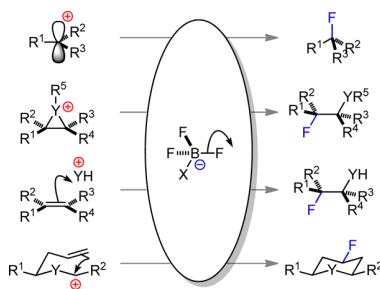


Beyond the Balz–Schiemann Reaction: The Utility of Tetrafluoroborates and Boron Trifluoride as Nucleophilic Fluoride Sources

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1. INTRODUCTION

Fluorine is the 13th most abundant element in the Earth's crust, and yet, despite its relatively high profusion, organofluorine compounds are scarce in nature, with only around a dozen fluorinated secondary metabolites identified to date.¹ The situation should be contrasted with several thousand known, naturally occurring organohalogens containing chlorine, bromine, and iodine.² This difference may be due to a variety of factors, such as the extremely low water solubility of CaF_2 (the most abundant form of natural fluoride), the very low nucleophilicity of the hydrated fluoride ion, and the extremely high reduction potential of fluorine ($E^\ominus = +3.06$ and $+2.87$ V in acidic and basic aqueous media,³ respectively).

With a mean energy of $105 \text{ kcal mol}^{-1}$ (441 kJ mol^{-1}),⁴ the C–F bond is the strongest known single bond to carbon, a fact that largely accounts for the relative chemical inertness of alkyl fluorides and the dearth of aliphatic nucleophilic substitution or oxidative insertion chemistry with such compounds, in contrast to the other halogens. Fluorine is the most electronegative of all of the elements ($\chi = 3.98$)⁵ and possesses the next smallest van der Waals radius (1.47 \AA) after hydrogen (1.2 \AA).⁶ Consequently, the C–F bond may serve as an isosteric but chemically orthogonal “mimic” of the C–H bond, a valuable trait for the design of enzyme inhibitors⁷ or nonracemizable analogues of bioactive compounds.⁸ The judicious replacement of hydroxyl groups with fluorine atoms has also proffered useful information regarding the relative importance of hydrogen bonding versus bond polarity in biological systems.⁹ In medicinal chemistry, fluorination is now applied routinely in lead optimization to tune properties such as metabolic stability, lipophilicity, and functional group acidity/basicity, factors that frequently impact decisively upon the bioavailability or target binding affinity of drugs.¹⁰ The placement of fluorine at stereogenic centers is also becoming an increasingly recognized

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tactic for biasing the conformation of organic molecules,¹¹ typified by the fluorine *gauche* effect.¹²

The ability of the C–F bond to provoke such remarkable changes in the physical, chemical, or biological properties of organic compounds^{3,4,13} has rendered site-selective fluorination an indispensable tool in the development of new pharmaceuticals,¹⁰ crop protection agents,¹⁴ organic materials,^{13e,15} and organocatalysts.¹⁷ Furthermore, the outstanding NMR profile of the ¹⁹F nucleus is readily exploited in the design of fluorinated small molecules as probes for biological macromolecules or binding interactions, as well as the study of metabolic processes.^{17,18} Another area of organofluorine chemistry of escalating importance is the use of the short-lived isotope ¹⁸F ($t_{1/2} = 109.7$ min) in positron emission topography (PET), a valuable imaging technique in clinical diagnosis.¹⁹

This myriad of applications has fueled the need for efficient, practical, and economical methods for the construction of C–F bonds, and, to this end, a range of electrophilic²⁰ and nucleophilic²¹ fluorinating agents have been devised.²² While catalysis remains paramount in the realization of otherwise challenging fluorination reactions [e.g., C(sp²)–F bond formation] and enantioselective fluorination processes,²³ an equally pressing objective is the identification of new or improved fluorinating agents offering superior performance, reduced cost, or safer handling.²⁴

Although it has long been recognized that the BF₄⁻ ion is not a completely “non-nucleophilic” anion,²⁵ what is less widely appreciated is the synthetic potential of tetrafluoroborates as nucleophilic fluoride sources for the formation of C–F bonds. Beyond the venerable Balz–Schiemann synthesis of aryl fluorides, reported in 1927,²⁶ a host of nucleophilic fluorination reactions reliant on fluoride transfer from the BF₄⁻ ion have been documented, including stereoselective fluorination protocols. Similarly, boron trifluoride etherate, BF₃·OEt₂, ubiquitous as a Lewis acid in synthetic organic chemistry,²⁷ has also served as an effective source of nucleophilic fluoride in a range of Lewis acid-mediated reactions, possibly via fluoride transfer from in situ generated fluoroborates of the form BF₃X⁻ (X = Lewis base). BF₃·OEt₂ is especially attractive as a source of nucleophilic fluoride due to its inexpensive nature, low molecular weight, high fluoride content, and ease of handling in standard borosilicate glassware.

With a view to increasing awareness of these transformations, as well as providing a footing for further advances to come, this Review offers a dedicated account of tetrafluoroborates and boron fluorides as nucleophilic fluoride sources for C–F bond formation, comprehensive to the end of 2013. While an effort has been made to emphasize reactions of demonstrated (or at least potential) preparative significance, some examples have been included purely to afford mechanistic insight, or to serve to highlight fundamental reactivity, which may inspire the development of future synthetic methods. Of the multitudinous ways to organize the material within, we have elected to arrange examples according to the following four reaction types: (i) nucleophilic substitutions, (ii) ring-opening fluorinations of strained rings, (iii) additions to alkenes, alkynes, and allenes, and (iv) cation–π cyclization-fluorinations. Within these major categories, examples are organized in a manner that best facilitates ease of discussion, whether that be by substrate or product class, reagent employed, or reaction subtype. Crucially, C–F bond formations featuring BF₃·OEt₂ in a catalytic role and not as the stoichiometric source of nucleophilic fluoride are

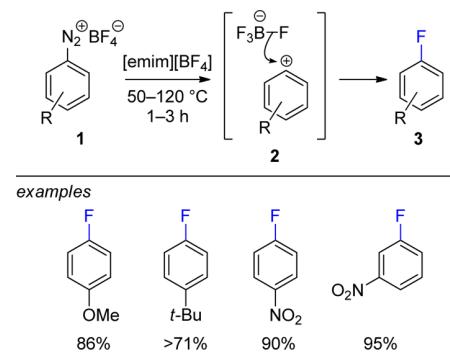
beyond the scope of this Review, even though such reactions may (at least in some cases) involve fluoride transfer from in situ formed BF₄⁻ ions.²⁸ Second, reactions involving fluoride transfer to elements other than carbon are not discussed [e.g., the excision of silicon-based protecting groups with BF₃·OEt₂ or BF₄⁻ sources,²⁹ and the formation of B–F,³⁰ Si–F,³¹ P–F,³² or M–F³³ bonds (M = metal) by fluoride transfer from BF₃·OEt₂ or the BF₄⁻ ion].

2. NUCLEOPHILIC SUBSTITUTIONS

2.1. Synthesis of Aryl Fluorides

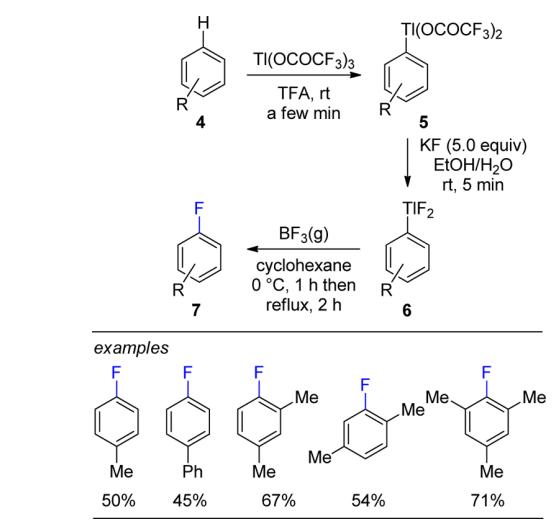
The Balz–Schiemann synthesis of aryl fluorides via the thermal decomposition of aryl diazonium tetrafluoroborate salts represents both the earliest and the most proverbial example of the BF₄⁻ ion as a nucleophilic fluoride source, and this landmark reaction has been the subject of several reviews.³⁴ Since its inception in 1927,²⁶ the value of this process has been borne out in its widespread application in the synthesis of aryl or heteroaryl fluorides which are inaccessible via the “Halex” (halogen exchange) approach, an alternative fluorination strategy that necessitates an electron-deficient aromatic ring (S_NAr reaction).³⁵ Mechanistic studies of the Balz–Schiemann reaction have accrued strong experimental support for an S_N1 mechanism via the intermediacy of an aryl cation, which is quenched by fluoride transfer directly from the BF₄⁻ ion.³⁶ The reaction has also been subject to a string of modifications designed to enhance its generality and practicality, such as the employment of alternative fluorinated counteranions (e.g., PF₆⁻, AsF₆⁻, SbF₆⁻)³⁷ as well as in situ diazotization protocols using *tert*-butyl nitrite/BF₃·OEt₂³⁸ or NOBF₄.³⁹ Contemporary investigations by Laali and Gettwert have indicated that ionic liquids (as recyclable reaction media) may offer several advantages, including operational simplicity and high reaction efficiency.⁴⁰ Thus, a range of aryl diazonium tetrafluoroborate salts 1 may be smoothly transformed into the corresponding aryl fluorides 3 using 1-ethyl-3-methylimidazolium tetrafluoroborate ([emim][BF₄]) as both the reaction solvent and the nucleophilic fluoride source (Scheme 1). By close analogy to

Scheme 1. Fluorination of Aryl Diazonium Tetrafluoroborate Salts 1



the Balz–Schiemann reaction, it is of interest to note that aryl fluorides have been isolated from the thermal decomposition of diaryliodonium tetrafluoroborate salts⁴¹ and O-(trifluoromethyl)dibenzofuranium tetrafluoroborate salts,⁴² although these observations are not necessarily of any preparative significance.

An alternative approach to the synthesis of aryl fluorides, which is also reliant on fluoride transfer from boron, is the reaction of arylthallium(III) difluorides **6** with gaseous BF_3 , which has been reported by Taylor and co-workers.⁴³ The required arylthallium(III) difluorides **6** can be prepared in situ in a two-step sequence involving thallation of an arene **4** with $\text{Ti}(\text{OCOCF}_3)_3$ to generate an arylthallium(III) bis(trifluoroacetate) species **5**, followed by anion exchange with KF (Scheme 2). The authors proposed that addition of BF_3 to the

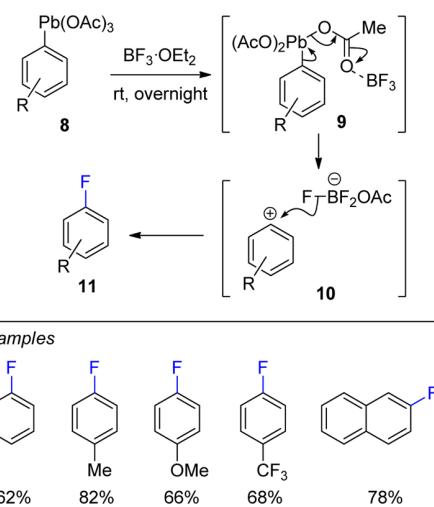
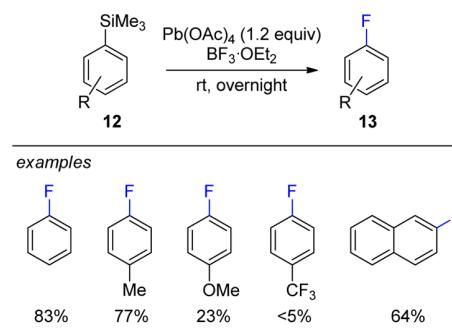
Scheme 2. Fluorination of Arenes **4**

difluorides **6** may produce unstable arylthallium(III) bis(tetrafluoroborate) species, which subsequently decompose to give aryl fluorides **7**. Some obvious drawbacks of this method include the requirement for stoichiometric amounts of highly toxic thallium, as well as the practical inconvenience and associated risks of handling gaseous BF_3 . Additionally, this route is not effective with aromatic substrates bearing either strong electron-withdrawing groups, or alkoxy/amino substituents, all of which deliver negligibly low yields of aryl fluoride products.

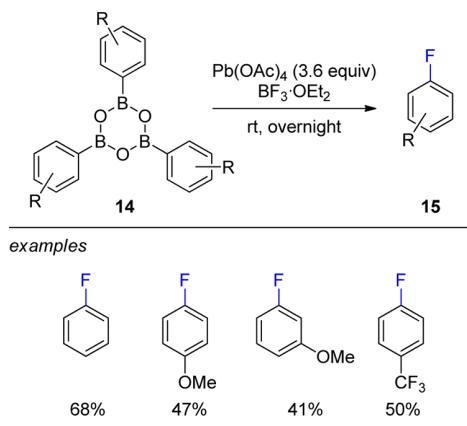
Subsequent work by Pinhey and co-workers has demonstrated the utility of aryllead(IV) triacetates **8** as precursors of aryl fluorides **11** by fluorodeplumbation with excess $\text{BF}_3\cdot\text{OEt}_2$, a method that delivers the aryl fluorides in low to good yield (nine examples, 14–82% yield by GC analysis).⁴⁴ The authors suggested that these reactions may proceed via a BF_3 -assisted heterolytic cleavage of the C–Pb bond to generate aryl cation intermediates **10**, followed by fluoride transfer from the AcOBF_3^- ion (Scheme 3).

To obviate the isolation of aryllead(IV) triacetates **8**, the reaction could also be performed directly on aryltrimethylsilanes **12** upon treatment with stoichiometric $\text{Pb}(\text{OAc})_4$ in $\text{BF}_3\cdot\text{OEt}_2$ as the reaction solvent. However, the slow rate of transmetalation from silicon to lead for electron-poor aryl substrates resulted in low yields (by GC analysis) of aryl fluorides **13** in these cases. In the case of the *p*-anisyl substrate, the low yield was tentatively ascribed to competing complexation of the methoxy group with BF_3 (Scheme 4).⁴⁴

Alternatively, the use of triarylboroxines **14** as substrates led to improved yields (by GC analysis) of the corresponding aryl fluorides **15** from both the *p*-(trifluoromethyl)phenyl and the *p*-

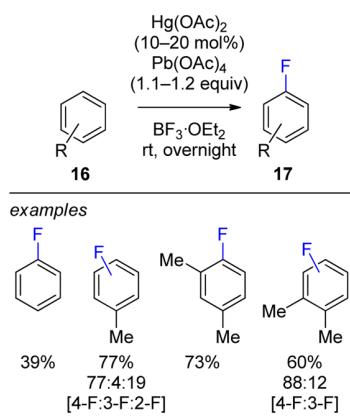
Scheme 3. Fluorination of Aryllead Triacetates **8**Scheme 4. Fluorination of Arylsilanes **12**

anisyl substrates, and this was attributed to a more facile transmetalation from boron to lead (Scheme 5).⁴⁴

Scheme 5. Fluorination of Triarylborationes **14**

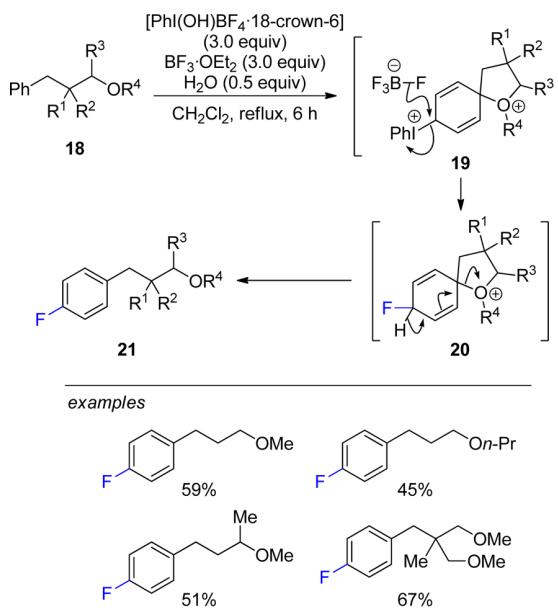
By inclusion of a substoichiometric amount of $\text{Hg}(\text{OAc})_2$, the reaction even proved applicable to simple arenes **16**, giving the corresponding aryl fluorides **15** in generally good yield (by GC analysis), presumably via initial electrophilic aromatic mercuration followed by transmetalation from mercury to lead (Scheme 6).⁴⁴

Scheme 6. Fluorination of Arenes 16



Other approaches to fluorinated arenes have been reported.⁴⁵ Lee et al. devised a silver-catalysed hexadehydro Diels-Alder reaction of poly-yynes followed by trapping of an intermediate silver-coordinated aryne by fluoride transfer from the BF_4^- ion to give fluorinated arenes (twelve examples, 75–93% yield).^{45a} Meanwhile, Miyamoto et al. have described the *para*-selective fluorination of 3-phenylpropyl ethers 18 by reaction with hydroxy(phenyl)- λ^3 -iodane 18-crown-6 complex [$\text{PhI}(\text{OH})\text{BF}_4 \cdot 18\text{-crown-6}$] in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ and H_2O as additives (six examples, 44–67% yield).^{45b} A mechanism proceeding via electrophilic iodination at the *para*-position of 18 and intramolecular nucleophilic attack by the ether oxygen to furnish an intermediate 19 was proposed, followed by substitution of the phenyl- λ^3 -iodanyl group via fluoride transfer from the BF_4^- ion and subsequent rearomatization to give the 3-(4'-fluorophenyl)propyl ether product 21 (Scheme 7). An ether function as well as a 3-carbon linker between this group and the aryl ring were both found to be critical to the success of this reaction.

Scheme 7. Fluorination of 3-Phenylpropyl Ethers 18



2.2. Synthesis of Alkenyl Fluorides

The paucity of synthetic methods available for accessing simple alkenyl diazonium salts, coupled with the sensitivity of these species,⁴⁶ has precluded the development of a vinylic counterpart to the Balz–Schiemann reaction. However, Okuyama and co-workers have shown that the thermolysis of alkenyl(phenyl)iodonium tetrafluoroborates can give rise to alkenyl fluoride products, with the reaction proceeding via either an $S_{\text{N}}1$ ($S_{\text{N}}\text{V}1$) or an “in-plane” $S_{\text{N}}2$ ($S_{\text{N}}\text{V}\sigma$) pathway,⁴⁷ depending on the substrate.⁴⁸ Specifically, the thermolysis of (*E*)- β -alkyl alkenyl iodonium tetrafluoroborate salts 22 gave (*Z*)-configured alkenyl fluoride products 23, presumably via $S_{\text{N}}\text{V}\sigma$ substitution of the phenyl- λ^3 -iodonio group by fluoride transfer from the BF_4^- ion, a process that occurs with inversion of configuration (Table 1, entries 1–3). Conversely, reaction of

Table 1. Fluorination of Alkenyl(phenyl)iodonium Tetrafluoroborates 22

	$\text{Ph}-\text{CH}=\text{CH}-\text{I}^{\oplus}\text{BF}_4^-$	$\xrightarrow[\text{reflux}]{\text{CHCl}_3}$	$\text{R}-\text{CH}=\text{CH}-\text{F}$	$+ \text{R}-\text{C}\equiv\text{C}$	
	22		23	24	
		$\text{Ph}-\text{CH}=\text{CH}-\text{I}^{\oplus}\text{BF}_4^-$	$\xrightarrow[\text{reflux}]{\text{CHCl}_3}$	$\text{Ph}-\text{CH}=\text{CH}-\text{F}$	$+ \text{Ph}-\text{C}\equiv\text{C}$
		22	23	24	
entry	R	time (h)	23:24 ratio	23 yield % (GC analysis)	24 yield % (GC analysis)
1	Me	34	93:7		
2	<i>n</i> -C ₈ H ₁₇	40	95:5	62	
3	<i>t</i> -Bu	40	22:78		
4	Ph	336		24	22

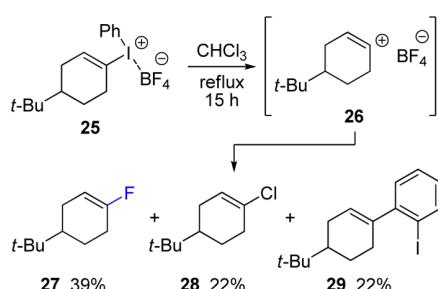
(*E*)- β -styrenyl iodonium tetrafluoroborate salt 22 produced the corresponding (*E*)-styryl fluoride 23, a result attributed to an $S_{\text{N}}\text{V}1$ substitution with retention of configuration, due to anchimeric assistance from the phenyl group (Table 1, entry 4). In all cases, alkyne products 24 were also obtained due to competing elimination processes, and this proved to be the major pathway in the presence of a bulky *t*-Bu substituent (Table 1, entry 3).

For 4-*tert*-butyl-1-cyclohexenyl(phenyl)iodonium tetrafluoroborate 25, which is unable to react via an $S_{\text{N}}\text{V}\sigma$ pathway, ionization to give an alkenyl cation 26 occurred in preference, producing alkenyl fluoride 27 (39% yield by GC analysis), as well as products 28 (22% yield by GC analysis) and 29 (22% yield by GC analysis), derived by chloride abstraction from CHCl_3 and Friedel–Crafts-type alkylation of the PhI by-product, respectively (Scheme 8). Addition of Bu_4NBF_4 to this reaction failed to improve the yield of 27, suggesting that the ionization step occurs from an undissociated alkenyl(phenyl)iodonium tetrafluoroborate contact ion pair.⁴⁸

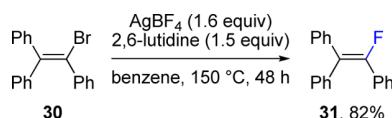
The formation of alkenyl fluorides upon treatment of alkenyl bromides or iodides with AgBF_4 has also been observed in some cases.⁴⁹ For example, the reaction of triphenylvinyl bromide 30 with AgBF_4 and 2,6-lutidine in benzene gave alkenyl fluoride 31 in 82% yield, presumably via the intermediacy of an alkenyl cation (Scheme 9).^{49c}

Similarly, Griesbaum and co-workers were able to prepare diastereoisomerically pure alkenyl fluoride 34 in multigram quantities via the deiodofluorination of *trans*-3,4-diiodohex-3-ene 32 with AgBF_4 , although the isolated yield of 34 was not

Scheme 8. Fluorination of 4-*tert*-Butyl-1-cyclohexenyl(phenyl)iodonium Tetrafluoroborate 25

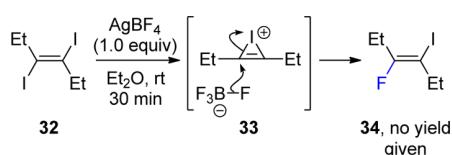


Scheme 9. Fluorination of Triphenylvinyl Bromide 30



disclosed.^{49d} To rationalize the complete retention of configuration observed, the authors invoked fluoride transfer from the BF_4^- ion to an iodinium ion intermediate **33** (Scheme 10).

