *J* = 6.5 Hz, 3 H, CH_3-(C(3)); IR 3583 (s, sh), 3300 (m, br), 3020 (s), 2975 (s), 2935 (s), 2865 (m), 1460 (m), 1454 (m), 1447 (m), 1436 (m), 1380 (m), 1357 (w), 1330 (w), 1322 (w), 1268 (m), 1222 (s), 1122 (w), 1045 (m), 968 (m), 957 (m), 927 (m), 858 (m); MS (70 eV), *m*/*z* (relative intensity) 161 (M^+, 3), 125 (12), 95 (15), 73 (20), 67 (32), 61 (59), 55 (30), 53 (12); HRMS[58] calcd for $C_7H_{12}NOCl$ 161.0607; found 161.0605.

(*E*)- and (*Z*)-*cis*-2-Chloro-3-methylcyclohexan-1-one (*tert*-butyldimethylsilyl)oxime (*cis*-12): method C, yield 91%, 1:1 *E*/*Z*; bp 80 °C (0.07 torr); ^{1}H NMR (220 MHz) δ 5.49 (s, 0.5 H, H-C(2), *Z* isomer), 4.56 (s, 0.5 H, H-C(2), *E* isomer), 3.25 (br d, *J* = 12.0 Hz, 0.5 H, equatorial H-C(6), *E* isomer),2.49 (d × t, *J* = 5.1, 13.7 Hz, 0.5 H, axial H-C(6), *Z* isomer), 2.27 (br d, *J* = 14.2 Hz, 0.5 H, equatorial H-C(6), *Z* isomer), 2.10–1.34 (m, 4 H), 0.91 and 0.90 (2 s, 9 H, $(CH_3)_3$C-C(4)); IR 3016 (m), 2590 (s), 2915 (s), 2859 (s), 1471 (m), 1462 (m), 1444 (w), 1433 (w), 1390 (w), 1378 (w), 1361 (w), 1252 (s), 1219 (m), 1210 (m), 968 (m), 950 (s), 933(s), 891 (m), 859 (s), 839 (s); MS (70 eV), *m*/*z* (relative intensity) 220 (19), 218 (55), 131 (11), 130 (96), 108 (86), 95 (10), 93 (27), 92 (21), 91 (13), 81 (93), 79 (15), 75 (100), 73 (14), 57 (10), 56 (61). Anal. Calcd for $C_{13}H_{26}NOClSi$: C, 56.60; H, 9.50; N, 5.08; Cl, 12.85. Found: C, 56.46; H, 9.24; N, 5.13; Cl, 12.84.

(*E*)-*trans*-2-Chloro-3-methylcyclohexan-1-one oxime ((*E*)-*trans*-10): method B, yield 53%, >95% *E*; mp 109.5–110.5 °C (petroleum ether); ^{1}H NMR (220 MHz) δ 9.30 (br s, 1 H, OH), 4.26 (d, *J* = 5.0 Hz, 1 H, H-C(2)), 2.69–2.61 (m, 2 H, 2H-C(6)), 2.22–2.12 (m, 2 H), 1.69–1.61 (m, 2 H), 1.43–1.35 (m, 1 H), 1.08 (d, *J* = 6.7 Hz, 3 H, CH_3-C(3)); IR 3580 (m), 3280 (s), 3015 (m), 2970 (s), 2945 (s), 2875 (m), 1467 (m), 1456 (s), 1442 (m), 1380 (m), 1331 (m), 1322 (w), 1282 (w), 1260 (w), 1236 (m), 1223 (s), 1121 (w), 1016 (w), 991 (m), 960 (s), 918 (m), 879 (m), 855 (m), 837 (m); MS (70 eV), *m*/*z* (relative intensity) 161 (M^+, 30), 148 (14), 146 (50), 132 (31), 126 (80), 125 (43), 108 (15), 89 (11), 82 (10), 81 (30), 80 (20), 79 (17), 77 (12), 69 (12), 68 (15), 67 (41), 66 (13), 65 (17), 59 (22), 55 (65), 54 (26), 53 (45), 51 (15). Anal. Calcd for $C_7H_{12}NOCl$: C, 52.07; H, 7.48; N, 8.67; Cl, 21.93. Found: C, 52.25; H, 7.56; N, 8.42; Cl, 22.19.