Scheme 10. Fluorination of *trans*-3,4-Diodohex-3-ene 32



2.3. Synthesis of Alkyl Fluorides

Unfortunately, there is little prospect of developing a synthetically useful aliphatic variant of the Balz–Schiemann reaction using simple alkyl diazonium tetrafluoroborate salts, primarily due to the extreme instability of these species^{46b} and the concomitant formation of water in diazotization processes with primary amines, not to mention the competitive elimination and rearrangement pathways of the alkyl carbocation intermediate.^{50,51} Limited success, however, has been achieved by Doyle and co-workers with the nitrosative decomposition of aliphatic cyano azides **35** with NOBF_4 , furnishing regiosomeric mixtures of cyano fluorides **36**–**38** in moderate yield (four examples, 50–81% combined yield), along with cyanoalkenes as minor products in all cases (1–13%) (Table 2).⁵² Curiously, the presence of a cyano group appeared to be critical in promoting fluorination over side reactions such as elimination and Curtius rearrangement, pathways that were predominant in the reactions of the corresponding azidoalkanes with NOBF_4 . The authors proposed a mechanism proceeding via alkyl carbocation intermediates,⁵³ in which association of the Lewis basic cyano group with the developing Lewis acid BF_3 may occur in the transition state for fluoride transfer from BF_4^- .^{52b} An alternative rationale invoking binding of the cyano group to the surface of solid NOBF_4 during the reaction was also suggested.^{52a}

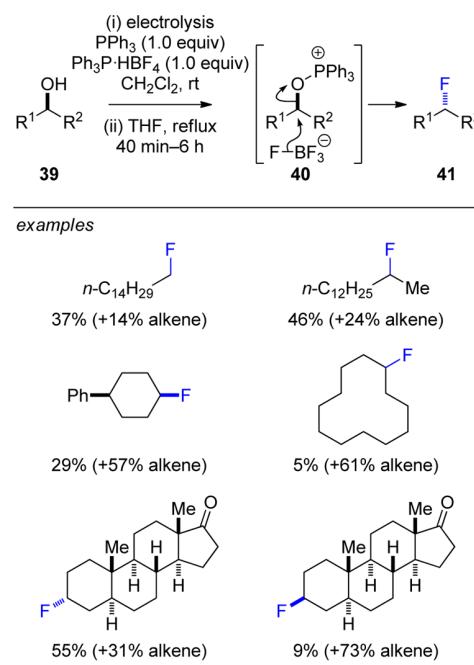
Another notable advance in this area has been the development by Ohmori and co-workers of a fluorinative variant of the Mitsunobu reaction, involving the electro-oxidative generation and subsequent thermal decomposition of

Table 2. Fluorination of Aliphatic Cyano Azides 35

entry	<i>n</i>	36+37+38 combined yield %	36:(37+38) ratio	
			36	37
1	1	50		
2	2	59		42:58
3	3	81		22:78
4	5	60		25:75

alkoxytriphenylphosphonium tetrafluoroborates **40**, allowing for the “one-pot” conversion of alcohols **39** to the corresponding alkyl fluorides **41** with inversion of configuration (where relevant).⁵⁴ Thus, constant current electrolysis (30 mA, 3–3.5 F mol⁻¹) of a mixture of alcohols **39** and PPh_3 in CH_2Cl_2 in an undivided cell, with $\text{PPh}_3\text{-HBF}_4$ as the supporting electrolyte, gave the alkoxytriphenylphosphonium tetrafluoroborates **40** from anodic oxidation [accompanied by reduction of $2\text{H}^+ \rightarrow \text{H}_2$ at the cathode (one H^+ from the alcohol **39** and the second H^+ from $\text{PPh}_3\text{-HBF}_4$)]. Following a solvent switch to THF, thermal decomposition of the alkoxytriphenylphosphonium tetrafluoroborates **40** provided the corresponding alkyl fluorides **41** (twelve examples, 2–73% yield), although competitive elimination processes meant that the isolated yields of the corresponding organofluorides were often too low to be synthetically useful (Scheme 11). To account for the inversion of configuration observed, the authors suggested that an $\text{S}_{\text{N}}2$ displacement of the triphenylphosphonio group by fluoride transfer from the BF_4^- ion may be in operation.

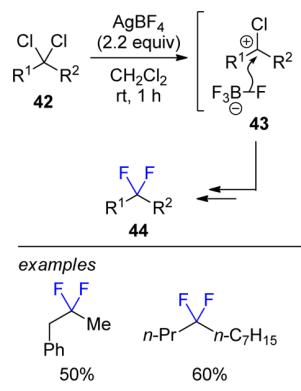
Scheme 11. Fluorination of Alcohols 39



2.4. Synthesis of *gem*-Difluorides

As stabilized carbocations that are less prone to elimination or rearrangement processes, the trapping of halocarbenium ion intermediates by fluoride transfer from the BF_4^- ion has been documented by Bloodworth, Mitchell, and co-workers, providing a convenient entry to *gem*-difluorides.⁵⁵ Thus, the action of AgBF_4 upon *gem*-dichlorides **42** in CH_2Cl_2 at ambient temperature gave the corresponding *gem*-difluorides **44** in moderate yields (five examples, 40–60% yield) (Scheme 12).

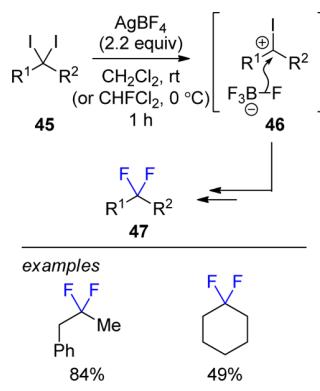
Scheme 12. Fluorination of *gem*-Dichlorides **42**



PhCCl_3 was also converted under these conditions to PhCF_3 in 48% isolated yield, although aliphatic trichlorides proved inert. Similarly, 2,2-dichlorocyclohexanone and 1,1-dichloro-2-methyl-2-phenylcyclopropane, which are reluctant to undergo $\text{S}_{\text{N}}1$ -type reactions, did not provide any *gem*-difluoride product. Notably, this method has been employed in an efficient synthesis of tetrafluoro[2,2]paracyclophanes, which have application as precursors to fluorinated polymers.⁵⁶

The reaction also proved applicable to *gem*-diiodides **45** (three examples, 35–84% yield), which were prepared from the corresponding hydrazones upon treatment with I_2 and Et_3N (Scheme 13).⁵⁵

Scheme 13. Fluorination of *gem*-Diiodides **45**

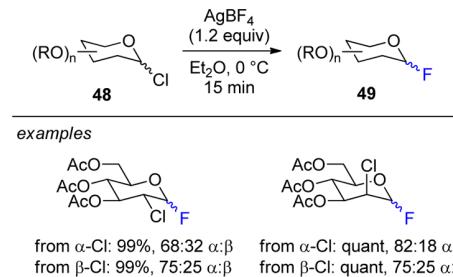


2.5. Synthesis of Glycosyl Fluorides

Oxocarbenium ions represent another class of stabilized carbocations, which have been shown to undergo productive trapping by fluoride transfer from the BF_4^- ion, generating α -fluoro ether products.⁵⁷ Most of the examples in this area relate to the synthesis of glycosyl fluorides, to which this section is

therefore dedicated.⁵⁸ These compounds are an important class of fluorinated carbohydrates that have found application as versatile glycosyl donors for glycosidation reactions⁵⁹ and as mechanism-based inhibitors and probes of enzymatic reactions.⁶⁰ Igarishi, Honma, and Irisawa have reported a convenient synthesis of glycosyl fluorides **49** from the corresponding chlorides **48** via treatment with AgBF_4 in Et_2O [three examples (discounting anomers), 81% quant yield by GC analysis].⁶¹ Starting from either the pure α - or the pure β -anomer of the requisite glycosyl chloride **48**, an anomeric mixture of the corresponding glycosyl fluorides **49** (favoring the α -anomer) was formed. No anomerization of either the starting materials or the products was observed under these conditions, implying that these ratios are the result of kinetic control. The nearly identical product ratios obtained from both the pure α - and the pure β -anomer of the glycosyl chlorides **48** are consistent with the reaction proceeding via a common oxocarbenium ion intermediate (Scheme 14). Alternatively,

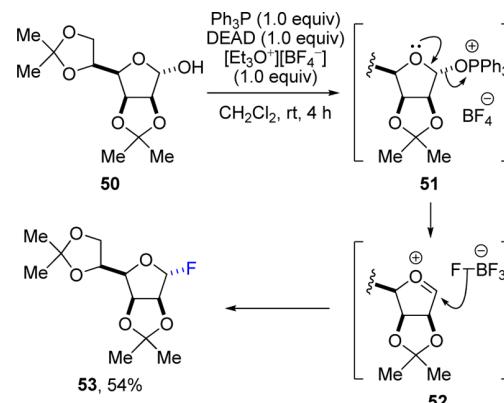
Scheme 14. Fluorination of Glycosyl Chlorides **48**



when toluene was employed as the solvent in place of Et_2O , the α -anomers of the glycosyl fluorides **49** were obtained almost exclusively (>95:5 α : β) and in high isolated yield (77–91%), possibly due to the reversibility of fluoride transfer from the BF_4^- ion in a non-Lewis basic solvent.

In a novel modification of the Mitsunobu reaction, Kunz and Sager achieved the conversion of 2,3:5,6-di-*O*-isopropylidene- α -D-mannofuranose **50** into glycosyl fluoride **53** via treatment with PPh_3 , diethyl azodicarboxylate (DEAD), and $[\text{Et}_3\text{O}^+][\text{BF}_4^-]$.⁶² The reaction was assumed to proceed via alkoxytriphenylphosphonium tetrafluoroborate intermediate **51**, which, after collapse to the glycosyl cation **52**, is attacked by fluoride, transferred from the BF_4^- ion (Scheme 15).

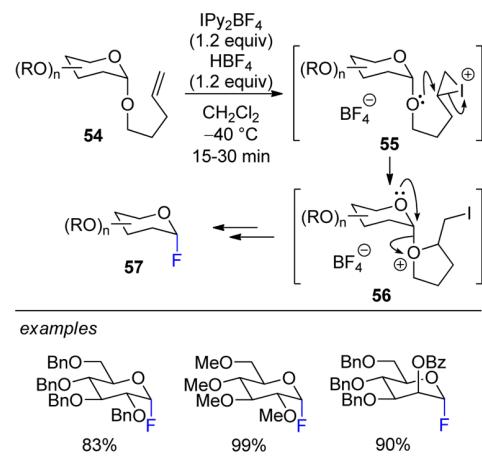
Scheme 15. Fluorination of 2,3:5,6-Di-*O*-isopropylidene- α -D-mannofuranose **50**



Similarly, Ohmori and co-workers have utilized their electro-oxidative fluorinative Mitsunobu protocol (section 2.3) to perform the same transformation **50** → **53** in 72% yield, although attempted extension of this fluorination method to 2,3,4,6-tetra-O-protected D-glucopyranoses failed.⁶³

Several protocols for the synthesis of glycosyl fluorides have relied on commercially available bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4)⁶⁴ as a source of both chemical activation (I^+) and nucleophilic fluoride (BF_4^-).⁶⁵ For example, Gómez, López, and co-workers have shown that IPy_2BF_4 is a useful reagent for the conversion of *n*-pent-4-enyl glycosides **54** to the corresponding glycosyl fluorides **57** (seven examples, 75–99% yield).^{65a} Mechanistically, it is plausible that the iodonium ion, I^+ , serves to activate the alkene toward iodoetherification, with subsequent sequential expulsion of 2-iodomethyltetrahydrofuran as a nucleofuge and trapping of the resultant glycosyl cation by fluoride transfer from the BF_4^- anion⁶⁶ (Scheme 16). HBF_4 was included as an additive to

Scheme 16. Fluorination of *n*-Pent-4-enyl Glycosides **54**

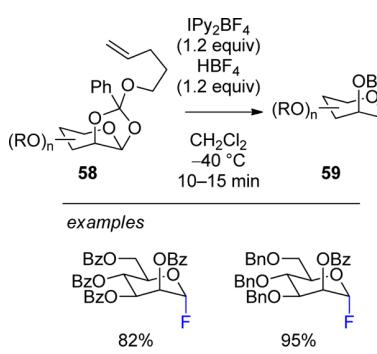


protonate the pyridine ligands of the IPy_2BF_4 reagent and prevent them competing as nucleophiles. In all cases, the α -anomers of the glycosyl fluorides **57** were obtained exclusively.

In an analogous fashion, *n*-pent-4-enyl orthoesters **58** could be converted to substituted glycosyl fluorides **59** using the same reagent combination (two examples, 82–95% yield) (Scheme 17).^{65a}

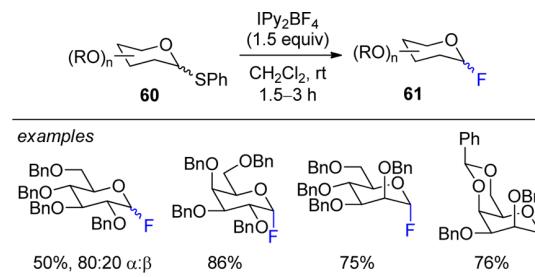
In addition to alkenes, thioethers are also readily activated by I^+ sources, and it is no surprise that IPy_2BF_4 has proven

Scheme 17. Fluorination of *n*-Pent-4-enyl Orthoesters **58**



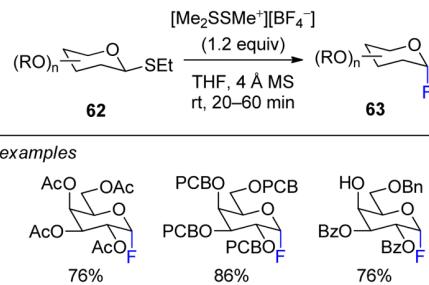
similarly effective in the conversion of glycosyl sulfides **60** (either pure α - or pure β -anomers) to glycosyl fluorides **61**, again with preferential formation of the corresponding α -anomers in all cases (four examples, 50–86% yield) (Scheme 18).^{65b} A similar protocol incorporating HBF_4 as an additive was subsequently published by Gómez, López, and co-workers (six examples, 64–99% yield, 62:38 to >99:1 α : β selectivity).⁶⁷

Scheme 18. Fluorination of Glycosyl Sulfides **60**



Another reagent capable of effecting the transformation of glycosyl sulfides **62** to glycosyl fluorides **63** is dimethyl-(methylthio)sulfonium tetrafluoroborate [$\text{Me}_2\text{SSMe}^+ \text{[BF}_4^-$], which is also commercially available (nine examples, 30–86% yield) (Scheme 19).⁶⁸ It was suggested that the high α -

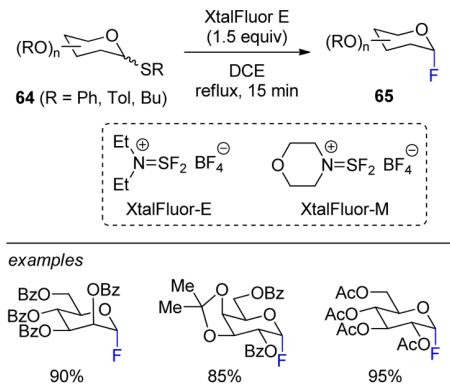
Scheme 19. Fluorination of Glycosyl Sulfides **62**



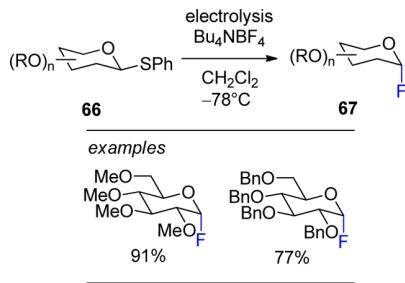
selectivity (>90:10) observed in all cases may be a result of BF_3^- -catalyzed anomeration of an initially formed α : β anomer mixture of glycosyl fluorides.

In a recent development, Williams and co-workers have demonstrated that commercially available aminodifluorosulfonium tetrafluoroborate reagents, XtalFluor-E and XtalFluor-M, are also able to effect the conversion of glycosyl sulfides **64** to glycosyl fluorides **65** (eleven examples, 45–94% yield) (Scheme 20).⁶⁹ In all cases, the α -anomers of the products were exclusively obtained. The reaction was also extended to glycosyl sulfoxides, selenides, and tellurides as substrates. Evidence for the BF_4^- anion as the source of nucleophilic fluoride came from control experiments with $[\text{Et}_2\text{NSF}_2^+] \cdot [\text{OTf}^-]$ as the reagent, which gave no glycosyl fluoride product. Notably, however, the addition of Bu_4NBF_4 as an additive to the reaction with $[\text{Et}_2\text{NSF}_2^+] \cdot [\text{OTf}^-]$ restored the reactivity, affording a glycosyl fluoride in high yield.

Glycosyl fluorides have also been obtained from the electrochemical oxidation of glycosyl sulfides in the presence of Bu_4NBF_4 as the supporting electrolyte.⁷⁰ For example, during attempts to accumulate glycosyl cations in a “cation pool”, Yoshida and co-workers found that anodic oxidation of glycosyl sulfides **66** in the presence of Bu_4NBF_4 as a supporting

Scheme 20. Fluorination of Glycosyl Sulfides 64

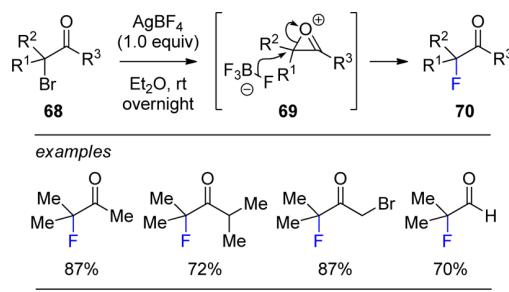
electrolyte delivered the α -anomers of glycosyl fluorides **67** in high yields, presumably via trapping of the putative glycosyl cations by fluoride transfer from the BF_4^- ion (two examples, 77–91% yield) (Scheme 21).

Scheme 21. Fluorination of Glycosyl Sulfides 66

Although not of demonstrated synthetic generality, it is interesting to note that isolated examples of the formation of glycosyl fluorides with $\text{BF}_3\cdot\text{OEt}_2$ as the nucleophilic fluoride source have also been observed.⁷¹

2.6. Synthesis of α -Fluoro Carbonyl Compounds

A mild and convenient protocol for the synthesis of α -fluoro carbonyl compounds **70** via the debromofluorination of α -bromo ketones or aldehydes **68** with AgBF_4 in Et_2O has been reported by Fry and Migran.⁷² Although elimination products are observed in all cases, this method delivered good yields of α -fluoro carbonyl compounds **70** in a number of cases (five examples, 30–87% yield by GC analysis). Primary bromides ($\text{R}^1 = \text{R}^2 = \text{H}$) and α -chloro carbonyl compounds do not react under these conditions, but this feature does allow for the execution of chemoselective monofluorinations of α,α' -dihalo carbonyl compounds. The authors suggested that Ag(I) -mediated ionization of the α -bromo carbonyl compounds **68** may be assisted by neighboring group participation from the carbonyl group, to give 2*H*-oxirenium ions **69** as intermediates, which may then undergo nucleophilic attack by fluoride transfer from the BF_4^- ion (Scheme 22). Such a mechanism implies retention of configuration at the halogen-bearing carbon, but unfortunately none of the reported examples allow the stereochemical course of the reaction to be discerned. Related syntheses of α -fluoro carbonyl compounds from epoxides bearing a nucleophile on the oxirane ring have also been described, and these reactions may also proceed via similar intermediates (sections 3.1.2 and 3.1.5).

Scheme 22. Fluorination of α -Bromo Carbonyl Compounds 68

The nucleophilic fluorination of α -diazo- β -keto esters with $\text{HBF}_4\cdot\text{OEt}_2$ has recently been described by Hayes, Moody, and co-workers as a general synthetic protocol to access α -fluoro- β -keto esters.⁷³ During screening experiments, they found that the treatment of α -diazo- β -keto ester **71** with CsF or TBAF in the presence of rhodium or copper catalysts, or $\text{Py}\cdot\text{HF}$ (Olah's reagent) under metal-free conditions, resulted in partial decomposition and/or no reaction. However, use of $\text{BF}_3\cdot\text{OEt}_2$ in Et_2O furnished α -fluoro- β -keto ester **72** in 25% yield, which could be improved to 45% by using CH_2Cl_2 as the reaction solvent.⁷⁴ However, with $\text{HBF}_4\cdot\text{OEt}_2$ as the fluorinating agent, **72** was obtained in a much improved yield of 82%. The authors also showed that the fluorination reaction proceeded with equal efficiency in a flow reactor, thus minimizing the hazards associated with working with diazo compounds (Table 3).

Table 3. Fluorination of α -Diazo- β -keto Ester **71**

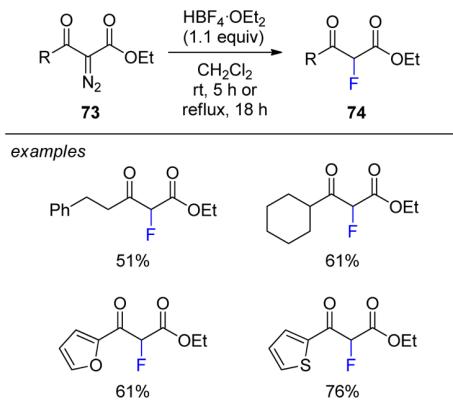
entry	F⁻ source	conditions	72 yield %
1	$\text{BF}_3\cdot\text{OEt}_2$	Et_2O , rt, 24 h	25
2	$\text{BF}_3\cdot\text{OEt}_2$	CH_2Cl_2 , rt, 24 h	45
3	$\text{HBF}_4\cdot\text{OEt}_2$	CH_2Cl_2 , rt, 5 h	82
4	$\text{HBF}_4\cdot\text{OEt}_2$	CH_2Cl_2 , 70 °C, 10 min, in flow	84

This protocol proved similarly effective with several other α -diazo- β -keto esters **73**, which could be converted to the corresponding α -fluoro- β -keto esters **74** in good yield upon treatment with $\text{HBF}_4\cdot\text{OEt}_2$ (1.1 equiv) in CH_2Cl_2 [four examples (excluding **71**), 51–76% yield] (Scheme 23). The utility of the fluorinated products **74** was demonstrated by their one-step conversion into a variety of different fluorinated heterocycles, including fluorinated pyrimidines, pyrazoles, and coumarins.

Similarly, α -fluoro ketones have also been isolated in several cases from the decomposition of α -diazo ketones with $\text{BF}_3\cdot\text{OEt}_2$, although the generality of this reaction has yet to be explored.⁷⁵

3. RING-OPENING FLUORINATIONS OF STRAINED RINGS**3.1. Ring-Opening Fluorinations of Epoxides**

$\text{BF}_3\cdot\text{OEt}_2$ has found widespread application as a Lewis acid catalyst for a variety of reactions of epoxide substrates,

Scheme 23. Fluorination of α -Diazoo- β -keto Esters 73

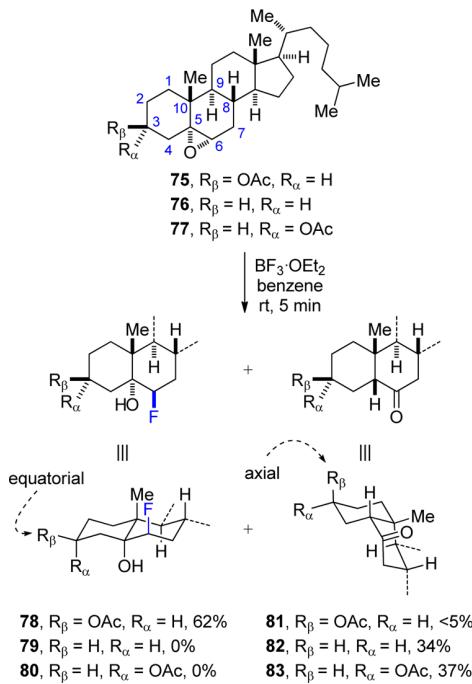
including polymerization,⁷⁶ addition of nucleophiles,⁷⁷ and rearrangement to carbonyl compounds⁷⁸ or allylic alcohols.⁷⁹ In a number of cases, however, the formation of vicinal fluorohydins arising from epoxide ring-opening by fluoride (derived from $\text{BF}_3\cdot\text{OEt}_2$) has been reported.^{80,81} Interestingly, $\text{BF}_3\cdot\text{OEt}_2$ was one of the earliest reagents employed (other than anhydrous HF)⁸² to effect the ring-opening fluorination of epoxides,⁸³ predating the more modern amine–HF reagents (introduced by Olah in the early 1970s)⁸⁴ by 16 years. The material in this section is divided into five subsections. For historical reasons, the fluorination of steroidal epoxides is first covered as a discrete topic (section 3.1.1), followed by the ring-opening fluorination of nonsteroidal aliphatic epoxides with either $\text{BF}_3\cdot\text{OEt}_2$ or $\text{HBF}_4\cdot\text{OEt}_2$ (section 3.1.2). Considering the predilection of donor-substituted⁸⁵ epoxides to undergo nucleophilic ring-opening with retention of configuration under Lewis acidic conditions,⁸⁶ the ring-opening fluorinations of aryl (section 3.1.3), alkenyl and propargyl (section 3.1.4), and α -heteroatom-containing (section 3.1.5) epoxides are then treated separately from the aforementioned nondonor-substituted (i.e., steroidal and nonsteroidal aliphatic) epoxides.

One issue of mechanistic interest that has arisen on numerous occasions is whether or not fluorohydins (as their O-boryl derivatives *in situ*) are intermediates in the $\text{BF}_3\cdot\text{OEt}_2$ -promoted rearrangement of epoxides to carbonyl compounds. From the evidence available,⁸⁷ it seems that fluorohydrin intermediacy is almost certainly operative in some cases but not in others, and that both the substrate geometry and the reaction solvent can influence the precise mechanistic pathway.

3.1.1. Steroidal Epoxides. The synthesis of fluorohydins from steroidal epoxides upon treatment with $\text{BF}_3\cdot\text{OEt}_2$ has been well documented for 5,6-epoxy-,^{83,87a,88} 4,5-epoxy-,^{88e,h,89} and 5,10-epoxysteroids,⁹⁰ primarily during studies conducted in the late 1950s through to the early 1970s into the Lewis acid-catalyzed rearrangements of steroidal epoxides. Far from being a mere curiosity, the ring-opening fluorination of 5,6-epoxysteroids with $\text{BF}_3\cdot\text{OEt}_2$ has been harnessed as a key step in the synthesis of biologically active fluorinated steroids.^{88a,b,91} Isolated examples of fluorohydrin formation upon treatment with $\text{BF}_3\cdot\text{OEt}_2$ have also been observed with 2,3-epoxy-,⁹² 14,15-epoxy-,⁹³ 16,17-epoxy-,⁹⁴ 20,21-epoxy-,⁹⁵ and 24,25-epoxysteroids,⁷³ as well as for 12,13-epoxy-⁹⁶ and 13,17-epoxy-C-nor-D-homosteroids,⁹⁷ and 1,2-epoxy-A-norsteroids,⁹⁸ although the isolated yields of fluorohydins were low in most of these cases. As some of this chemistry was previously reviewed in 1974,⁹⁹ coverage here will be limited to selected

examples of the ring-opening fluorination of 5,6-epoxysteroids with $\text{BF}_3\cdot\text{OEt}_2$.

The ring-opening fluorination of 5,6-epoxysteroids with $\text{BF}_3\cdot\text{OEt}_2$ was first reported in 1957 by Henbest and Wrigley during investigations into the reactivity of 3-substituted 5,6-epoxycholestanes.⁸³ For 3 β -acetoxy-5 α ,6 α -epoxycholestane 75, the presence of the 3 β -OAc substituent on the steroid A-ring was found to promote ring-opening fluorination at the expense of isomerization to C(6)-ketone 81, giving fluorohydrin 78 in 62% yield (in addition to 18% of returned starting material 75). The relative configuration within fluorohydrin 78 was assigned as *anti* on the basis that base-induced ring-closure led to recovery of epoxide 75. Notably, extended reaction times caused the yield of fluorohydrin 78 to fall (41% after 15 min; 24% after 2 h). Curiously, either the absence of a 3-substituent (i.e., 76) or the inclusion of an (epimeric) 3 α -OAc group on the A-ring (i.e., 77) gave only the corresponding C(6)-ketone products 82 and 83, in 34% and 37% yield, respectively (Scheme 24).

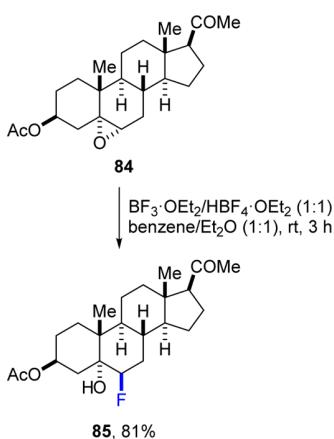
Scheme 24. Fluorination of 3 β -Acetoxy-5 α ,6 α -epoxycholestane 75

The role of the 3 β -OAc substituent in directing the course of the reaction of 75 with $\text{BF}_3\cdot\text{OEt}_2$ was rationalized using electronic and conformational arguments.⁸³ It was reasoned that inductive withdrawal by the 3 β -OAc substituent may deter ionization of the C(S)-O bond of the oxirane, a prerequisite for the [1,2]-hydride shift to form C(6)-ketone 81. Second, the formation of 81 was postulated to be disfavored on steric grounds due to developing 1,3-diaxial interactions on the equatorial to axial conformational change of the 3 β -OAc group during C(6)-ketone formation. With C(6)-ketone 81 formation suppressed, an S_N2-type ring-opening fluorination of the activated epoxide to give fluorohydrin 78 may compete, with the regioselectivity of this reaction being consistent with the predictions of the Fürst–Plattner rule for *trans*-diaxial ring-opening.¹⁰¹ In the case of the epimeric 3 α -OAc substrate 77,

Henbest and Wrigley have reasoned that the formation of C(6)-ketone **83** is likely favored due to the alleviation of 1,3-diaxial interactions on moving the 3α -OAc substituent from an axial to an equatorial position.¹⁰²

The identity of the active fluoride nucleophile in this reaction is not certain, but experiments with epoxide **75** have shown that traces of HBF_4 present in unpurified $\text{BF}_3 \cdot \text{OEt}_2$ are critical in promoting ring-opening fluorination over Lewis acid-catalyzed rearrangements;^{88c} this suggests that the BF_4^- ion may in fact be the active fluoride donor. Interestingly, Bowers and Ringold have reported that a 1:1 mixture of $\text{BF}_3 \cdot \text{OEt}_2$ and $\text{HBF}_4 \cdot \text{OEt}_2$ is a superior reagent system to $\text{BF}_3 \cdot \text{OEt}_2$ alone for the ring-opening fluorination of 5,6-epoxysteroids.¹⁰³ Using this reagent, 3β -acetoxy- $5\alpha,6\alpha$ -epoxypregnane-20-one **84** (possessing the same relative configuration of the epoxide and acetoxy functionalities as **75**) was transformed to the corresponding fluorohydrin **85** in 81% yield,¹⁰³ as compared to just 39% under similar conditions using $\text{BF}_3 \cdot \text{OEt}_2$ alone^{88a} (Scheme 25).

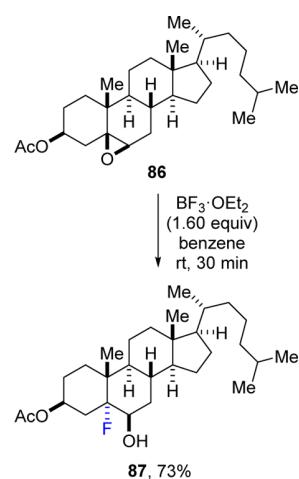
Scheme 25. Fluorination of 3β -Acetoxy- $5\alpha,6\alpha$ -epoxypregnane-20-one **84**



Having identified some key structural and electronic features that facilitate the ring-opening fluorination of $5\alpha,6\alpha$ -epoxysteroids with $\text{BF}_3 \cdot \text{OEt}_2$, Henbest and Wrigley extended their studies to 3β -acetoxy- $5\beta,6\beta$ -epoxycholestane **86**, to probe the effect of inverting the epoxide stereochemistry.⁸³ Hence, upon treatment of **86** with $\text{BF}_3 \cdot \text{OEt}_2$ in benzene at room temperature for 30 min, fluorohydrin **87** was obtained in 73% yield (Scheme 26). As before, in the absence of a 3β -acetoxy group, only the corresponding C(6)-ketone was obtained. The regioselectivity of attack of fluoride [at C(5) in this case] is in line with a *trans*-diaxial ring-opening following the prediction of the Fürst-Plattner rule.¹⁰¹ The relative *anti*-configuration within fluorohydrin **87** was assigned by chemical correlation to epoxide **86** by means of base-induced ring-closure.

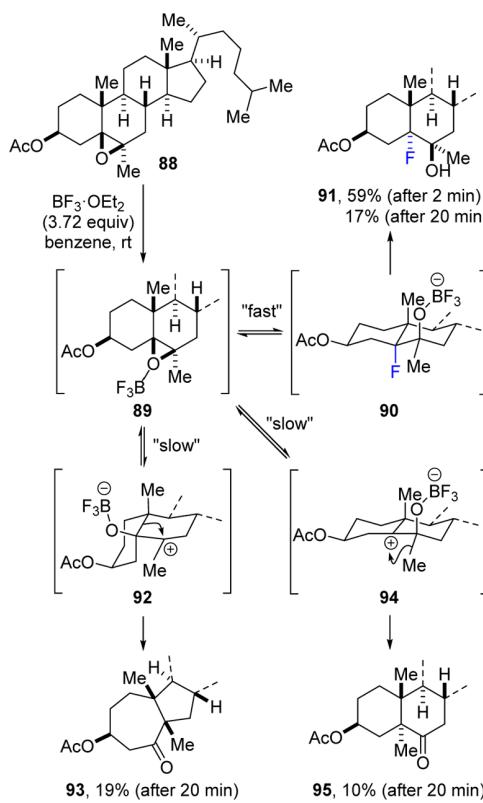
Blunt, Hartshorn, and Kirk reported similar results with 3β -acetoxy- $5\beta,6\beta$ -epoxy- 6α -methyl- 5β -cholestane **88**, which gave fluorohydrin **91** in 59% yield after exposure to $\text{BF}_3 \cdot \text{OEt}_2$ in benzene for 2 min.^{87a} On extension of the reaction time to 20 min, ketones **93** and **95** were produced additionally, at the expense of fluorohydrin **91** (the isolated yields after chromatography were 17% for **91**, 19% for **93**, and 10% for **95**). The authors suggested that fluorohydrin O-trifluoroborate **90** is the kinetic product of the reaction, but that its formation in the presence of excess BF_3 is reversible and the system will

Scheme 26. Fluorination of 3β -Acetoxy- $5\beta,6\beta$ -epoxycholestane **86**



favor the thermodynamically more stable ketones **93** and **95** with extended reaction times (Scheme 27).

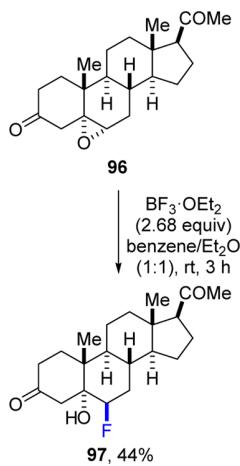
Scheme 27. Fluorination of 3β -Acetoxy- $5\beta,6\beta$ -epoxy- 6α -methyl- 5β -cholestane **88**



In an attempt to distinguish the relative importance of electronic versus steric factors in dictating the reactivity of $5\alpha,6\alpha$ -epoxides toward $\text{BF}_3 \cdot \text{OEt}_2$, Bowers and co-workers chose to evaluate 3-oxo- $5\alpha,6\alpha$ -epoxides as substrates for ring-opening fluorination with $\text{BF}_3 \cdot \text{OEt}_2$, under the assumption that the steric influence of the 3-oxo substituent should be negligible.^{88b} Thus, $5\alpha,6\alpha$ -epoxypregnane-3,20-dione **96** was reacted with $\text{BF}_3 \cdot \text{OEt}_2$ in benzene/Et₂O (1:1) at room

temperature for 3 h to give fluorohydrin **97** in 44% isolated yield (Scheme 28). The relative configuration within

Scheme 28. Fluorination of $5\alpha,6\alpha$ -Epoxypregnan-3,20-dione **96**



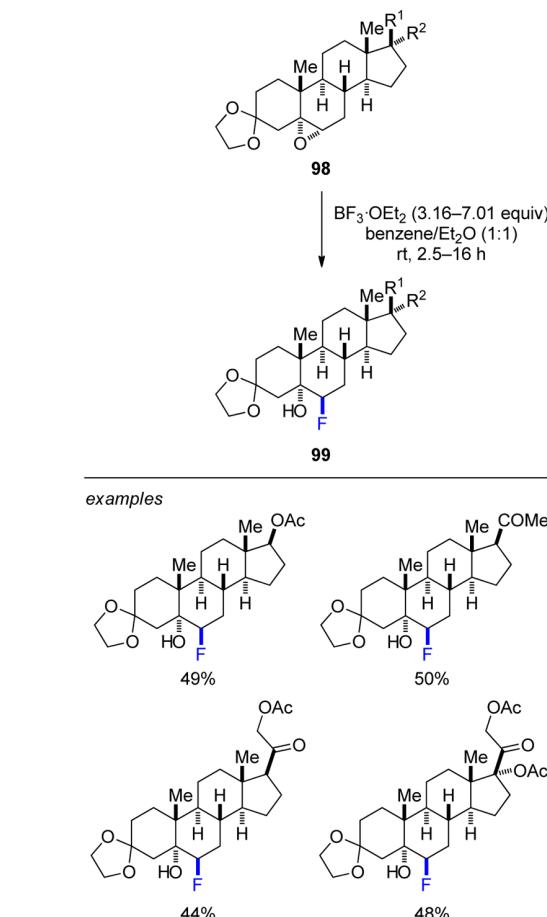
fluorohydrin **97** was assigned as *anti* on the basis that its base-induced ring-closure led to recovery of starting epoxide **96**. This result indicated that ring-opening fluorination of $5\alpha,6\alpha$ -epoxides with $\text{BF}_3 \cdot \text{OEt}_2$ should be favored for substrates bearing 3-substituents that exert a strong inductive-withdrawal effect on coordination with BF_3 , assuming that there are no overriding conformational factors in opposition.

Having established the utility of a 3-oxo group in promoting fluorohydrin formation, Bowers and co-workers reasoned that $5\alpha,6\alpha$ -epoxides bearing a 3,3-ethylenedioxy motif might function in an analogous manner on treatment with $\text{BF}_3 \cdot \text{OEt}_2$, as coordination of two molecules of BF_3 to the ketal oxygens¹⁰⁴ should cause a strong inductive-withdrawal effect, and the symmetrical nature about C(3) should eliminate conformational factors such as axial to equatorial interchange.^{88b} In support of this proposal, a range of 3,3-ethylenedioxy- $5\alpha,6\alpha$ -epoxides **98** gave, upon treatment with $\text{BF}_3 \cdot \text{OEt}_2$ in benzene/Et₂O (1:1) at room temperature, fluorohydribs **99** in moderate yields (five examples, 44–50% yield) (Scheme 29).

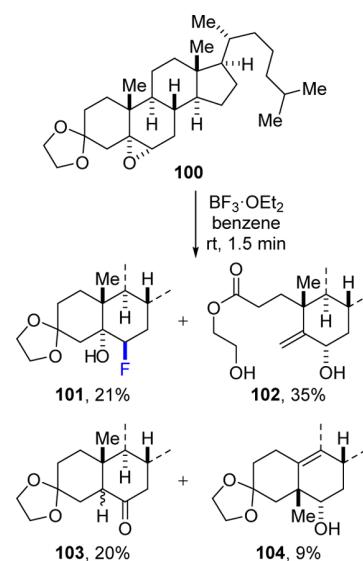
To allow for a more direct comparison with the conditions employed by Henbest and Wrigley,⁸³ Coxon, Hartshorn, and Sutherland investigated the ring-opening fluorination of 3,3-ethylenedioxy- $5\alpha,6\alpha$ -epoxycholestane **100** with $\text{BF}_3 \cdot \text{OEt}_2$ in benzene as the reaction solvent (i.e., in the absence of Et₂O as a cosolvent).⁸⁸ⁱ However, under these reaction conditions, fluorohydrin **101** was isolated in only 21% yield, in addition to a number of rearrangement products **102**–**104** postulated to have arisen via a C(5) carbocation intermediate (Scheme 30).

The latter observation served to highlight the critical role of the solvent in dictating the course of the reaction of steroidal epoxides with $\text{BF}_3 \cdot \text{OEt}_2$, a factor that had not received any explicit scrutiny in previous studies. In general, investigations have shown that the scope of the ring-opening fluorination of $5,6$ -epoxysteroids with $\text{BF}_3 \cdot \text{OEt}_2$ may be greatly improved by the inclusion of Et₂O as an additive/cosolvent with benzene (or simply by performing the reaction in Et₂O alone), and that substrates lacking strongly electron-withdrawing C(3)-substituents can undergo efficient ring-opening fluorination with $\text{BF}_3 \cdot \text{OEt}_2$ under these conditions.^{87a,88f,h,j} As has been observed in other cases,^{87b,g} the rate of the ring-opening fluorination

Scheme 29. Fluorination of 3,3-Ethylenedioxy- $5\alpha,6\alpha$ -epoxides **98**



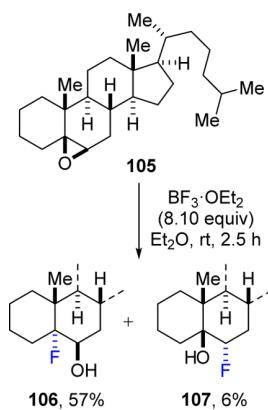
Scheme 30. Fluorination of 3,3-Ethylenedioxy- $5\alpha,6\alpha$ -epoxycholestane **100**



reaction decreases significantly as the concentration of Et₂O is increased,^{87a,88h} and this effect has been ascribed to a lower concentration of the active epoxide– BF_3 complex in the

presence of excess Et₂O as a competing Lewis base.¹⁰⁵ Thus, treatment of 5 β ,6 β -epoxycholestane **105** with 3.15 equiv of BF₃·OEt₂ in benzene at room temperature gave rapid conversion (2 min) to a mixture of nonfluorinated rearrangement products, whereas reaction with 8.10 equiv of BF₃·OEt₂ in Et₂O at room temperature was much slower (2.5 h) and gave fluorohydrin **106** as the major product, which was isolated in 57% yield, along with another fluorinated compound, which was tentatively assigned as the regioisomeric fluorohydrin **107** and isolated in 6% yield (Scheme 31).^{88h}

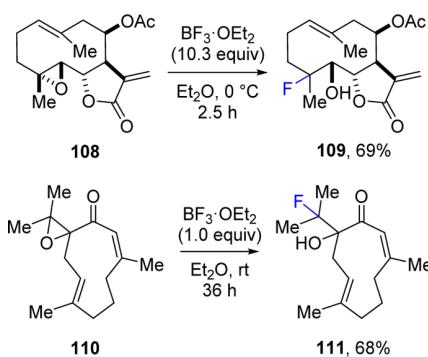
Scheme 31. Fluorination of 5 β ,6 β -Epoxycholestane 105