(*E*)-*trans*-2-Chloro-3-methylcyclohexan-1-one (*tert*-butyldimethylsilyl)oxime ((*E*)-*trans*-12): method C, yield 85%, >95% *E*; bp 70 °C (0.1 torr); ^{1}H NMR (220 MHz) δ 4.34 (d, *J* = 2.4 Hz, 1 H, H-C(2)), 3.11 (br d, *J* = 14.5 Hz, 1 H, equatorial H-C(6)), 2.32–2.11 (m, 3 H), 1.63–1.41 (m, 3 H), 0.98 (d, *J* =7.3 Hz, 3 H, CH_3-C(3)), 0.91 (s, 9 H, $(CH_3)_3$C-Si), 0.15 (s, 6 H, $(CH_3)_3$Si); IR 3019 (w), 2950 (s), 2930 (s), 2895 (m), 2882 (m), 2860 (m), 1474 (m), 1464 (m), 1445 (w), 1390 (w), 1380 (w), 1362 (w), 1320 (2), 1253 (m), 1222 (m), 1215 (m), 1122 (w), 1018 (w), 970 (m), 957 (s), 932 (s), 889 (s), 853 (s), 841 (s), 808 (m); MS (70 eV), *m*/*z* (relative intensity) 220 (36), 219 (15), 218 (100), 182 (12), 93 (17), 81 (38), 74 (48). Anal. Calcd for $C_{13}H_{26}NOClSi$: C, 56.60; H, 9.50; N, 5.08; Cl, 12.85. Found: C, 56.59; H, 9.35; N, 4.97; Cl, 13.04.

(*E*)-2-Chloro-3-[(*E*)-(4-hexenyl)]-3-methylcyclohexan-1-one (*tert*-butyldimethylsilyl)oxime ((*E*)-13): method C, yield 82%, >95% *E*: bp 110 °C (0.04 Torr); ^{1}H NMR (90 MHz) δ 5.42 (m, 2 H, -CH=C-), 3.99 (br s, 1 H, H-C(2)), 3.26 (br d, *J* = 15 Hz, 1 H equatorial H-C(6)), 2.5–1.2 (14 H), 1.17–1.04 (2 s, 3 H, CH_3-C(3)), 1.10 (s, 9 H $(CH_3)_3$CSi), 0.34 (s, 6 H, $(CH_3)_2$Si); IR 2900 (s), 2840 (m), 1455 (m), 1400 (w), 1375 (w), 1360 (w), 1250 (m), 1202 (m), 975 (s), 958 (s), 938 (m).

(*E*)- and (*Z*)-2,3-Epoxy-2,5,5-trimethylcyclohexan-1-one (*tert*-butyldimethylsilyl)oxime ((*E*)- and (*Z*)-18): method C, yield 92%, 55:45 *E*/*Z*; bp 95 °C (0.07 torr); ^{1}H NMR (220 MHz) δ 4.12 (s, 0.45 H, H-C(2), *Z* isomer), 3.35 (s, 0.55 H, H-C(2), *E* isomer), 2.71 (d, *J* = 14.8 Hz, 0.55 H, equatorial H-C(6) *E* isomer), 2.15 (d, *J* = 13.6 Hz, 0.45 H, equatorial H-C(6), *Z* isomer), 1.8–1.52 (3 H), 1.36 (s, 3 H, CH_3-C(3)), 0.95 and 0.82 (2 s, 6 H, 2(CH_3-C(5))), 0.92 (s, 9 H, $(CH_3)_3$CSi), 0.15 (s, 6 H $(CH_3)_2$Si); IR 3018 (w), 2959 (s), 2930 (s), 2860 (m), 1473 (m), 1463 (m), 1447 (w), 1409 (w), 1398 (w), 1390 (w), 1369 (m), 1362 (w),1348 (w), 1258 (m), 1222 (m), 1213 (m), 1133 (w), 1050 (w), 960 (s), 934 (s), 908 (s), 882 (m), 853 (s), 840 (s); MS (70 eV), *m*/*z* (relative intensity) 226 (29), 83 (11), 75 (100), 73 (13), 55 (11). Anal. Calcd for $C_{15}H_{29}NO_2Si$: C, 63.55; H, 10.31; N, 4.94. Found: C, 63.64; H, 10.07; N, 4.92.