3.1.2. Nonsteroidal Aliphatic Epoxides. Following a promising debut in the synthesis of fluorinated steroids through the late 1950s to the early 1970s, BF₃·OEt₂ as a reagent for the ring-opening fluorination of nondonor-substituted epoxides has since been superseded by more selective and versatile nucleophilic fluoride sources,¹⁰⁶ of which amine–HF complexes are frequently the reagents of choice.¹⁰⁷ Nevertheless, reagents (or catalysts) that can assist nucleophilic ring-opening via Lewis or Brønsted acid activation of an oxirane can promote mild fluorinations without recourse to highly elevated temperatures⁷⁷ (a frequent issue when employing more basic conditions), and BF₃·OEt₂ remains a privileged reagent in this regard. Unfortunately, acid-promoted side reactions such as polymerization¹⁰⁸ or rearrangement¹⁰⁹ can be an unwelcome accompaniment to ring-opening fluorination under Lewis or Brønsted acidic conditions, and the action of BF₃·OEt₂ on most nondonor-substituted epoxides generally leads, in the absence of a competent nucleophilic trap, to products of epoxide rearrangement.¹¹⁰ In fact, beyond the environs of steroid chemistry, reports of fluorohydrin formation from the reaction of nondonor-substituted epoxides with BF₃·OEt₂ are rare, and this has spawned the notion that this protocol may be limited to complex tri- or tetrasubstituted epoxides.^{106b} Representative examples include the sesquiterpene epoxides lipiferolide **108**¹¹¹ and 7,11-epoxyisogermacrone **110**,¹¹² which have been reported to afford fluorohydriins **109** and **111**, respectively, as the major products upon treatment with BF₃·OEt₂ in Et₂O, although unfortunately the relative configuration within **109** was not established (Scheme 32).¹¹³

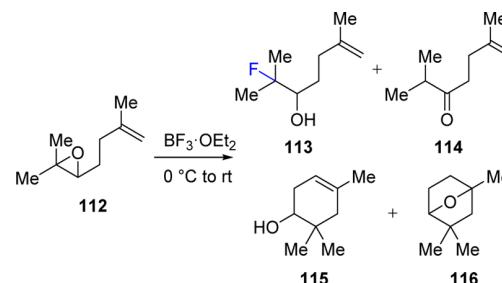
A closer examination of the literature, however, demonstrates that substrate structural complexity is not a prerequisite to efficient ring-opening fluorination with BF₃·OEt₂. For instance, in his seminal study on epoxyalkene cyclization in 1962, Goldsmith observed the formation of fluorohydrin **113** as the major product upon treatment of geraniolene monoepoxide

Scheme 32. Fluorination of Lipiferolide 108 and 7,11-Epoxyisogermacrone 110



112 with 0.3 equiv of BF₃·OEt₂ in Et₂O (Table 4, entry 1).¹¹⁴ On increasing the quantity of BF₃·OEt₂ employed in the

Table 4. Fluorination of Epoxide 112



reaction to 1.5 equiv, however, the product distribution became increasingly weighted toward ketone **114** and cyclized product **115**, at the expense of fluorohydrin **113** (Table 4, entry 2). Moreover, no fluorohydrin **113** could be isolated from the same reaction conducted in benzene, whereby only a mixture of ketone **114** and cyclization products **115**–**116** was evident (Table 4, entry 3). Both of these observations parallel similar findings for steroid epoxides^{87a,g,88f,h,j} (section 3.1.1) and aryl epoxides^{87b,115} (section 3.1.3), the implication being that fluorohydrin formation from nondonor-substituted epoxides on reaction with BF₃·OEt₂ is favored in Et₂O as opposed to benzene. Goldsmith has suggested that the origin of this effect may lie in the attenuation of S_N1-like character during the epoxide ring-opening step in a Lewis basic solvent like Et₂O.¹¹⁴ Indeed, Fujimoto et al. have inferred, using ¹³C-labeling techniques, that the ring-opening fluorination of a similar 2,2-dimethyl-3-alkyloxirane with BF₃·OEt₂ proceeds with inversion of configuration, supporting an S_N2-type mechanism rather than an S_Ni mechanism.^{87g} It is also possible that (O-boryl)fluorohydriins are the kinetic products in both benzene and Et₂O, but that they have a longer lifetime in a Lewis basic solvent like Et₂O, where the concentration of free BF₃ is lower.^{87b} Other examples of the formation of fluorohydriins as minor products in epoxyalkene cyclizations promoted by BF₃·OEt₂ are also on record,¹¹⁶ and they have even been implicated as intermediates in such cyclizations.^{116c}

Fluorohydrin formation has also been observed by Yamamoto and co-workers for a structurally similar trisubstituted epoxide **117**, during studies on the Lewis acid-mediated rearrangement of epoxides.¹¹⁷ Specifically, the agency of $\text{BF}_3\cdot\text{OEt}_2$ on **117** in Et_2O gave fluorohydrin **118** as the major product (Table 5, entry 1), although none of **118** was

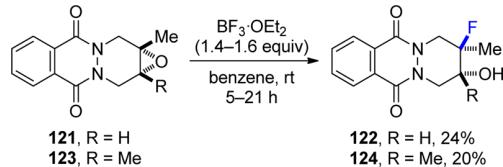
Table 5. Fluorination of Epoxide **117**

entry	solvent	temp (°C)	time (h)	118 yield %	117		
					118	119	120
1	Et_2O	0	1	"major product"			
2	benzene	rt	2	0			
3	toluene	-78	2	42			

detectable when benzene was employed as the reaction solvent and only ketone **119** and aldehyde **120** were isolated (Table 5, entry 2). However, when the reaction was conducted at low temperature (-78°C) in toluene, fluorohydrin **118** could be isolated in 42% yield (Table 5, entry 3).

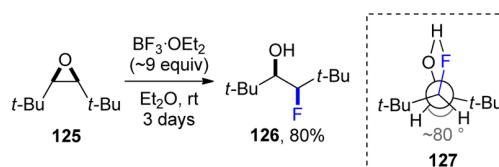
In accordance with the aforementioned results for steroidal epoxides (section 3.1.1), inversion of configuration appears to be the usual stereochemical course for ring-opening fluorinations of tri- and tetrasubstituted epoxides with $\text{BF}_3\cdot\text{OEt}_2$. As a nonsteroidal example, the fluorination of 1,2-diaza-4,5-epoxycyclohexanes **121** and **123** with $\text{BF}_3\cdot\text{OEt}_2$ in benzene has been shown to proceed with inversion of configuration to give *anti*-fluorohydriins **122** and **124**, respectively, albeit in low isolated yields, with the relative configurations being assigned on the basis of ^1H NMR spectroscopic analysis, including measurement of $^1\text{H}-^{19}\text{F}$ ^3J NMR coupling constants (Scheme 33).¹¹⁸

Scheme 33. Fluorination of 1,2-Diaza-4,5-epoxycyclohexanes



A few examples of the ring-opening fluorination of 1,2-dialkyl-substituted epoxides with $\text{BF}_3\cdot\text{OEt}_2$ have also been reported, and inversion of configuration again appears to be in operation. During a study on the rearrangements of substituted ethylene oxides, Coxon, Hartshorn, and co-workers found that the treatment of *cis*-2,3-di-*tert*-butyloxirane **125** with ~ 9 equiv of $\text{BF}_3\cdot\text{OEt}_2$ in Et_2O at room temperature for 3 days gave *syn*-fluorohydrin **126** in 80% yield (Scheme 34).¹¹⁹ In the non-Lewis basic solvent CCl_4 , however, epoxide **125** suffered fragmentation to 2-methylbut-2-ene and pivaldehyde. On the basis that no coupling between the vicinal protons in **126** was detectable in the ^1H NMR spectrum in CCl_4 , the authors

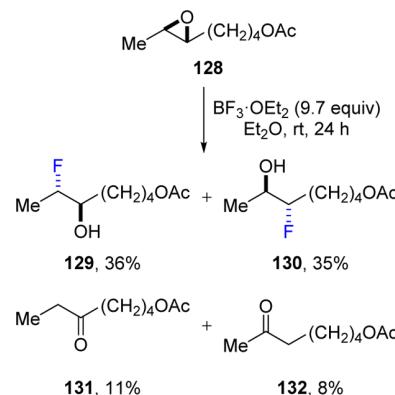
Scheme 34. Fluorination of *cis*-2,3-Di-*tert*-butyloxirane **125**



assigned a *syn*-relative configuration to **126**, assuming a solution-phase conformation **127** with approximately orthogonal vicinal protons and stabilization via intramolecular O–H…F hydrogen bonding. Curiously, attempted ring-opening fluorination of the diastereoisomeric *trans*-2,3-di-*tert*-butyloxirane with $\text{BF}_3\cdot\text{OEt}_2$ in Et_2O gave no reaction, and this may be attributable to steric hindrance to epoxide– BF_3 complex formation.¹²⁰

In a subsequent study on acetoxy neighboring group participation in acyclic epoxide systems, Coxon et al. again isolated fluorohydrin products using $\text{BF}_3\cdot\text{OEt}_2$ as a Lewis acid.¹²¹ For example, the reaction of *trans*-epoxide **128** with $\text{BF}_3\cdot\text{OEt}_2$ in Et_2O gave a mixture of regioisomeric fluorohydriins **129** and **130** in 36% and 35% yield, respectively. Ketones **131** and **132** were also obtained in 11% and 8% yield, respectively, as products of Meinwald rearrangement (Scheme 35).

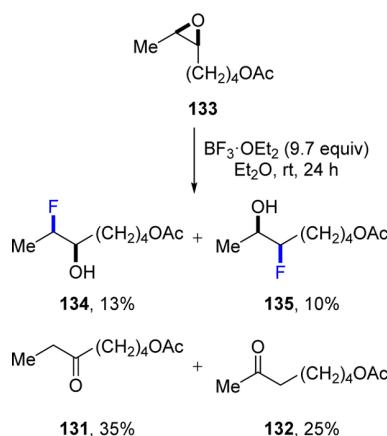
Scheme 35. Fluorination of Epoxide **128**



Under the same reaction conditions, the corresponding *cis*-epoxide diastereoisomer **133** returned mainly ketonic products **131** and **132** in 35% and 25% yield, in addition to fluorohydriins **134** and **135** in 13% and 10% yield, respectively (Scheme 36). The relative configurations within fluorohydriins **129**, **130**, **134**, and **135** were inferred from the products obtained upon their treatment with *t*-BuOK in *t*-BuOH. Coxon et al. have also proposed the intermediacy of fluorohydriins in the $\text{BF}_3\cdot\text{OEt}_2$ -catalyzed cyclization of epoxy alcohols in Et_2O , in which cyclized products resulting from epoxide-opening with net retention of configuration were observed: the presumed result of $\text{S}_{\text{N}}2$ -type ring-opening with fluoride followed by $\text{S}_{\text{N}}2$ -type displacement of fluoride (probably BF_3 assisted).¹²²

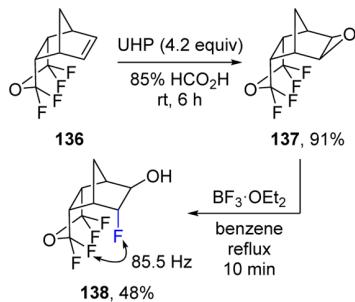
Further support for the inversion of configuration in these types of ring-opening fluorination reactions with $\text{BF}_3\cdot\text{OEt}_2$ can be found in a study by Nowak and co-workers on the possibility of through-space deactivation of π -bonds by proximal fluorine atoms.¹²³ After subjection of their alkene model system **136** to epoxidation with urea hydrogen peroxide complex (UHP) in 85% HCO_2H (among other electrophilic addition protocols, all of which were completely *exo*-selective), they showed that

Scheme 36. Fluorination of Epoxide 133



treatment of the resultant epoxide 137 with $\text{BF}_3\cdot\text{OEt}_2$ in refluxing benzene gave fluorohydrin 138 in 48% yield (Scheme 37). A large through-space coupling J_{FF} 85.5 Hz of the CHF

Scheme 37. Fluorination of Epoxide 136

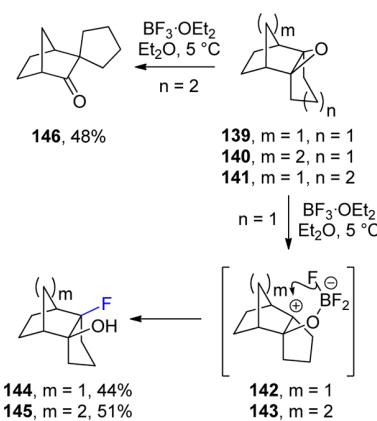


group to a fluorine of one of the CF_2 groups within 138 showed that the newly formed C–F bond was *endo*-configured, supportive of the ring-opening fluorination proceeding with inversion of configuration. Thus, as for steroidal epoxides (section 3.1.1), ring-opening fluorination of other nondonor-substituted epoxides with inversion of configuration appears to be in operation with $\text{BF}_3\cdot\text{OEt}_2$, although the precise nature of the nucleophile (e.g., F^- , BF_4^- , etc.) remains uncertain, and a catalytic role for adventitious HBF_4 in unpurified $\text{BF}_3\cdot\text{OEt}_2$ cannot be excluded.^{88c}

In an unusual occurrence of ring-opening fluorination of aliphatic epoxide substrates with retention of configuration using $\text{BF}_3\cdot\text{OEt}_2$, Takaishi et al. have described the isolation of *syn*-fluorohydrin products 144 and 145 from epoxides 139 and 140, respectively.¹²⁴ A reaction pathway involving intramolecular fluoride delivery to an intermediate carbocation 142 or 143 was proposed to account for the production of 144 and 145, respectively, and it was reasoned that competing [1,2]-alkyl shifts (to give spirocyclic ketones) or eliminations (to give allylic alcohols) may be disfavored due to the presumed high strain energy of the corresponding products. Accordingly, the reaction of substrate 141 (a more flexible homologue of 139) with $\text{BF}_3\cdot\text{OEt}_2$ produced spirocyclic ketone 146 (the product of a [1,2]-alkyl shift) in 48% yield (Scheme 38).

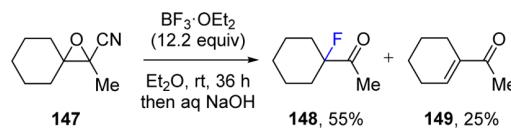
For epoxides bearing an α -nucleofuge, a regioselective ring-opening fluorination followed by expulsion of the nucleofugal group can provide direct access to α -fluoro carbonyl

Scheme 38. Fluorination of Epoxides 139–141

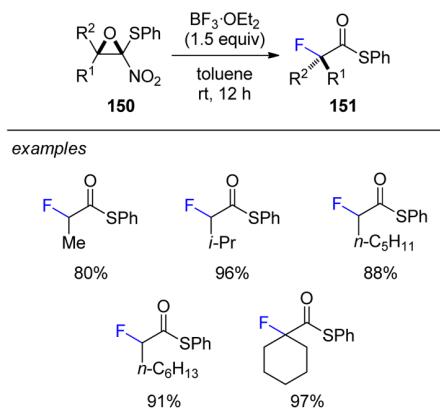


compounds. For example, in an early study concerned with the synthesis and reactivity of glycidonitriles, Stork and co-workers noted that the spirocyclic glycidonitrile derivative 147 could be transformed into α -fluoroketone 148 in 55% yield by reaction with excess $\text{BF}_3\cdot\text{OEt}_2$ in Et_2O , followed by a basic workup. The α,β -unsaturated ketone byproduct 149 could easily be separated via distillation (Scheme 39).¹²⁵

Scheme 39. Fluorination of Glycidonitrile Derivative 147



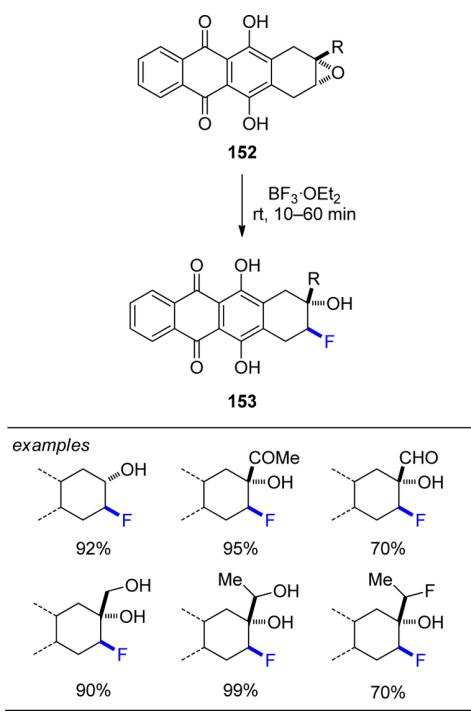
Similarly, in an attempt to investigate Lewis acid-catalyzed rearrangements of α -nitro- α -phenylthio epoxides 150, Jackson and co-workers found that their treatment with $\text{BF}_3\cdot\text{OEt}_2$ in toluene at room temperature gave α -fluoro phenylthio esters 151 in high yields (five examples, 80–97% yield) (Scheme 40).¹²⁶ Notably, the use of Et_2O as solvent resulted in no reaction, while the use of either TBAF in THF or KF/18-crown-6 in toluene proved inferior to $\text{BF}_3\cdot\text{OEt}_2$ and led to unidentified byproducts. As the analogous α -phenylsulfonyl- α -phenylthio epoxides gave only mixtures of products under the same reaction conditions, it was suggested that interaction

Scheme 40. Fluorination of α -Nitro- α -phenylthio Epoxides 150

between the nitro group and BF_3 may be responsible for the observed reactivity.¹²⁷

Despite the limited current understanding of the ring-opening fluorination of nondonor-substituted epoxides with $\text{BF}_3\cdot\text{OEt}_2$, it is noteworthy that this method has proven to be of value in the synthesis of fluorinated analogues of natural products. For example, Giannini has exploited $\text{BF}_3\cdot\text{OEt}_2$ as a reagent in the ring-opening fluorination of anthracycline aglycone 8,9-epoxides **152** to 8-fluoroanthracyclones **153**, the latter of which are valuable precursors to biologically active 8-fluoroanthracyclines.¹²⁸ Dissolution of a range of anthracycline aglycone 8,9-epoxides **152** in neat $\text{BF}_3\cdot\text{OEt}_2$ for brief periods at ambient temperature afforded the corresponding *anti*-fluorohydrins **153** with high regioselectivity and in excellent isolated yields (seven examples, 65–99% yield) (Scheme 41).¹²⁹ Notably, the use of Py·9HF (Olah's reagent) as an alternative fluorinating agent failed to deliver the desired fluorohydrin products **153**.

Scheme 41. Fluorination of Anthracycline Aglycone 8,9-Epoxides **152**



Lombardi and co-workers have applied this fluorination reaction as a key step in the total synthesis of (8*S*)-8-fluoro-4-demethoxydaunorubicin **162**, a fluorinated analogue of the naturally occurring anthracycline daunorubicin, which displays potent antitumor activity.¹³⁰ Thus, oxidation of racemic epoxy alcohol **155** (available in 3 steps from **154**)¹³¹ with DMSO and Ac_2O gave epoxy ketone **156** in 65% yield, which was then subjected to ring-opening fluorination with neat $\text{BF}_3\cdot\text{OEt}_2$ to give fluorohydrin **157** in 80% yield. Ketalization and allylic bromination using polystyrene-supported pyridine hydrobromide perbromide gave bromide **158** in 30% yield, which was then deprotected and hydrolyzed to give **159** in 90% yield. Glycosylation of **159** with an enantiopure daunosamine derivative **160** followed by separation of the resultant diastereoisomers gave **161**, and deprotection then gave (8*S*)-

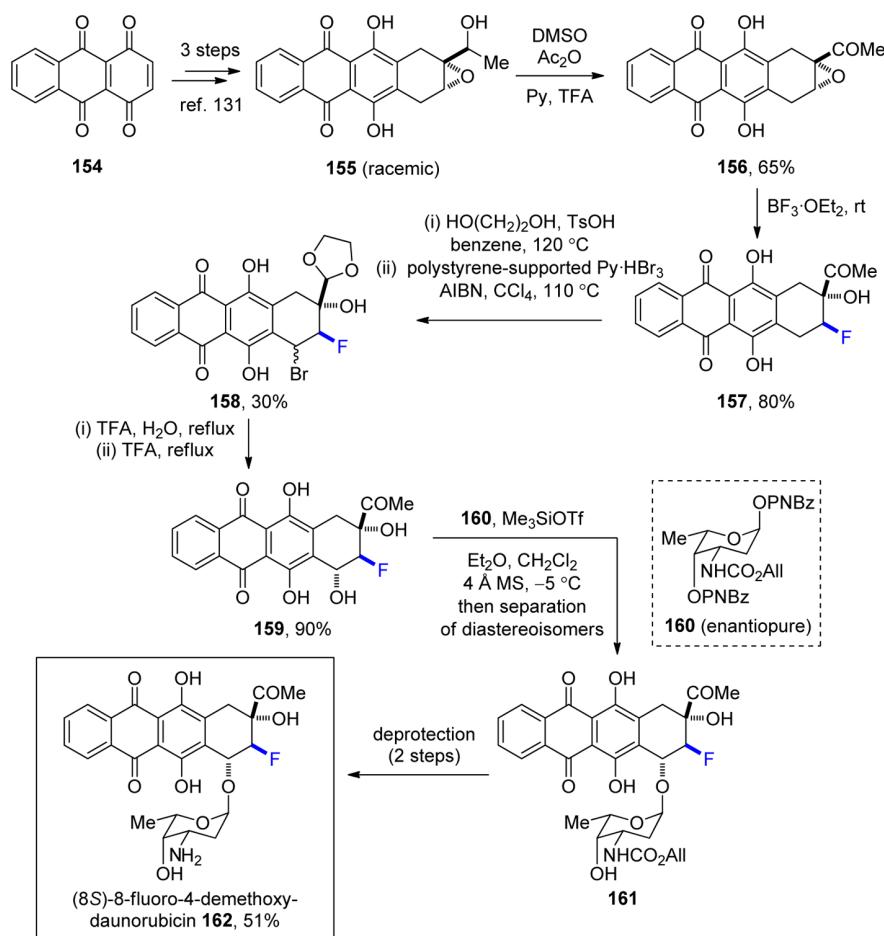
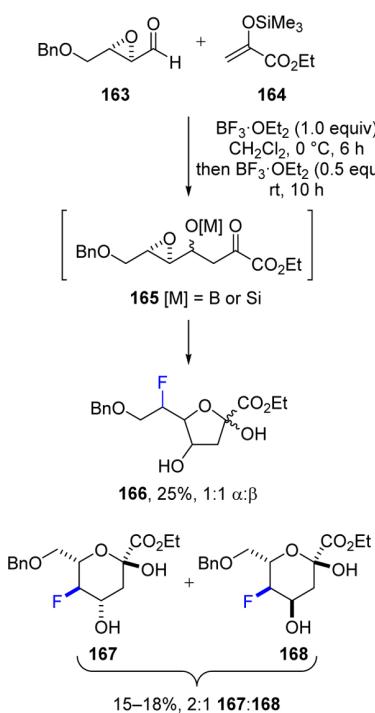
8-fluoro-4-demethoxydaunorubicin **162** in 51% yield (Scheme 42).

In another interesting application to the synthesis of fluorinated analogues of natural products (this time purely serendipitous), Baltas and co-workers have reported a route to monofluorinated ethyl dideoxyheptulosonates **166–168**.¹³² Specifically, the $\text{BF}_3\cdot\text{OEt}_2$ -promoted Mukaiyama aldol addition of enantiopure *trans*- α,β -epoxyaldehyde **163** with silyl enol ether **164** gave **166–168**, albeit in low isolated yields. NMR spectroscopic analyses of **166–168** indicated that ring-opening fluorination had occurred with inversion of configuration on each carbon of the oxirane. Subjection of *trans*- α,β -epoxyaldehyde **163** to $\text{BF}_3\cdot\text{OEt}_2$ in the absence of silyl enol ether **164** led only to degradation, suggesting a mechanism proceeding via initial aldolization to give aldotate **165**, which undergoes further reaction with $\text{BF}_3\cdot\text{OEt}_2$ to generate fluorohydrin products that subsequently cyclize (Scheme 43).

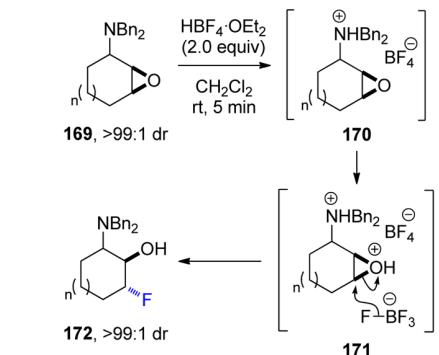
Davies and co-workers have described the utility of $\text{HBF}_4\cdot\text{OEt}_2$ as a nucleophilic fluorinating agent for the ring-opening fluorination of cyclic 2,3-epoxy amines (readily prepared by ammonium-directed epoxidation of the corresponding allylic amines),¹³³ providing a practical and scalable synthesis of stereodefined amino fluorohydrins.¹³⁴ Thus, treatment of a range of carbocyclic 2,3-epoxy amines **169** with 2.0 equiv of $\text{HBF}_4\cdot\text{OEt}_2$ in CH_2Cl_2 at room temperature for 5 min delivered the corresponding amino fluorohydrins **172** as single diastereoisomers (Scheme 44). A plausible mechanistic rationale for this transformation is that initial *N*-protonation of the amine by HBF_4 ¹³⁵ to give epoxy ammonium species **170** is followed by O-protonation of the oxirane to give dication **171**, and then $\text{S}_{\text{N}}2$ -type ring-opening by transfer of fluoride from a BF_4^- ion to give **172**. The regioselectivity of the latter is consistent with previous observations concerning the ring-opening of these 2,3-epoxy amines¹³³ (and other related epoxides)¹³⁶ with a variety of Brønsted acids: the destabilizing electron-withdrawing influence of the ammonium moiety on the transition state is less pronounced if ring-opening occurs at the carbon atom distal to it.^{86a} The importance of the amino moiety within epoxides **169** in promoting this transformation was underscored by the attempted ring-opening fluorination of cyclohexene oxide and *syn*-1,2-epoxy-3-benzyloxycyclohexane, both of which underwent cationic polymerization¹³⁷ under these conditions, presumably via an $\text{S}_{\text{N}}2$ -type ring-opening mechanism.¹³⁸ It is well precedented that electrostatic repulsion between like-charged monomers can retard polymerization processes,¹³⁹ and it is plausible that polymerization of the epoxy ammonium species **170** may be suppressed by the same effect.¹⁴⁰ The ammonium moiety may also serve to disfavor ionization of the protonated oxirane by imparting a strong inductive withdrawal effect, preventing carbocationic pathways from competing with nucleophilic attack by fluoride transfer from a BF_4^- ion.⁸³

This ring-opening fluorination protocol proved equally amenable to acyclic 2,3- and 3,4-epoxy amine substrates **173**, and again an inversion of configuration (where relevant) was observed, leading to fluorohydrins **174** (Scheme 45).¹³⁴

The applicability of this methodology to the preparation of stereodefined β -fluoro amines was also showcased in an asymmetric synthesis of (*S,S*)-3-deoxy-3-fluorosafingol **183**.¹³⁴ Thus, 2,3-epoxy amine **178**, which can be readily prepared from the corresponding enantiopure epoxy alcohol **176**, was subjected to $\text{HBF}_4\cdot\text{OEt}_2$ in CH_2Cl_2 for 5 min to give amino fluorohydrin **179** in 79% yield as a single stereoisomer (>99:1

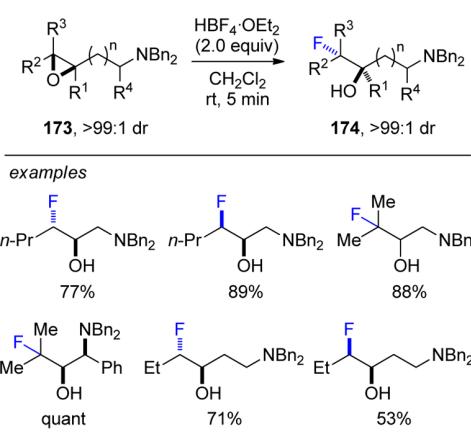
Scheme 42. Synthesis of (8*S*)-8-Fluoro-4-demethoxydaunorubicin 162Scheme 43. Fluorination of *trans*- α,β -Epoxyaldehyde 163

Scheme 44. Fluorination of Carbocyclic 2,3-Epoxy Amines 169



dr, >98% ee). The conversion of fluorohydrin 179 to chloride 181 via an Appel chlorination occurred with retention of configuration, consistent with reaction via an aziridinium ion intermediate 180, which undergoes reversible ring-opening with chloride ion to give the thermodynamic product 181.

Scheme 45. Fluorination of Acyclic 2,3- and 3,4-Epoxy Amines 173



Reformation of the aziridinium ion **180** in *N,N*-dimethylformamide (DMF) at 100 °C in the presence of KOAc led to irreversible ring-opening with acetate ion at the least-substituted carbon atom, effecting the net migration of the amino group from C(1) to C(2).¹⁴¹ Cleavage of the acetate with K₂CO₃ in MeOH to give amino alcohol **182** was followed by hydrogenolytic *N*-debenzylolation, giving (*S,S*)-3-deoxy-3-fluorosafingol **183** in 38% overall yield over the seven steps from allylic alcohol **175** (Scheme 46).¹³⁴

3.1.3. Aryl Epoxides. The first example of the ring-opening fluorination of an aryl epoxide with BF₃·OEt₂ was described by House in 1956, during his seminal studies on the mechanism of the acid-catalyzed rearrangement of α,β -epoxy ketones.^{115a} Specifically, the treatment of chalcone oxide **184** with 0.5 equiv of BF₃·OEt₂ in Et₂O at reflux for 30 min unexpectedly gave fluorohydrin **186** in 59% yield, with the anticipated [1,2]-acyl migration product **187**, isolated in only 3% yield as the corresponding copper(II) complex **188** by addition of cupric acetate during workup (Table 6, entry 1). Although not mentioned in the original report, the *syn*-configuration within **186** was subsequently assigned by House in a follow-up publication, in which the reactivity of **186** was compared to the analogous *syn*- and *anti*-chlorohydrins of known relative

Table 6. Fluorination of Chalcone Oxide 184

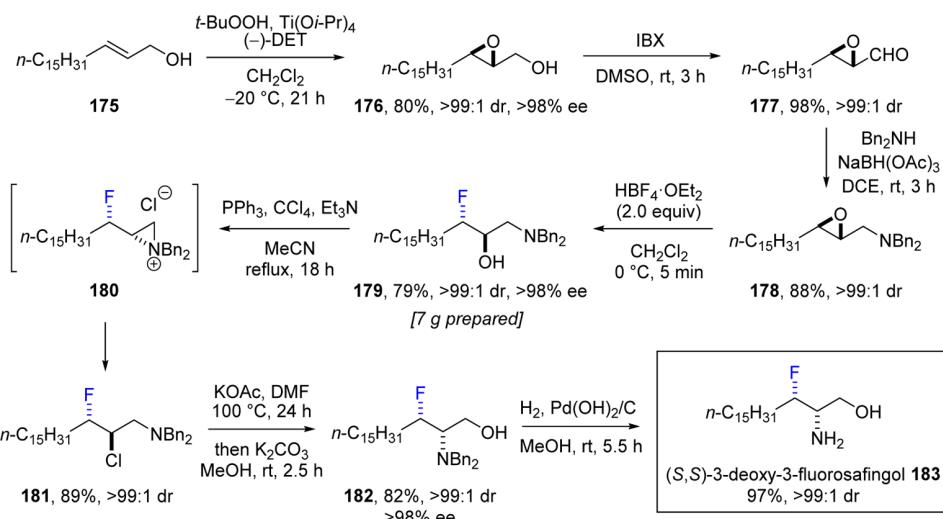
184 **185** **186**

187 **188** **189**

entry	conditions	186 yield %	187 yield %
1	BF ₃ ·OEt ₂ (0.5 equiv), Et ₂ O, reflux, 30 min	59	3 (as 188)
2	BF ₃ ·OEt ₂ (5.0 equiv), Et ₂ O, reflux, 30 min	7	65 (as 188)
3	BF ₃ ·OEt ₂ (2.0 equiv), benzene, rt, 20 min	0	quant (as 189)

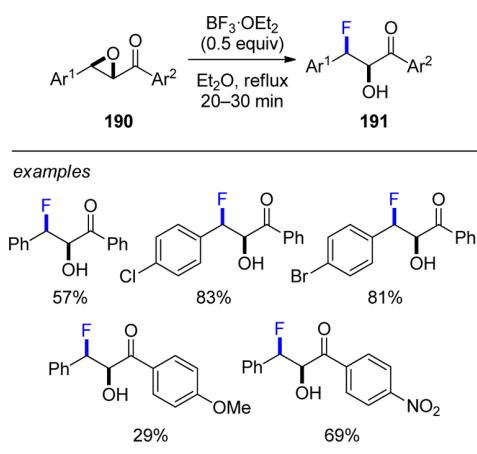
configuration¹⁴² (this stereochemical assignment was later confirmed in 1994 by other investigators via single-crystal X-ray diffraction analysis of a derivative of **186**).¹⁴³ Mechanistically, it was proposed that fluorohydrin **186** may arise from the BF₃-epoxide complex **185** via a concerted epoxide cleavage and intramolecular fluoride transfer process.^{115c} It was also found that increasing the quantity of BF₃·OEt₂ to 5.0 equiv resulted in a lower yield (7%) of fluorohydrin **186**, with an attendant increase in the yield (65%) of β -keto aldehyde **187** (Table 6, entry 2).^{115a} In benzene as the reaction medium, only β -keto aldehyde **187** was produced (and isolated as either complex **188** or pyrazole **189**, the latter formed upon addition of phenylhydrazine on workup) and no fluorohydrin **186** could be obtained, regardless of the quantity of BF₃·OEt₂ employed (Table 6, entry 3). Although fluorohydrin **186** could be converted to **187** upon exposure to excess BF₃·OEt₂ in either Et₂O or benzene, kinetic studies probing the possibility of an O-difluoroboryl derivative of fluorohydrin **186** as an intermediate in the [1,2]-acyl migration reaction from epoxide **184** were inconclusive.

Scheme 46. Synthesis of (*S,S*)-3-Deoxy-3-fluorosafingol 183



The generality of House's reaction conditions in the ring-opening fluorination of a range of aryl-substituted chalcone oxide derivatives **190** with $\text{BF}_3\cdot\text{OEt}_2$ has been demonstrated by Weber and co-workers (nine examples, 40–92% yield), with *syn*-configurations assigned to the fluorohydrins **191** on the basis of $^1\text{H}-^1\text{H}$, $^1\text{H}-^{19}\text{F}$, and $^1\text{H}-^{13}\text{C}$ coupling constant analyses (Scheme 47).¹⁴⁴ Other isolated examples of the

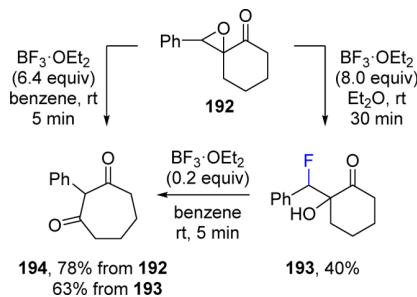
Scheme 47. Fluorination of Aryl-Substituted Chalcone Oxide Derivatives **190**



formation of fluorohydrins as minor products from the reaction of *trans*-chalcone oxide derivatives with $\text{BF}_3\cdot\text{OEt}_2$ have also been reported,¹⁴⁵ and *syn* relative configurations have later been speculated by other investigators.¹⁴³

In further studies concerning the mechanism of the acid-catalyzed rearrangement of α,β -epoxy ketones, House and Wasson observed that the treatment of epoxide **192** with excess $\text{BF}_3\cdot\text{OEt}_2$ in Et_2O at room temperature gave fluorohydrin **193** in 40% yield.^{115b} However, the relative configurations within epoxide **192** and fluorohydrin **193** were not assigned. As before, the use of benzene as the reaction solvent led exclusively to 1,3-diketone **194**, which could also be obtained by exposure of fluorohydrin **193** to $\text{BF}_3\cdot\text{OEt}_2$ in benzene (Scheme 48). Hinoue, Nojima, and Tokura have studied the

Scheme 48. Fluorination of Epoxide **192**

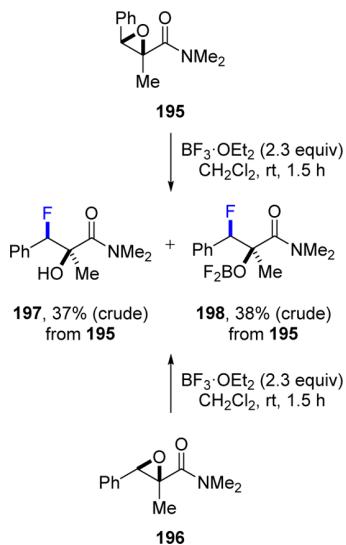


reaction of epoxide **192** with $\text{BF}_3\cdot\text{OEt}_2$ more closely, using concentration–time plots to monitor the change of product distribution with time in both Et_2O and benzene as solvents.^{87b} The results indicated that 1,3-diketone **194** is formed from epoxide **192** via the intermediacy of fluorohydrin **193** (as its *O*-difluoroboryl derivative) in both Et_2O and benzene as the reaction solvent, but that a competitive pathway involving

direct isomerization of **192** may also be operative in benzene. Also, the rate of formation and decomposition of fluorohydrin **193** was significantly more rapid in benzene as compared to Et_2O . Interestingly, in liquid SO_2 as the solvent at -70°C , only 1,3-diketone **194** was formed, with no fluorohydrin **193** detectable at any stage of the reaction, implying that direct isomerization of **192** to **194** may occur exclusively in this particular solvent.

By analogy to the $\text{BF}_3\cdot\text{OEt}_2$ -mediated [1,2]-acyl migrations of α,β -epoxy ketones, the corresponding reaction with α,β -epoxy tertiary amides has been studied by Wemple et al., and fluorohydrin formation has also been observed in this case.^{87c} Thus, the treatment of both diastereoisomers of *N,N*-dimethyl-2-methyl-3-phenylglycamide **195** and **196** with $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 at room temperature afforded the same fluorohydrin diastereoisomer **197**, in addition to its *O*-difluoroboryl derivative **198**, although only crude product yields from **195** were provided (Scheme 49). By analogy to the reaction of both

Scheme 49. Fluorination of *N,N*-Dimethyl-2-methyl-3-phenylglycamides **195** and **196**

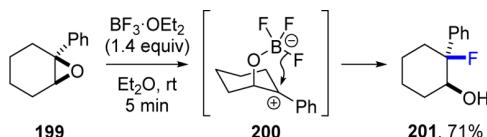


diastereoisomers of *N,N*-diethyl-3-phenylglycamides with HCl in benzene,¹⁴⁶ the authors assigned the relative configuration within **197** as (*RS,RS*). Further investigations revealed that, under more forcing conditions (i.e., a larger amount of $\text{BF}_3\cdot\text{OEt}_2$, higher temperature, extended reaction time), the initially formed fluorohydrin *O*-difluoroboryl derivative **198** suffers partial epimerization to give the (*RS,SR*)-diastereoisomer, accompanied by degradation via [1,2]-migration of the methyl or carboxamido groups.

Berti and co-workers have also reported fluorohydrin formation during investigations into the rearrangement of 1-phenylcyclohexene oxide **199** with $\text{BF}_3\cdot\text{OEt}_2$.^{115d} Under the agency of 1.4 equiv of $\text{BF}_3\cdot\text{OEt}_2$ in Et_2O at room temperature for 5 min, epoxide **199** gave *syn*-fluorohydrin **201** in 71% yield. The relative configuration within **201** was assigned on the basis of a $^1\text{H}-^{19}\text{F}$ 3J NMR coupling constant of 25.5 Hz, indicative of an antiperiplanar arrangement. To explain the retention of configuration, the authors conceived a mechanism involving epoxide cleavage by BF_3 , followed by an intramolecular fluoride transfer from the *O*-tethered alkoxytrifluoroborate moiety to the benzylic carbocation **200** (Scheme 50). On attempting the

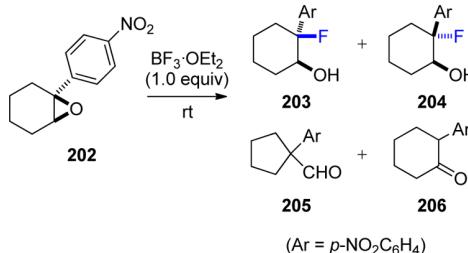
same transformation in benzene, fluorohydrin **201** could not be detected, and only carbonyl compounds arising from rearrangement were isolated.

Scheme 50. Fluorination of 1-Phenylcyclohexene Oxide 199



To study the stereochemical course of $\text{BF}_3\cdot\text{OEt}_2$ -mediated rearrangements of electron-poor aryl epoxides, which are less prone to $\text{S}_{\text{N}}1$ -like ring-opening reactions, Berti et al. extended their investigations to include 1,2-epoxy-1-(*p*-nitrophenyl)-cyclohexane **202**.¹⁴⁷ Upon reaction of **202** with 1.0 equiv of $\text{BF}_3\cdot\text{OEt}_2$ in benzene at room temperature for 2 min, a 92:8 mixture of *syn*-fluorohydrin **203** and aldehyde **205** was obtained, respectively, with no further change after 20 min. In CH_2Cl_2 , an 85:14:1 mixture of *syn*-fluorohydrin **203**, aldehyde **205**, and ketone **206**, respectively, was returned after 2 min, although after 1 h the reaction had reached completion to give a 97:3 ratio of aldehyde **205** and ketone **206**. The reaction of **202** with $\text{BF}_3\cdot\text{OEt}_2$ proved much slower in Et_2O , and, after 48 h, a 51:44:5 mixture of *syn*-fluorohydrin **203**, *anti*-fluorohydrin **204**, and aldehyde **205**, respectively, was evident (Table 7). The relative configurations within *syn*-

Table 7. Fluorination of Epoxide 202



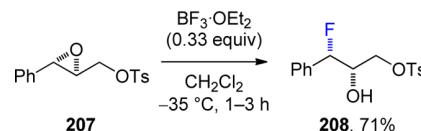
entry	solvent	time	203:204:205:206 ratio
1	benzene	2 min	92:0:8:0
2	benzene	20 min	92:0:8:0
3	CH_2Cl_2	2 min	85:0:14:1
4	CH_2Cl_2	7 min	37:0:61:2
5	CH_2Cl_2	1 h	0:0:97:3
6	CH_2Cl_2	3 h	0:0:97:3
7	Et_2O	48 h	51:44:5:0

fluorohydrin **203** and *anti*-fluorohydrin **204** were assigned by analysis of the $^1\text{H}-^{19}\text{F}$ $^3J_{\text{HF}}$ coupling constants involving the CHOH protons ($^3J_{\text{HF}} = 20$ Hz for *syn*-**203** versus $^3J_{\text{HF}} = 9$ Hz for *anti*-**204**). The authors commented that for epoxides lacking electron-releasing substituents, fluorohydriins may be the primary reaction products on treatment with a low concentration of $\text{BF}_3\cdot\text{OEt}_2$ in Et_2O , although they are not necessarily intermediates between epoxides and carbonyl compounds.

In 2004, Pericàs and co-workers divulged an efficient ring-opening fluorination of several enantiopure *trans*-3-arylglycidol derivatives using $\text{BF}_3\cdot\text{OEt}_2$ as a nucleophilic fluoride source to give the corresponding fluorohydriins as single diastereoisomers (twelve examples, 34–75% yield).¹⁴⁸ For example, treatment of **207** with 0.33 equiv of $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 at -35°C for 1 h

was shown to give *syn*-fluorohydrin **208** in 71% yield (Scheme 51).¹⁴⁹ The use of only 0.33 equiv of $\text{BF}_3\cdot\text{OEt}_2$ demonstrated

Scheme 51. Fluorination of Epoxide 207



that all three fluorine atoms within $\text{BF}_3\cdot\text{OEt}_2$ were transferable in this process. Epoxide substrates bearing electron-rich aryl groups returned only β -benzyloxy aldehydes as the sole products, and attempted reaction of an aliphatic epoxide returned only starting material, even following extended treatment with $\text{BF}_3\cdot\text{OEt}_2$ at 0°C .