General Procedure for UV–Vis Experiments. Oximes. A ca. 0.05 M solution of the α-chloro or α,β-epoxy oxime in acetonitrile was transferred to a Pyrex UV cuvette fitted with a Teflon brand stopcock and a septum. The UV-vis spectrum was recorded between 550 and 850 nm to give a base line. The reagent (triethylamine or DBU) was then injected through the septum, and the UV–vis spectrum was immediately recorded at a sweep rate of 240 nm/min. The decay of absorbance bands was then monitored by scans at regular intervals.

Silyloximes. A ca. 0.05 M solution of the α-chloro or α,β-epoxy silyl oxime in the appropriate solvent (usually acetonitrile) was placed in the Pyrex cuvette described above, and a base-line spectrum (550–850 nm) was recorded. A preweighed portion of tetrabutylammonium fluoride trihydrate was dried by azeotropic removal of water with dry benzene or acetonitrile (3 × 5 mL) followed by high vacuum. The residue was taken up in 1.0 mL of the same solvent, and the appropriate volume was injected into the cuvette. The UV–vis spectrum was recorded immediately and then at regular intervals to measure rate of decay.

Preparative-Scale Reaction of (*E*)-*trans*-12 with Tetrabutylammonium Fluoride. A solution of 203 mg (0.819 mmol) of (*E*)-*trans*-12 in 12 mL of dry acetonitrile under argon was treated with a solution of 271 mg (0.860 mmol) of tetrabutylammonium fluoride trihydrate (dried as described above) in 4 mL of dry acetonitrile via syringe. The blue color that formed immediately faded within 10 s. After 15 min, the solution was poured into 30 mL of water and was extracted with Et_2O (3 × 30 mL). The individual organic extracts were washed in series with water (2 × 30 mL) and brine (1 × 30 mL) and then combined and dried (Na_2SO_4). Rotary evaporation of the Et_2O left an oil, which was combined with the product of the UV experiment (51 mg) and purified by silica gel chromatography with 2:1 H–EA to afford 93 mg of an oil identified as a mixture of diastereomers of 14: ^{1}H NMR (360 MHz) δ 8.59 (s, 1 H, OH), 5.93 (br s, 1 H, H-C(2')), 4.28 (d, *J* = 5.9 Hz, 1 H, H-C(2)), 3.1–1.15 (13 H), 1.82 (2 s, 3 H, CH_3-C(3')), 1.07 and 1.00 (2 d, 3 H(?), *J* = 6.9 Hz, CH_3-C(3)); IR 3520 (w), 3240 (m), 2895 (s), 1650 (w), 1455 (m), 1380 (m), 1100 (m), 1065 (m), 1015 (s), 993 (s), 962 (s), 912 (s), 883 (s); MS (70 eV), *m*/*z* (relative intensity) 250 (M^+, 12), 126 (100), 125 (63), 108 (17), 93 (13), 81 (40), 80 (30), 79 (33), 77 (13), 67 (24), 65 (12), 55 (25), 54 (14), 53 (33).

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(58) Despite repeated purifications, satisfactory combustion data could not be obtained.

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Registry No. 1, 822-87-7; *cis*-**2**, 16508-33-1; *trans*-**2**, 15175-18-5; *cis*-**3**, 63603-21-4; *trans*-**3**, 63603-22-5; (2*R**,3*R**)-**4**, 88589-61-1; (2*R**,3*S**)-**4**, 88643-63-4; **5**, 55373-58-5; **6a**, 930-68-7; **6b**, 70681-91-3; **7**, 88589-62-2; (*E*)-**8**, 88589-63-3; (*Z*)-**8**, 88589-64-4; (*E*)-*cis*-**9**, 88589-65-5; (*E*)-*trans*-**9**, 88589-66-6; (*Z*)-*trans*-**9**, 88589-67-7; (*E*)-*cis*-**10**, 88589-68-8; (*Z*)-*cis*-**10**, 88643-64-5; (*E*)-*trans*-**10**, 88643-65-6; (*E*)-*cis*-**11**, 88589-69-9; (*E*)-*cis*-**12**, 88589-70-2; (*Z*)-*cis*-**12**, 88643-66-7; (*E*)-*trans*-**12**, 88643-67-8; (*E*)-**13**, 88589-71-3; **14**, 88589-72-4; **15**, 88589-73-5; **16**, 88609-56-7; **17**, 67730-51-2; (*E*)-**18**, 88589-74-6; (*Z*)-**18**, 88589-75-7; **18** (ketone), 10276-21-8; Me_3SiCl, 75-77-4; *t*-$BuSiMe_2ONH_2$, 41879-39-4; *n*-$Bu_4N^+F^-$, 429-41-4.

Supplementary Material Available: Improved, large-scale preparations of **6** and O-(*tert*-butyldimethylsilyl)hydroxylamine are reported (5 pages). Ordering information is given on any current masthead page.

A Novel Electrophilic Fluorination of Activated Aromatic Rings Using Acetyl Hypofluorite, Suitable also for Introducing ^{18}F into Benzene Nuclei

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Acetyl hypofluorite (1) is a new compound that serves as a novel electrophilic fluorinating agent. It is special in the sense that, while it is very reactive, it is still a milder reagent than other fluoroxy compounds such as CF_3OF or CF_3COOF. It is synthesized directly from elemental fluorine and is used without any isolation or purification. The hypofluorite **1** reacts efficiently and selectively with activated aromatic rings, particularly phenol and aniline derivatives after suitable protection of the hydroxyl and the amino groups. The net result of the reaction is partly according to classical aromatic electrophilic substitution. Unlike such a substitution, however, the electrophilic fluorine atom of **1** substitutes mainly an ortho hydrogen and only occasionally small amounts of *p*-fluoro derivatives are found. Evidence supports the mechanism for this aromatic fluorination as being mainly an addition–elimination one. In many cases the electrophilic aromatic fluorinations can replace the classical 60-year-old Balz–Schiemann method, which until today is probably the most used procedure. Since aromatic fluorination with **1** is a very fast reaction and since **1** is produced directly from elemental fluorine, this is probably one of the best ways for introduction of the short-living radioisotope ^{18}F into activated aromatic rings. This will greatly encourage the synthesis of compounds suitable for use in the rapidly developing field of positron emitting transaxial tomography, which in itself depends on the efficient and easy supply of compounds possessing positron emitting isotopes.

Introducing fluorine in specific sites of aromatic rings is a very important task from both chemical and pharmaceutical points of view. Chemically, the 60-year-old Balz–Schiemann[1] method is still the most generally employed, although numerous attempts have been made in order to find more direct and convenient alternatives.[2] Oddly enough, however, although the last decades are witness to an enormous growth of organic chemistry and of the invention of most sophisticated synthetic methods, the decomposition of aromatic diazonium tetrafluoroborate salts is still the most used way of preparing fluoro aromatic compounds.

Fluorination of aromatic compounds is, of course, biologically very important as well. Pharmacologists usually replace hydrogen by the isosteric fluorine in order to elevate hydrophobicity and to retard metabolism.[3] There is also a huge interest in the pharmaceutical industry in introducing the fluorine atom into the aromatic nuclei in existing as well as in newly designed drugs. In many cases such changes proved to be very rewarding.[4]

Another most important problem is to find an efficient way to introduce ^{18}F into various aromatic nuclei. The field of positron emitting transaxial tomography (PETT) is developing today at a very rapid pace.[5] Consequently, there is a constant search for new efficient and relatively fast ways for introducing fluorine into biologically important molecules. Time, of course, is a very important factor, since the half-life of ^{18}F is about 110 min. This and the fact that the Balz–Schiemann reaction is very inefficient from a radiochemical point of view[6] have created an urgent need for developing new and fast reaction patterns not based on the use of the conventional BF_3/HF method. In the last decade several attempts have been made to introduce fluorine into aromatic nuclei by using reagents possessing electrophilic fluorine. Fluoroxytrifluoromethane, CF_3OF, was probably the most popular reagent for this purpose. It was successful in several cases, but in many others it did not produce the desired monofluoro

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