Subsequent investigations by Davies et al. into the ring-opening fluorination of aryl epoxides **209**–**216** with $\text{BF}_3\cdot\text{OEt}_2$ established that *trans*- β -methyl-substituted **211** was a privileged substrate, and all other epoxide substitution patterns gave only very low levels (typically <10%, by ^{19}F NMR spectroscopic analysis of the crude reaction mixture against fluorobenzene as a standard) of fluorine incorporation (Table 8).¹⁵⁰ Thus, upon

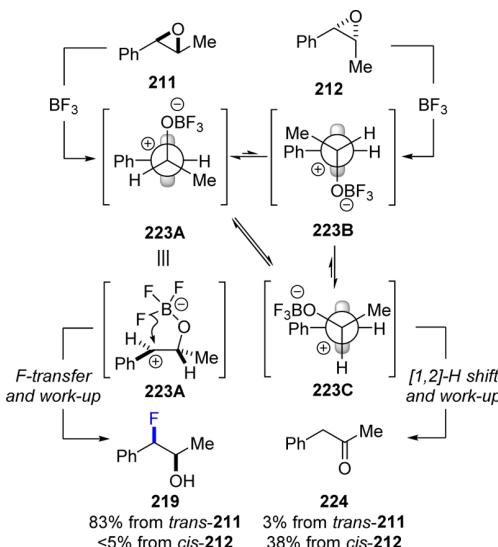
Table 8. Fluorination of Epoxides 209–216

entry	epoxide	R ¹	R ²	R ³	fluorohydrin yield %
1	209	H	H	H	217, 8 (NMR)
2	210	Me	H	H	218, 0
3	211	H	Me	H	219, 83
4	212	H	H	Me	219, 5 (NMR)
5	213	Me	H	Me	220, 13 (NMR)
6	214	Me	Me	H	220, 0
7	215	H	Me	Me	221, 0
8	216	Me	Me	Me	222, 8

treatment of *trans*- β -methyl-substituted aryl epoxide **211** (>99:1 dr) with 0.33 equiv of $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 at -20°C for 5 min, fluorohydrin **219** was obtained as a single diastereoisomer in 83% isolated yield. Single-crystal X-ray diffraction analysis of the *p*-nitrobenzoate derivative allowed the relative configuration within fluorohydrin **219** to be unambiguously assigned as *syn*. The complete conversion of starting material under these conditions demonstrates that all three fluorine atoms within $\text{BF}_3\cdot\text{OEt}_2$ are transferable in the ring-opening fluorination process (in accordance with the observation of Pericàs et al.);¹⁴⁸ in fact, the use of greater than 0.33 equiv of $\text{BF}_3\cdot\text{OEt}_2$ resulted in inferior yields of fluorohydrin **219**.

The retention of configuration¹⁵¹ in the ring-opening fluorination of *trans*-epoxide **211** with $\text{BF}_3\cdot\text{OEt}_2$ was rationalized by invoking the intermediacy of benzylic carbocation **223**. This cation would be formed in conformation **223A**, and rapid intramolecular delivery of fluoride would give *syn*-fluorohydrin **219** (after aqueous workup). An alternative pathway involving C–C bond rotation (to conformation **223C**) and subsequent [1,2]-hydride shift would ultimately result in the formation of ketone **224**. The effect of the *trans*- β -methyl substituent may be

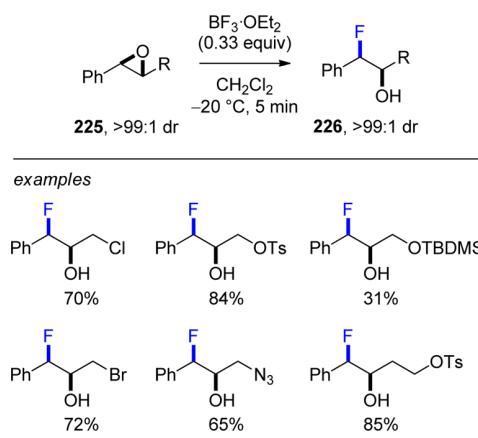
to sterically bias the carbocation intermediate in its initial conformation **223A**, increasing the activation barrier to C–C bond rotation and decreasing the rate of this process (which leads to ketone **224**) relative to fluoride transfer. The observation that ketone **224** is the major product from the reaction of *cis*-epoxide **212** with $\text{BF}_3\text{-OEt}_2$ is consistent with ionization of the epoxide– BF_3 complex to give a benzylic carbocation in initial conformation **223B**, followed by rapid C–C bond rotation to conformer **223C** to alleviate the steric interaction between the Ph and Me substituents. A rapid [1,2]-hydride shift may then ensue to give ketone **224**. The formation of <5% of *syn*-fluorohydrin **219** from *cis*-**212** implies that some interconversion of conformer **223C** to conformer **223A** occurs in competition with the [1,2]-hydride shift (Scheme 52).¹⁵⁰ Some support for this mechanistic hypothesis

Scheme 52. Fluorination of Epoxides **211** and **212**

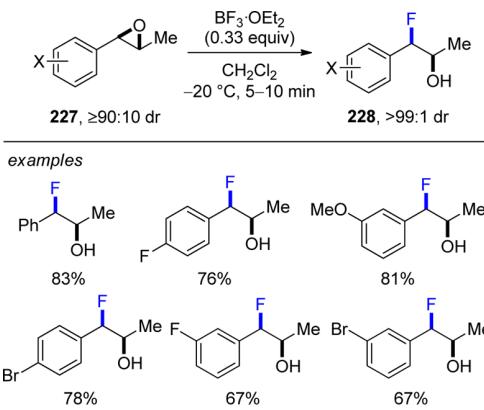
can be found in studies of Lewis acid-catalyzed epoxide rearrangements by Coxon and co-workers, in which the activation barrier to rotation about a C⁺–C bond was found to be comparable to that for a [1,2]-hydride shift.^{120,152} In other words, C⁺–C bond rotation does not occur rapidly relative to the product-determining step.

A variety of synthetically versatile functional groups appended to the oxirane ring were also tolerated in this ring-opening fluorination process, and retention of configuration was again observed. Thus, the reaction of functionalized epoxides **225** with $\text{BF}_3\text{-OEt}_2$ delivered *syn*-fluorohydribs **226** (eight examples, 31–85% yield) as single diastereoisomers in all cases (Scheme 53).¹⁵⁰

A survey of epoxides **227** bearing a diverse range of aryl substituents showed that the electronics of the aryl ring were also an important factor, with a balance in electron-releasing/withdrawing capacity required for efficient fluorination.¹⁵⁰ Specifically, arene substituents with σ^* values in the range –0.07 (X = *p*-F) to +0.41 (X = *m*-Br) were well tolerated, giving the desired *syn*-fluorohydribs in 64–81% yield. However, epoxides bearing electron-releasing aryl substituents (e.g., X = *p*-OMe, *p*-Ph, *p*-Me) gave only mixtures of nonfluorinated products containing the corresponding arylpropan-2-ones as major components, and this was attributed to the reduced electrophilicity of the intermediate benzylic carbocations. On

Scheme 53. Fluorination of Epoxides **225**

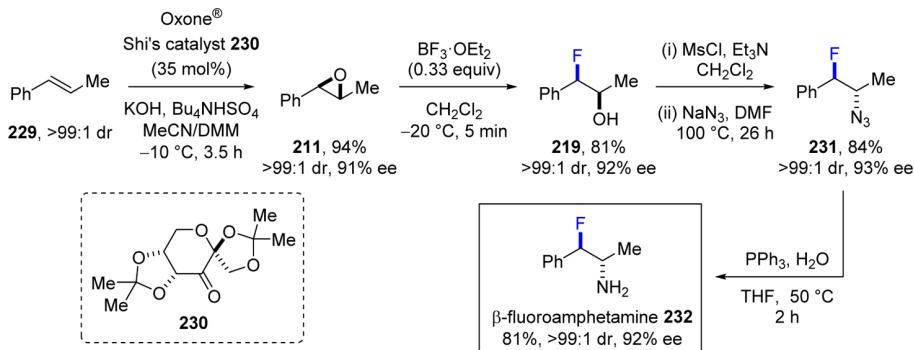
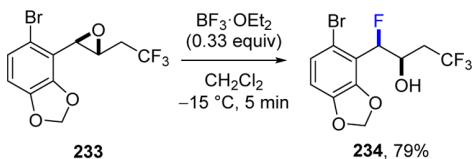
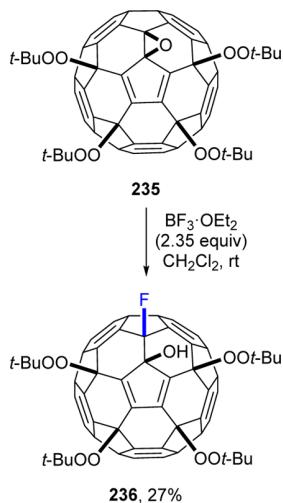
the other hand, epoxides incorporating strongly electron-withdrawing substituents on the aryl ring (e.g., X = *p*-CF₃) gave only very low conversion, and the reactions were accompanied by the formation of mixtures of unidentified, nonfluorinated products (Scheme 54).

Scheme 54. Fluorination of Epoxides **227**

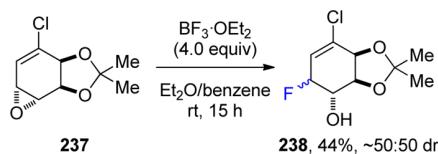
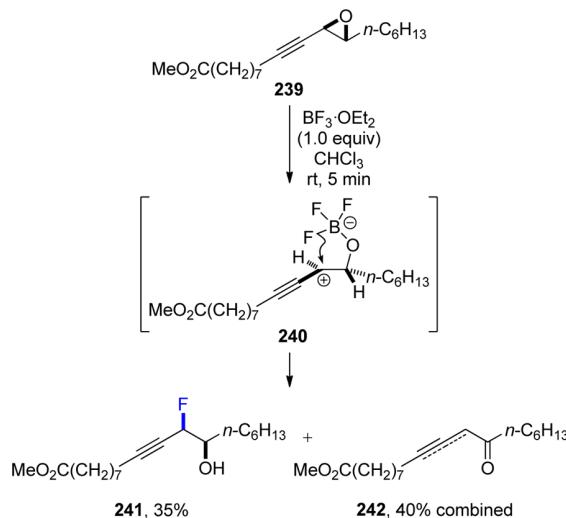
The synthetic utility of the *syn*-fluorohydrin products obtained from these reactions was also demonstrated by their elaboration to a range of β -fluoroamphetamines, including an asymmetric synthesis of (*αS,βR*)- β -fluoroamphetamine **232** using the Shi asymmetric epoxidation¹⁵³ as a key step (Scheme 55).¹⁵⁰ Overall, this sequence comprises a valuable synthetic entry to enantioenriched β -fluoro β -aryl amines, a class of fluorinated compounds that are otherwise challenging to prepare in stereodefined form.¹⁵⁴

In the course of their studies on copper-catalyzed alkene oxytrifluoromethylation reactions, Buchwald and co-workers applied this ring-opening fluorination reaction to a more heavily functionalized aryl epoxide substrate **233**, delivering the fluorohydrin **234** in 79% yield (Scheme 56).¹⁵⁵

Although not strictly an aryl epoxide, an interesting example has been disclosed of the ring-opening fluorination of a [60]fullerene epoxide **235** with $\text{BF}_3\text{-OEt}_2$ to give a fluorohydrin **236**, albeit in low (27%) isolated yield (Scheme 57).¹⁵⁶ Similarly, $\text{BF}_3\text{-OEt}_2$ has also been employed as a fluoride source in the fluorination of graphene oxide, which is proposed to occur by ring-opening fluorination of surface-based epoxides.¹⁵⁷

Scheme 55. Synthesis of ($\alpha S,\beta R$)- β -Fluoroamphetamine 232**Scheme 56. Fluorination of Epoxide 233****Scheme 57. Fluorination of [60]Fullerene Epoxide 235**

3.1.4. Alkenyl and Propargyl Epoxides. The formation of fluorohydrins from the subjection of alkenyl epoxides to $BF_3 \cdot OEt_2$ has been observed in some cases,¹⁵⁸ although this reaction has not yet been explored as a preparative fluorination method to date. In the course of studies into the synthesis of halogenated conduritols, Hudlicky and co-workers reported that the treatment of epoxide **237** with 4.0 equiv of $BF_3 \cdot OEt_2$ gave fluorohydrins **238** (as an ~50:50 mixture of diastereoisomers) in 44% yield (Scheme 58).^{158a} They suggested an S_N1 mechanism via an allylic cation to account for the stereochemical outcome. The same reaction was later studied by Méndez and co-workers and found to be initially *syn*-selective (78:22 *syn:anti* ratio after 2 min); however, *syn*-**238** is unstable and decomposes over time, although it was found not to transform into *anti*-**238**.^{158d} Density functional theory (DFT) calculations suggested the viability of a reaction mechanism proceeding via a concerted epoxide cleavage and fluoride transfer through a single transition state.

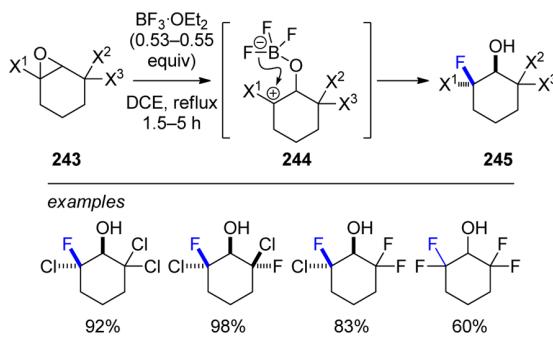
Scheme 58. Fluorination of Epoxide 237**Scheme 59. Fluorination of Epoxide 239**

Only a single example of the fluorination of a propargylic epoxide with $BF_3 \cdot OEt_2$ has been described in the literature. Brief exposure of epoxide **239** to $BF_3 \cdot OEt_2$ (1.0 equiv) in $CHCl_3$ gave *syn*-fluorohydrin **241** in 35% isolated yield, in addition to propargylic and allenic ketone byproducts **242** in 40% combined yield (Scheme 59).¹⁵⁹ The *syn*-configuration within **241** was established by comparison with an authentic sample of the corresponding *anti*-diastereoisomer, and this assignment was supported by 1H NMR coupling constant analysis. The authors proposed an S_N1 -type mechanism via a propargylic carbocation **240**, involving intramolecular delivery of a fluoride from the alkoxytrifluoroborate moiety.

3.1.5. α -Heteroatom-Containing Epoxides. The efficient regio- and stereoselective ring-opening fluorination of a number of 1,3,3-trihalogeno-7-oxabicyclo[4.1.0]heptanes **243** with $BF_3 \cdot OEt_2$ has been accomplished by Duhamel and co-workers.¹⁶⁰ The reactions were conducted with 0.53–0.55 equiv¹⁶¹ of $BF_3 \cdot OEt_2$ in 1,2-dichloroethane (DCE) at reflux, and gave the corresponding fluorohydrins **245** in excellent yield

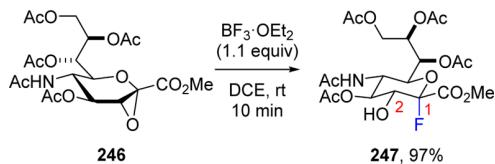
with retention of configuration (five examples, 60–98% yield). To rationalize the stereochemical outcome, the authors proposed an $S_{N}i$ -type mechanism involving epoxide cleavage to give a stabilized chlorocarbenium ion **244**, followed by an intramolecular delivery of fluoride from the alkoxytrifluoroborate moiety (Scheme 60).

Scheme 60. Fluorination of 1,3,3-Trihalogeno-7-oxabicyclo[4.1.0]heptanes **243**



Similarly, Goto and co-workers showed that the treatment of glycal epoxide **246** with $\text{BF}_3\cdot\text{OEt}_2$ in DCE gave glycosyl fluoride **247** in 97% yield with retention of configuration (Scheme 61).^{71a} The relative configuration within **247** was

Scheme 61. Fluorination of Glycal Epoxide **246**



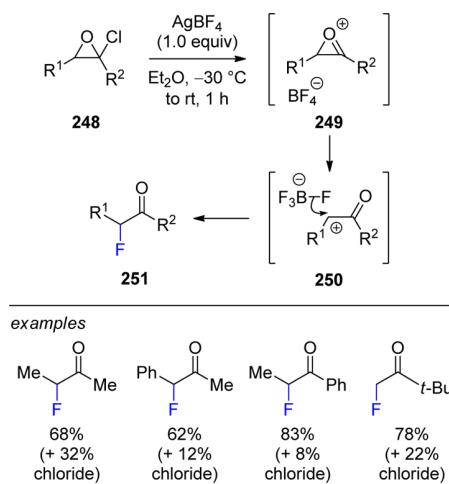
assigned on the basis of a vicinal coupling constant of 22.6 Hz between the axial $\text{C}(2)\text{H}$ proton and the $\text{C}(1)\text{F}$ atom. A similar reaction involving the ring-opening fluorination of a substituted chromone epoxide with $\text{BF}_3\cdot\text{OEt}_2$ has also been reported.¹⁶²

Griesbaum and co-workers have published a series of papers investigating the conversion of α -chloro epoxides to α -fluoro carbonyl compounds upon treatment with AgBF_4 .^{49d,163} For example, the reaction of α -chloro oxiranes **248** with AgBF_4 in Et_2O was shown to give α -fluoro carbonyl compounds **251** in good yield (five examples, up to 83% yield by GC analysis), in addition to the corresponding α -chloro carbonyl compounds as minor products.^{163a} The authors proposed a mechanism proceeding via initial formation of 2H -oxirenium ions **249** followed by electrocyclic ring-opening to highly electrophilic α -carbonyl cations **250**. Fluoride transfer from the BF_4^- ion would then give α -fluoro ketones **251**, whereas abstraction of chloride by **250** from starting material **248** would give the corresponding α -chloro ketones (Scheme 62). Furthermore, the subjecting of α,β -dichloro epoxides to AgBF_4 under various sets of reaction conditions was also shown to deliver α -fluoro- α -chloro ketones in variable yield (three examples, 28–61% yield).

3.2. Ring-Opening Fluorinations of Aziridines

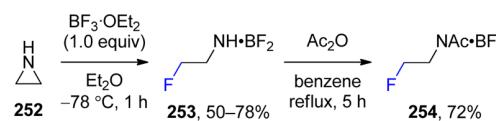
The first example of the ring-opening fluorination of an aziridine with BF_3 was documented by Voronkov and Fedotova in 1966.¹⁶⁴ Specifically, the reaction of aziridine **252** with 1.0

Scheme 62. Fluorination of α -Chloro Epoxides **248**



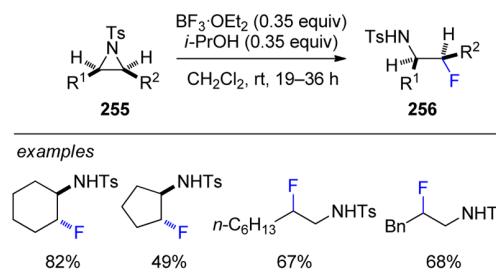
equiv of $\text{BF}_3\cdot\text{OEt}_2$ in Et_2O at -78°C gave *N*-(β -fluoroethyl)-difluoroborazene **253** in 50–78% yield, in addition to some oligomeric material. Acetylation of **253** with Ac_2O gave *N*-acetyl-*N*-(β -fluoroethyl) difluoroborazene **254** in 72% yield (Scheme 63).

Scheme 63. Fluorination of Aziridine **251**



The ring-opening fluorination of a range of aliphatic *N*-Ts aziridines **255** with $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 has been described by Hou and co-workers, affording *N*-Ts β -fluoro amines **256** in good yield (seven examples, 49–83% yield) (Scheme 64).¹⁶⁵

Scheme 64. Fluorination of Aziridines **255**

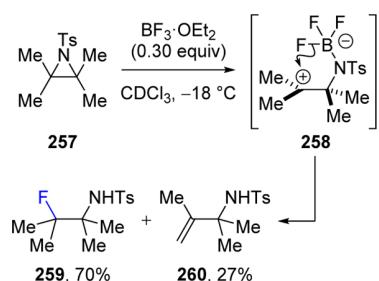


As has also been observed with aryl epoxides,^{148,150} all three fluorine atoms within $\text{BF}_3\cdot\text{OEt}_2$ were transferable in this process, necessitating the use of only 0.35 equiv of $\text{BF}_3\cdot\text{OEt}_2$. The inclusion of alcohols as additives provided a significant rate acceleration, with 0.35 equiv of *i*-PrOH proving optimal, although the role of this additive is unclear. Although not suggested by the authors, it is possible that the active fluorinating agent may in fact be $[\text{H}^+][\text{i-PrOBF}_3^-]$, with H^+ serving to activate the aziridine and *i*-PrOBF₃⁻ as the fluoride donor.

Similarly, an *N*-Ts β -fluoro amine **259** has been isolated in 70% yield from the brief treatment of *N*-Ts tetramethylaziridine **257** with 0.30 equiv of $\text{BF}_3\cdot\text{OEt}_2$ in CDCl_3 . In this case, the

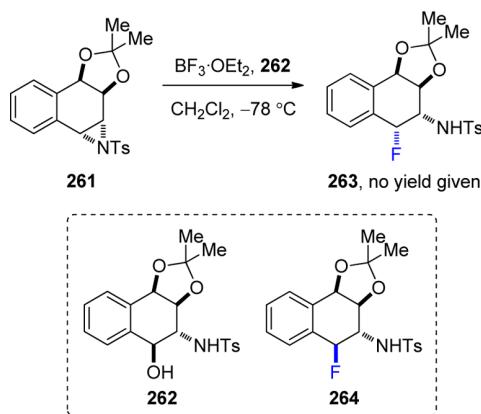
authors proposed an $S_{N}i$ -type mechanism involving carbocation intermediate 258 (Scheme 65).¹⁶⁶

Scheme 65. Fluorination of Aziridine 257



Single examples of the ring-opening fluorination of an N -2-(trimethylsilyl)ethoxycarbonyl aziridine,¹⁶⁷ N -Boc aziridine,¹⁶⁸ and an N -diethoxyphosphoryl aziridine¹⁶⁹ with $\text{BF}_3\cdot\text{OEt}_2$ have also been reported, as has the formation of N -Ts β -fluoro amines in low yield ($\leq 30\%$) from the reaction of N -Ts aziridines with either LiBF_4 ¹⁷⁰ or $[\text{Et}_3\text{O}^+][\text{BF}_4^-]$.¹⁷¹ A single example of the ring-opening fluorination of an aryl aziridine was reported by Hudlicky and co-workers,¹⁷² during the synthesis of conduramine analogues. In an attempted coupling of aziridine 261 with alcohol 262 in the presence of $\text{BF}_3\cdot\text{OEt}_2$, fluoride 263 was obtained as the only isolated product, although no yield was given (Scheme 66). The relative

Scheme 66. Fluorination of Aziridine 261



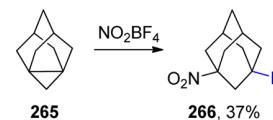
configuration within 263 was assigned by comparison of the ^1H NMR spectrum to that of an authentic sample of its diastereoisomer 264, which was prepared via the ring-opening of aziridine 261 with tetrabutylphosphonium fluoride dihydrofluoride. The retention of configuration observed upon ring-opening fluorination of 261 with $\text{BF}_3\cdot\text{OEt}_2$ is in complete accordance with the stereochemical course of the analogous reaction with aryl epoxides (section 3.1.3) and suggests that intramolecular delivery of fluoride within a benzylic carbocation intermediate may be operative.

3.3. Ring-Opening Fluorinations of Cyclopropanes

Although the ring-opening fluorination of cyclopropanes has proven valuable in the synthesis of a variety of fluorinated compounds,¹⁷³ relatively few instances of this reaction using boron fluorides or fluoroborates as the fluorinating agents are on record. For example, during studies on the reactivity of

propellane hydrocarbons with nitronium salts, Fokin and co-workers described the ring-opening nitrofluorination of 1,3-dehydroadamantane 265 with NO_2BF_4 (solvent and reaction conditions not specified), which gave fluoride 266 in 37% yield (Scheme 67). Interestingly, non-nitrated fluorinated prod-

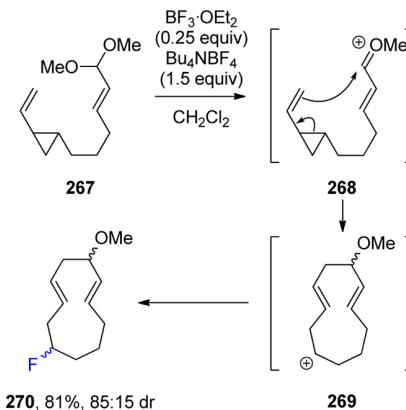
Scheme 67. Fluorination of 1,3-Dehydroadamantane 265



ucts (a difluoride, an acetoxy fluoride, or an acetamido fluoride, depending on the solvent) were obtained upon treatment of the homologous cyclobutane compound 3,6-dehydrohomoadamantane with NO_2BF_4 .

Other examples have involved the generation of a carbocation adjacent to a cyclopropane to induce ring-opening, resulting in the formation of homoallylic fluoride products. For example, during investigations into the synthesis of 11-membered rings via the intramolecular trapping of allylic carbocations with alkenyl cyclopropanes, Gassman and Riehle showed that treatment of alkenyl cyclopropane 267 with $\text{BF}_3\cdot\text{OEt}_2$ and Bu_4NBF_4 in CH_2Cl_2 gave an 85:15 mixture of diastereoisomeric fluorides 270 in 81% combined yield (Scheme 68).¹⁷⁵ Similar reactions of alkenyl cyclopropanes leading to homoallylic fluorides have been observed during acylfluorinations with $[\text{RCO}^+][\text{BF}_4^-]$ reagents (section 4.5).

Scheme 68. Fluorination of Cyclopropane 267

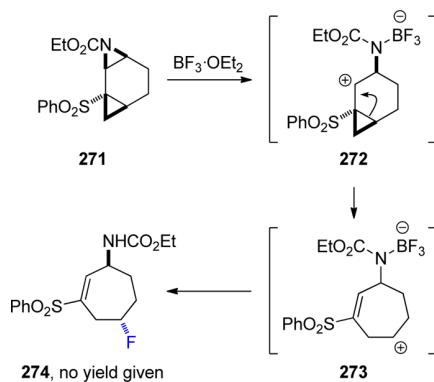


Similarly, during an attempted synthesis of the azabicyclic skeleton of the tropane alkaloids by a ring-expansion/intramolecular nucleophilic attack strategy, Löfström and Bäckvall found that the treatment of N -CO₂Et aziridine cyclopropane 271 with $\text{BF}_3\cdot\text{OEt}_2$ led not to the desired bicyclic framework but to a fluorinated aminocycloheptene 274 as the sole product, although no yield was given (Scheme 69).¹⁷⁶

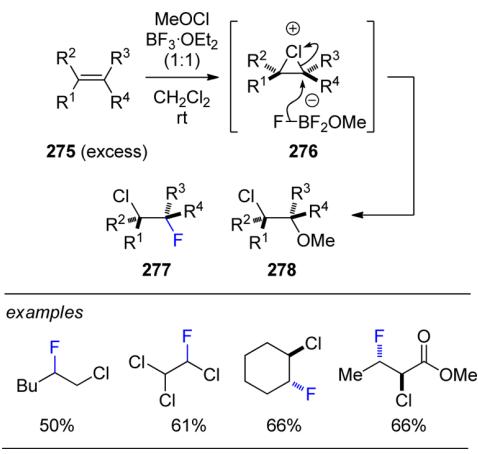
4. ADDITIONS TO ALKENES, ALKYNES, AND ALLENES

4.1. Halofluorination

Heasley, Heasley, and co-workers have reported a protocol for the chlorofluorination and bromofluorination of a range of alkenes using methyl hypohalites, MeOCl or MeOBr , in combination with $\text{BF}_3\cdot\text{OEt}_2$.¹⁷⁷ Although this method benefits from operational simplicity, short reaction times, and

Scheme 69. Fluorination of Aziridine Cyclopropane 271

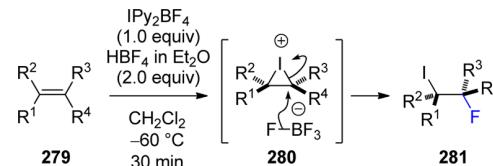
inexpensive reagents, the formation of α -methoxy halide byproducts arising from competitive methoxy transfer is a drawback, as these must be separated from the desired α -fluoro halides. With MeOCl as the hypohalite reagent, treatment of a 5-fold excess of alkenes 275 with a 1:1 mixture of MeOCl and $\text{BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 gave mixtures of β -fluoro chloride 277 and β -methoxy chloride 278 products (nine examples, 8–76% yield of 277 by GC analysis, based on MeOCl as the limiting reagent).^{177b} The factors affecting the ratio of products 277 to 278 were also evaluated. Specifically, (i) chloriranium ions proved more fluorophilic than bromiranium ions; (ii) use of the less polar CCl_4 rather than CH_2Cl_2 gave more F incorporation; (iii) electron-rich and electron-poor alkenes were comparable, although styrene gave very low F incorporation; and (iv) the ratio of 277 to 278 increased markedly on raising the temperature from -78 to 25 °C. The mechanism of this reaction was postulated to involve fluoride transfer to a chloriranium ion intermediate 276 from the MeOBF_3^- ion (Scheme 70).¹⁷⁸ In a follow-up study, the authors also showed

Scheme 70. Chlorofluorination of Alkenes 275

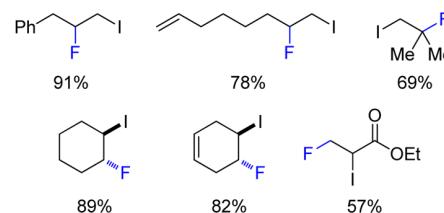
that *N*-chloro and *N*-bromo amines and amides were potential replacements for methyl hypohalites, and that the α -fluoro halide products could be more easily separated from the *N*-nucleophile addition products, although the yields were often low.¹⁷⁹

Barluenga and co-workers have demonstrated that the iodofluorination of a range of alkenes 279 can be achieved using bis(pyridine)iodine(I) tetrafluoroborate (IPy_2BF_4)⁶⁴ in conjunction with HBF_4 in Et_2O to give the corresponding α -

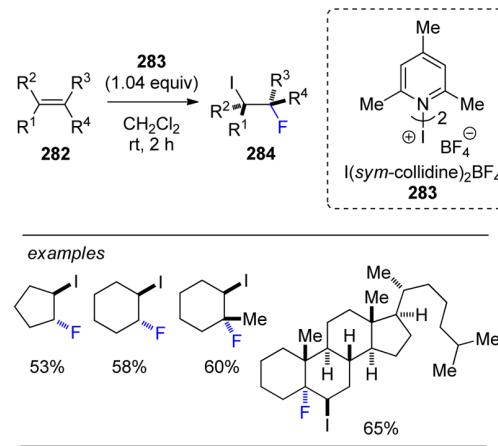
fluoro iodides 281 in good to excellent yields (eight examples, 57–91% yield).¹⁸⁰ The HBF_4 was required to protonate the pyridine and prevent it from competing as a nucleophile. The authors proposed the intermediacy of iodiranium ions 280, which are attacked by fluoride transfer from a BF_4^- ion (Scheme 71).

Scheme 71. Iodofluorination of Alkenes 279

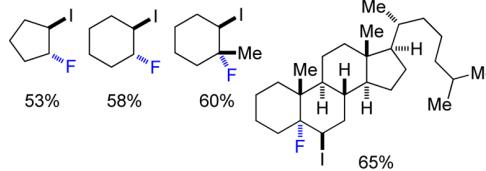
examples



Similarly, Evans and Shauble have shown that bis(*sym*-collidine)iodine(I) tetrafluoroborate [$\text{I}(\text{sym-collidine})_2\text{BF}_4$] 283 can be used in the absence of HBF_4 to effect the iodofluorination of alkenes 282 in good yields (four examples, 53–65% yield) (Scheme 72).¹⁸¹

Scheme 72. Iodofluorination of Alkenes 282

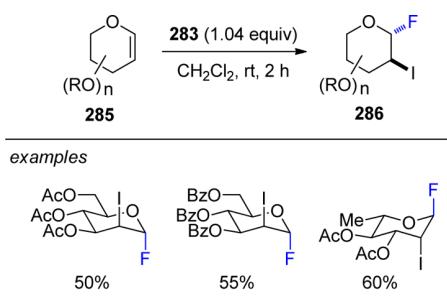
examples



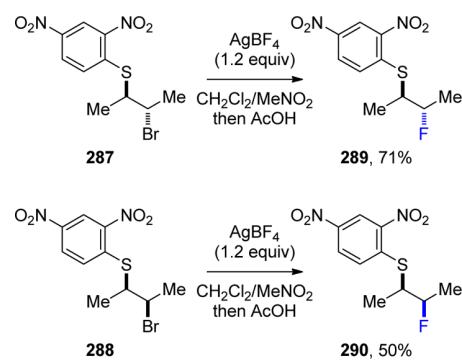
Evans and Shauble also showcased the utility of $[\text{I}(\text{sym-collidine})_2\text{BF}_4]$ 283 as a reagent for the iodofluorination of glycals 285 to give glycosyl fluorides 286 (five examples, 10–60% yield) (Scheme 73).¹⁸¹ Although regio- and stereoisomeric products were also formed in small amounts, the major products could be isolated cleanly upon chromatographic purification.

4.2. Sulfenylfluorination

The ability of thiiranium ion intermediates to undergo stereospecific nucleophilic ring-opening by fluoride transfer from the BF_4^- ion has been demonstrated by Smit and co-workers. Thus, treatment of the diastereoisomeric β -bromo

Scheme 73. Iodofluorination of Glycals 285

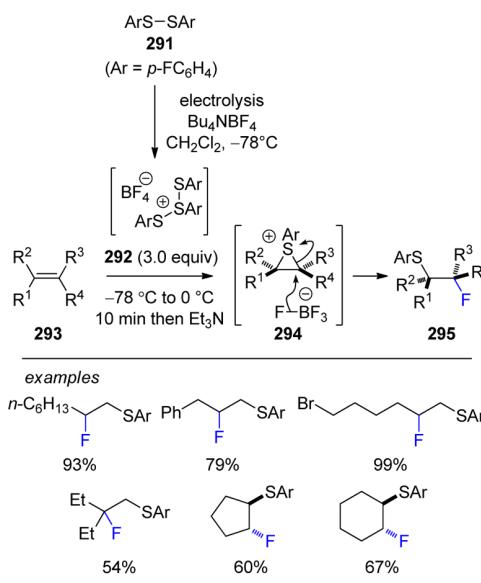
thioethers **287** and **288** with AgBF_4 in $\text{CH}_2\text{Cl}_2/\text{MeNO}_2$ followed by AcOH , gave the corresponding β -fluoro thioethers **289** and **290**, respectively, with overall retention of configuration (Scheme 74).¹⁸²

Scheme 74. Fluorination of β -Bromo Thioethers **287 and **288****

Although several isolated examples of the direct sulfonyl-fluorination of bicyclic alkenes (accompanied by Wagner–Meerwein skeletal rearrangements) with $\text{BF}_3\cdot\text{OEt}_2$ ¹⁸³ or BF_4^- sources¹⁸⁴ are on record, these reactions are not of general synthetic utility. However, Yoshida et al. have developed a general sulfonyl-fluorination of alkenes utilizing arylbis(arylsulfanyl)sulfonium tetrafluoroborates **292** as reagents, which are pregenerated in situ by anodic oxidation of ArSSAr **291** ($\text{Ar} = p\text{-FC}_6\text{H}_4$) in CH_2Cl_2 , with Bu_4NBF_4 as the supporting electrolyte.¹⁸⁵ Using this method, a range of alkenes **293** could be converted to the corresponding β -fluoro thioethers **295** in good to excellent yield (six examples, 54–99% yield) (Scheme 75).

The method also proved applicable to the *anti*-stereoselective sulfonyl-fluorination of internal alkynes. While the symmetrical alkyne 4-octyne **296** afforded a single (*E*)- β -fluoro alkenyl thioether product **297** in 81% yield, the unsymmetrical alkyne 2-heptyne **298** returned a mixture of regioisomeric products **299** and **300** in 35% and 32% yield, respectively. Interestingly, reaction of a propargylic ether substrate **301** led to formation of (*E*)- β -fluoro alkenyl thioether **303** as a single regioisomer in 86% yield. The authors suggested that coordination of the ether moiety as a Lewis base to the sulfur atom of the thiirenium ion intermediate **302** may be responsible for the high regioselectivity of attack by the BF_4^- ion (Scheme 76).

Similarly, Spagnolo and co-workers have disclosed an interesting method for the synthesis of (*E*)- β -fluoro alkenyl thioethers **308** via the regioselective and stereospecific *anti*-sulfonyl-fluorination of a range of terminal and internal alkynes

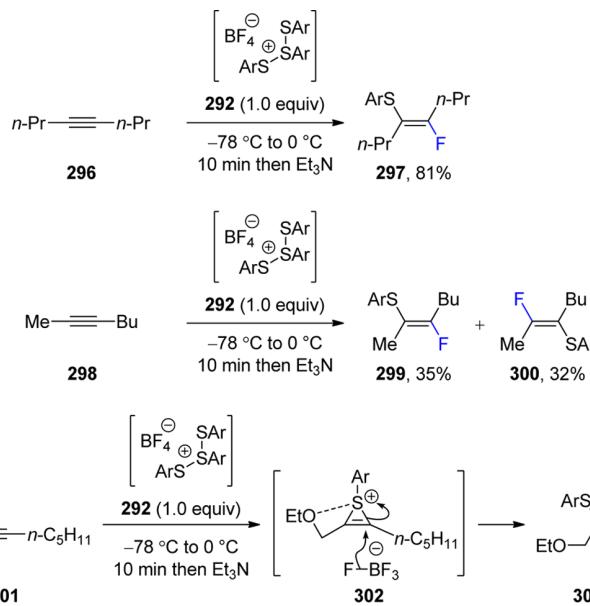
Scheme 75. Sulfonyl-fluorination of Alkenes **293**

304 using 4'-nitrobenzenesulfenylanilide (NBSA) **305** in the presence of $\text{BF}_3\cdot\text{OEt}_2$ and Bu_4NBF_4 (thirteen examples, 6–87% yield based on NBSA as the limiting reagent).¹⁸⁶ A mechanism involving transfer of fluoride to a thiirenium ion intermediate **307** from either BF_4^- or ArNHBF_3^- was favored by the authors (Scheme 77).

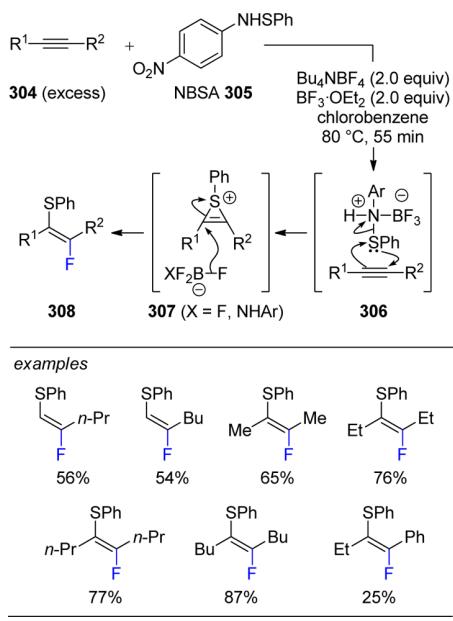
4.3. Hydroxyfluorination

In a merger of their work on the ammonium-directed olefinic oxidation of alkenyl amines¹³³ and the ring-opening fluorination of 2,3- and 3,4-epoxy amines with $\text{HBF}_4\cdot\text{OEt}_2$,¹³⁴ Davies and co-workers have developed a protocol for the direct hydroxyfluorination of allylic amines to the corresponding amino fluorohydrins, using *meta*-chloroperbenzoic acid (*m*-CPBA) as the oxidant and $\text{HBF}_4\cdot\text{OEt}_2$ in a dual role as both a Brønsted acid *N*-protecting agent and a nucleophilic fluoride source.¹⁸⁷ For example, the action of 2.0 equiv of $\text{HBF}_4\cdot\text{OEt}_2$ and 2.0 equiv of *m*-CPBA on allylic amine **309** in CH_2Cl_2 led to a mixture of compounds containing an 85:15 ratio of diastereoisomeric amino fluorohydrins **312** and **315**. After acetylation of the crude product mixture followed by chromatographic purification and methanolysis of the resultant acetate, **312** was isolated as a single diastereoisomer in 45% yield. The formation of amino fluorohydrin **312** is consistent with a mechanism proceeding via ammonium-directed epoxidation to give an intermediate *syn*-epoxide **311**,^{133a} followed by a highly regioselective and stereospecific $\text{S}_{\text{N}}2$ -type ring-opening fluorination of the oxirane with $\text{HBF}_4\cdot\text{OEt}_2$.¹³⁴ Curiously, if the amount of $\text{HBF}_4\cdot\text{OEt}_2$ employed in the reaction was increased to 20 equiv, the reaction diastereoselectivity was reversed, giving the diastereoisomeric amino fluorohydrin **315** as the major product. Moreover, the rate of reaction in the presence of 20 equiv of $\text{HBF}_4\cdot\text{OEt}_2$ was significantly faster than the corresponding hydroxyfluorination with only 2.0 equiv of $\text{HBF}_4\cdot\text{OEt}_2$.¹⁸⁸ Following an acetylation–purification–methanolysis sequence, **315** could be isolated as a single diastereoisomer in 49% yield (Scheme 78).¹⁸⁷ To reconcile these observations, it was proposed that protonation of the *m*-CPBA occurs at high concentrations of $\text{HBF}_4\cdot\text{OEt}_2$, leading to a more reactive oxidizing agent that

Scheme 76. Sulfenylfluorination of Alkynes 296, 298, and 301



Scheme 77. Sulfenylfluorination of Alkynes 304

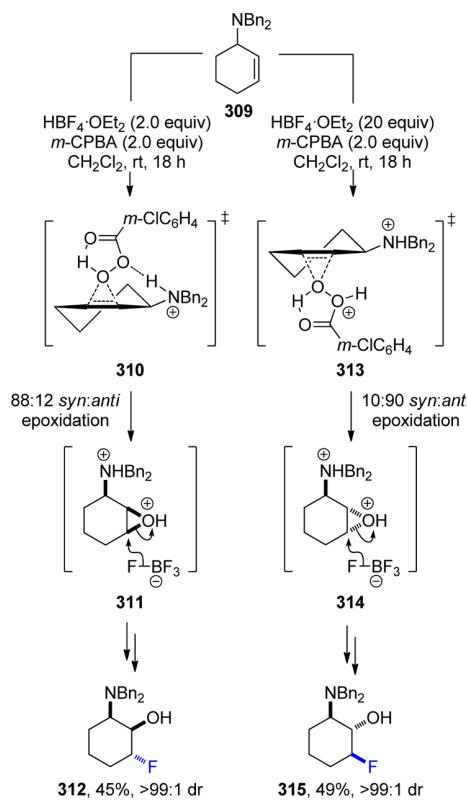


reacts preferentially on the face of the olefin opposite to the ammonium moiety, to minimize destabilizing steric, electrostatic, or dipole–dipole repulsion effects.

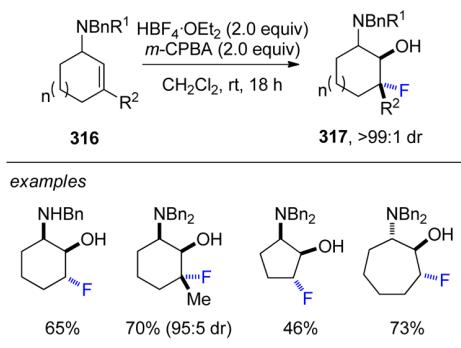
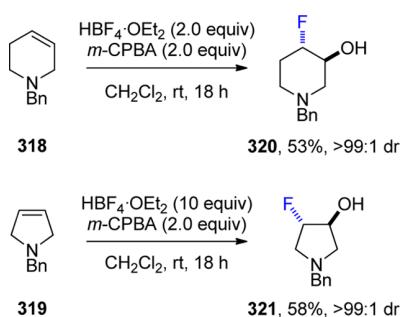
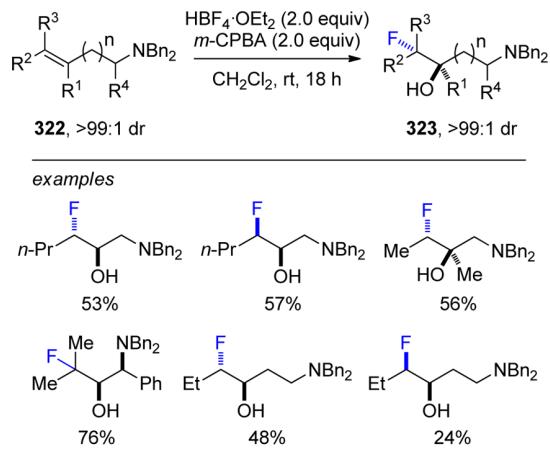
This transformation proved applicable to a range of carbocyclic allylic amines **316** upon treatment with 2.0 equiv of $\text{HBF}_4\cdot\text{OEt}_2$ and 2.0 equiv of *m*-CPBA (Scheme 79).¹⁸⁷ Azacyclic allylic amine substrates **318** and **319** were also viable substrates for this reaction, providing a convenient entry to fluorinated piperidine **320** and pyrrolidine **321** (Scheme 80).

Finally, the applicability of this hydroxyfluorination reaction to acyclic allylic and homoallylic amines **322** was assessed, and the corresponding amino fluorohydrins **323** were obtained as single diastereoisomers in moderate to good yields (nine examples, 24–82% yield) (Scheme 81).

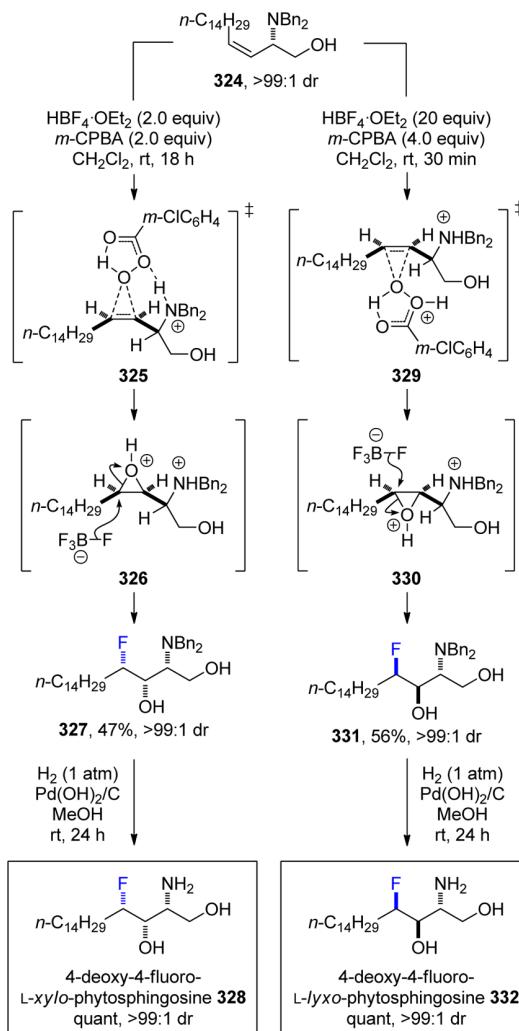
Scheme 78. Hydroxyfluorination of Allylic Amine 309



To showcase the utility of this fluorination methodology, it was then applied to a diastereodivergent synthesis of 4-deoxy-4-fluorophytosphingosines.¹⁸⁷ Thus, enantiopure allylic amine **324** (readily derived in three steps from Garner's aldehyde) was subjected to 2.0 equiv of $\text{HBF}_4\cdot\text{OEt}_2$ and 2.0 equiv of *m*-CPBA in CH_2Cl_2 to give 2,3-*syn*-3,4-*syn* amino fluorohydrin **327** as the major product, which was isolated in 47% yield as a single diastereoisomer. Alternatively, increasing the amount of $\text{HBF}_4\cdot\text{OEt}_2$ to 20 equiv reversed the diastereofacial selectivity

Scheme 79. Hydroxyfluorination of Allylic Amines 316**Scheme 80. Hydroxyfluorination of Allylic Amines 318 and 319****Scheme 81. Hydroxyfluorination of Allylic and Homoallylic Amines 322**

of the oxidation, instead leading to *2,3-anti-3,4-syn* amino fluorohydrin 331, which was isolated in 56% yield as a single diastereoisomer. In the latter case, increasing the amount of *m*-CPBA to 4.0 equiv and shortening the reaction time to 30 min proved vital to circumvent decomposition of fluorohydrin 331 to an undesired tetrahydrofuran product, a process involving a BF_3 -assisted, *5-exo-tet* cyclization of the C(1)-hydroxy group onto the C(4)-F bond. The diastereoselectivities in both cases are consistent with reactive conformations of the (protonated) allylic amine which minimize A^{1,3} strain. Finally, hydrogenolytic N-debenzylolation of amino fluorohydriins 327 and 331 furnished 4-deoxy-4-fluorophytosphingosines 328 and 332, respectively, in quantitative yield in each case (Scheme 82).

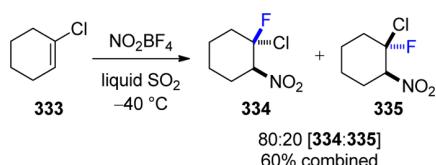
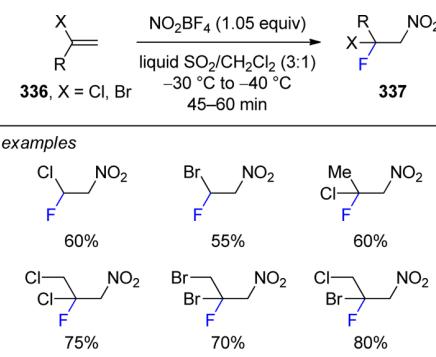
Scheme 82. Synthesis of 4-Deoxy-4-fluorophytosphingosines 328 and 332

4.4. Nitrofluorination

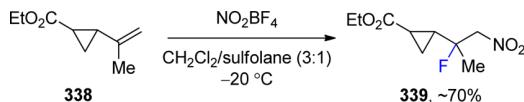
Several examples of the nitrofluorination of alkenes to furnish β -nitro fluorides have been reported using NO_2BF_4 as a reagent.¹⁸⁹ While the reaction of simple, unfunctionalized alkenes with NO_2BF_4 yields unsaturated nitro compounds with only low yields of β -nitro fluorides,¹⁹⁰ substrates that furnish more stabilized carbocation intermediates can lead to synthetically useful yields of the latter. For example, the reaction of alkenyl halides with NO_2BF_4 , in which the carbocation intermediate is stabilized by the halogen atom, gives β -nitro fluorides as the major products in generally good yields.^{190a,c,191} Thus, the reaction of 1-chlorocyclohexene 333 with NO_2BF_4 in liquid SO_2 at -40°C gave an 80:20 mixture of *syn*- and *anti*- β -fluoro- β -chloro nitro compounds 334 and 335, respectively, in 60% combined yield (Scheme 83).^{191a}

Under similar conditions, α -substituted alkenyl halides 336 have been shown to give β -nitro fluorides 337 in good yields on exposure to NO_2BF_4 (seven examples, 55–80% yield) (Scheme 84).^{191b}

Interestingly, a cyclopropyl substituent on the alkene also seems to be capable of sufficiently stabilizing the intermediate carbocation to allow for efficient nitrofluorination. Specifically, the reaction of alkenyl cyclopropane 338 with NO_2BF_4 gave β -

Scheme 83. Nitrofluorination of 1-Chlorocyclohexene 333**Scheme 84.** Nitrofluorination of Alkenyl Halides 336

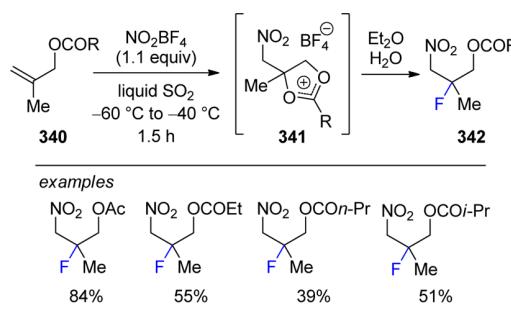
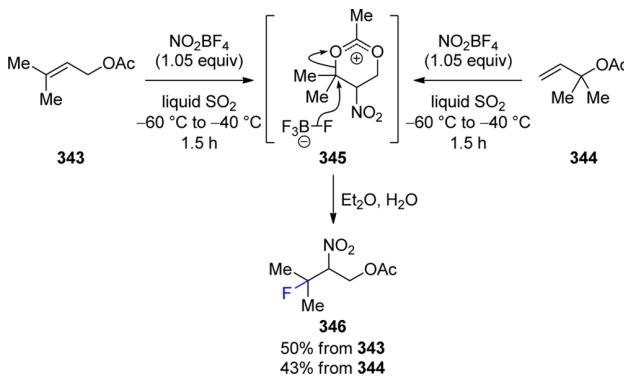
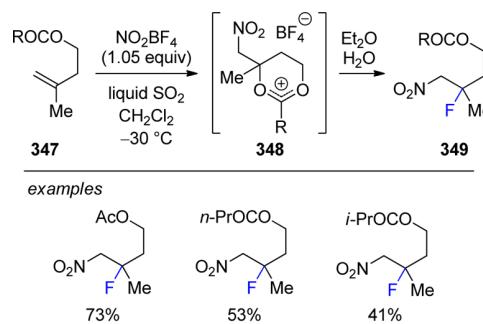
nitro fluoride 339 in $\sim 70\%$ yield. The absence of cyclobutyl or homoallylic fluoride products is likely a consequence of the reaction avoiding the buildup of carbocationic character β - to the electron-withdrawing ester group (Scheme 85).¹⁹²

Scheme 85. Nitrofluorination of Alkenyl Cyclopropane 338

Besides electronic stabilization of carbocation intermediates, neighboring group participation from proximal functional groups can also enable the efficient nitrofluorination of alkenes. For instance, allylic esters 340 have been shown to react with NO_2BF_4 in liquid SO_2 at -60 to -40°C , followed by workup with Et_2O and H_2O , to give β -nitro fluorides 342 in good yield and on multigram scale (four examples, 39–84% yield).¹⁹³ The corresponding β -nitro alcohols were also formed as byproducts from H_2O added during the workup. 1,3-Dioxolan-2-ylum ions 341 arising from neighboring group participation of the ester moiety were proposed as intermediates in these reactions, and these species could be detected as the major components of the reaction mixtures by ^1H NMR spectroscopy (in liquid SO_2 at -50°C) and could even be isolated by means of a nonaqueous workup with Et_2O .¹⁹⁴ The isolated 1,3-dioxolan-2-ylum salts 341 could be decomposed to β -nitro fluorides 342 upon treatment with Et_2O and H_2O (Scheme 86).

In accordance with the common intermediacy of a 1,3-dioxolan-2-ylum ion 345, the nitrofluorination of the regioisomeric allylic esters 343 and 344 with NO_2BF_4 produced the same β -nitro fluoride 346 in comparable yield (Scheme 87).¹⁹³

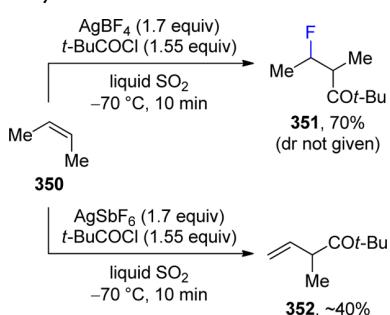
Similar fluorinations using NO_2BF_4 have also been reported with homoallylic esters 347, giving the corresponding β -nitro fluorides 349 in moderate yield (three examples, 41–73%). As before, β -nitro alcohols were also formed as byproducts from competitive hydrolysis of the putative 1,3-dioxolan-2-ylum ion intermediate 348 during the aqueous workup (Scheme 88).¹⁹⁵

Scheme 86. Nitrofluorination of Allylic Esters 340**Scheme 87.** Nitrofluorination of Allylic Esters 343 and 344**Scheme 88.** Nitrofluorination of Homoallylic Esters 347

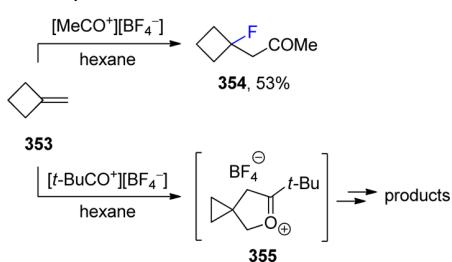
4.5. Acylfluorination

Serendipitous acylfluorinations of alkenes upon treatment with $[\text{RCO}^+][\text{BF}_4^-]$ salts¹⁹⁶ have been described in several cases during the attempted Friedel–Crafts-type acylation of alkenes.^{189b,197} For example, Smit et al. showed that the reaction of (*Z*)-2-butene (350) with $[\text{t-BuCO}^+][\text{BF}_4^-]$ (prepared from the reaction of *t*-BuCOCl with AgBF_4) in liquid SO_2 at -70°C gave β -fluoro ketone 351 in 70% yield (with $\leq 10\%$ yield of the β,γ -unsaturated ketone 352). Interestingly, however, the use of the hexafluoroantimonate salt $[\text{t-BuCO}^+][\text{SbF}_6^-]$ gave the β,γ -unsaturated ketone 352 as the sole product in $\sim 40\%$ isolated yield (mass loss ascribed to volatility) (Scheme 89).¹⁹⁸

The nature of the R group of the acylium ion salt $[\text{RCO}^+][\text{BF}_4^-]$ can also affect the course of the reaction. For example, Balenkova and co-workers have demonstrated that while methylenecyclobutane (353) forms a β -fluoro ketone 354 in 53% isolated yield upon treatment with $[\text{MeCO}^+][\text{BF}_4^-]$, the use of $[\text{t-BuCO}^+][\text{BF}_4^-]$ as the reagent leads entirely to

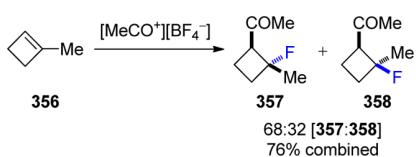
Scheme 89. Acylfluorination of Alkene 350

products derived from a putative spirocyclic carboxonium salt 355 (Scheme 90).¹⁹⁹ The influence of both the counteranion

Scheme 90. Acylfluorination of Alkene 353

and the R group of the acylium salts $[RCO^+][MF_n^-]$ on the reaction course may be a consequence of the structure of these reagents: more electron-releasing R groups (e.g., *t*-Bu)²⁰⁰ and less coordinating counteranions (e.g., SbF_6^-) favor the strongly electrophilic ionic form $[RCO^+][MF_n^-]$, whereas less electron-releasing R groups (e.g., Me) and more coordinating counteranions (e.g., BF_4^-) favor the more covalent Lewis acid–base adduct $[ROF \rightarrow BF_3]$.¹⁹⁶ For simplicity, all such reagents in this Review will be represented in the form $[RCO^+][BF_4^-]$.

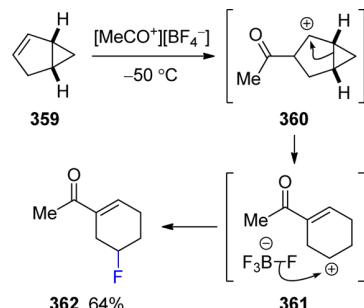
A similar acylfluorination of 1-methylcyclobutene 356 with $[MeCO^+][BF_4^-]$ afforded a 68:32 mixture of diastereoisomeric β -fluoro ketone products 357 and 358, respectively, in 76% combined yield, consistent with the intermediacy of a cyclobutyl carbocation (Scheme 91).²⁰¹ Similar fluorine

Scheme 91. Acylfluorination of Alkene 353

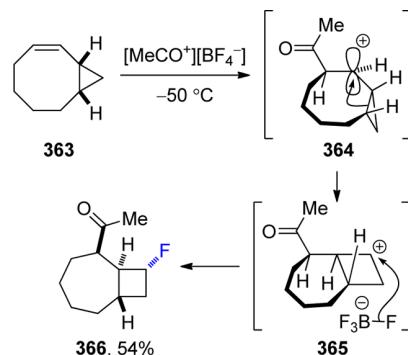
incorporation has been observed in the reaction of 1,3,3-trimethylcyclopropene with $[MeCO^+][BF_4^-]$, although fluoride trapping was preceded in this case by electrocyclic opening of the cyclopropyl cation, resulting in an allylic fluoride product.²⁰²

The treatment of alkenyl cyclopropanes with $[MeCO^+][BF_4^-]$ can lead to a variety of fluorinated products on account of the homoallyl cation or cyclobutyl cation character of the initially formed cyclopropylmethyl cation intermediate.²⁰³ For example, the reaction of bicyclo[3.1.0]hex-2-ene 359 with $[MeCO^+][BF_4^-]$ proceeded with ring-

expansion to give a homoallylic fluoride 362 in 64% yield (Scheme 92).^{203c}

Scheme 92. Acylfluorination of Bicyclo[3.1.0]hex-2-ene 359

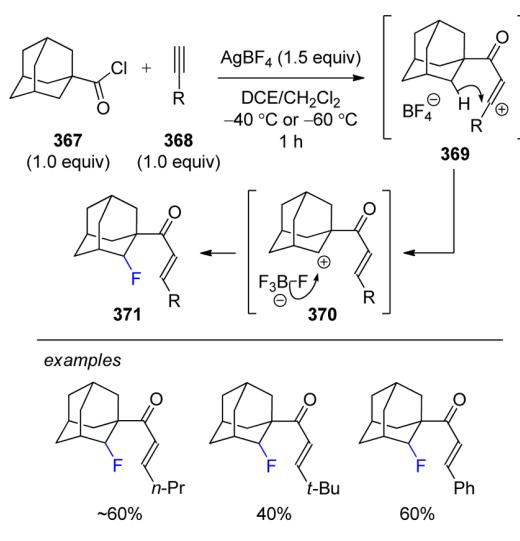
Conversely, the treatment of bicyclo[6.1.0]non-2-ene 363 with $[MeCO^+][BF_4^-]$ under the same conditions led to the formation of a cyclobutyl fluoride product 366 in 54% yield (Scheme 93).^{203c}

Scheme 93. Acylfluorination of Bicyclo[6.1.0]non-2-ene 363

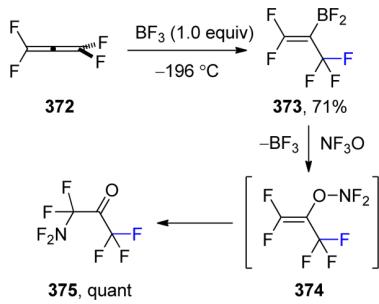
Some instances of the acylfluorination of alkynes with $[RCO^+][BF_4^-]$ salts in low yield are also known, but these reactions produce mixtures of compounds and are therefore not synthetically useful.²⁰⁴ However, for acyl chlorides (as acylium ion precursors) that possess β -hydrogen atoms, the initial electrophilic addition of the acylium ion to the alkyne can be followed by a rapid [1,5]-hydride shift to furnish an alkyl carbocation. This newly formed carbocation can then be intercepted by fluoride transfer from the BF_4^- ion to give alkyl fluoride products.^{204b,d,205,206} For example, the reaction of 1-adamantanoyl chloride 367, $AgBF_4$, and various terminal alkynes 368 gave the corresponding 2-fluoroadamantane derivatives 371 in moderate yield (six examples, 40–60% yield) (Scheme 94).^{205b,d} Similar results have been reported with cyclohexyl (as opposed to 1-adamantyl) acyl chlorides, giving fluorides in up to 40% yield.^{204d,205a} Formally, these reactions are fluorinations of unactivated $C(sp^3)-H$ bonds.

4.6. Borylfluorination

In the course of studies on the BF_3 -catalyzed addition of NF_3O to alkenes, Christe and co-workers reported that the reaction of tetrafluoroallene 372 with BF_3 gas at low temperature ($-196^\circ C$) led to formation of difluoroborane adduct 373 (formally the result of addition of F_2B-F across the double bond) in 71% isolated yield.²⁰⁷ Subsequent reaction of 373 with NF_3O gave O -difluorooxime species 374, which underwent tautome-

Scheme 94. Acylfluorination of Alkyne 368

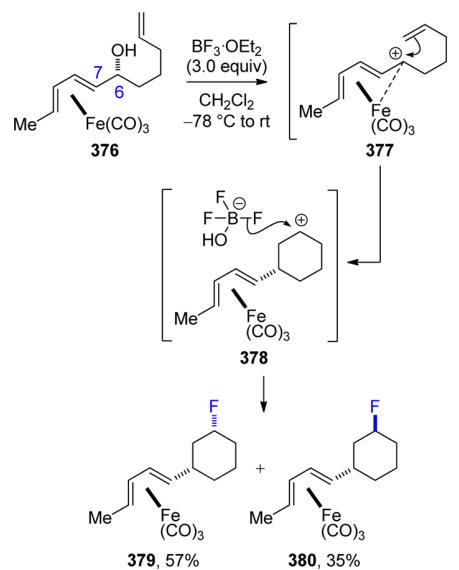
rization to the perfluorinated α -(*N,N*-difluoroamino)ketone 375 in quantitative yield (Scheme 95). Conversely, no reaction was observed between tetrafluoroethene ($\text{CF}_2=\text{CF}_2$) and BF_3 in CFCl_3 solution at -120°C .

Scheme 95. Borylfluorination of Allene 372

5. CATION- π CYCLIZATION-FLUORINATIONS

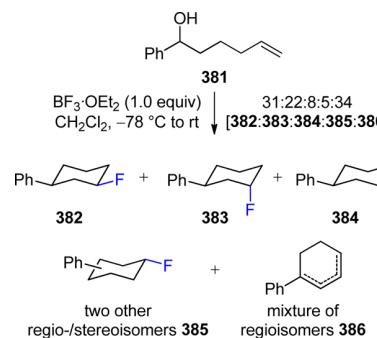
5.1. Synthesis of Fluorinated Carbocycles

During studies into the intramolecular nucleophilic trapping of in situ generated transoid pentadienyliron tricarbonyl, Pearson and co-workers found that the action of $\text{BF}_3\cdot\text{OEt}_2$ on (6*S*,7*R*)-(ω -pentenyl)pentadienol iron tricarbonyl complex Ψ -*exo*-376 led to the formation of the diastereoisomeric fluorides 379 and 380 in 57% and 35% isolated yield, respectively.²⁰⁸ A similar result was obtained with the C(6)-epimeric Ψ -*endo* (ω -pentenyl)pentadienol iron tricarbonyl complex, which gave 89% combined yield of an inseparable 73:27 mixture of diastereoisomeric fluorides. Mechanistically, the authors proposed that a BF_3 -induced ionization of the alcohol with anchimeric assistance from the iron led to stabilized cation 377, which underwent cyclization of the pendant alkene onto the face of the cation opposite to the $\text{Fe}(\text{CO})_3$ moiety. Fluoride transfer from the $[\text{HOBF}_3]^-$ ion to the incipient carbocation 378 was then proposed to account for the formation of fluorides 379 and 380 (Scheme 96). Subsequent reinvestigation of these reactions by Franck-Neumann et al. identified other minor fluorinated cyclohexane

Scheme 96. Cyclization-Fluorination of (ω -Pentenyl)pentadienol Iron Tricarbonyl Complex 376

products as well as cyclohexenes arising from competing elimination processes.²⁰⁹

Franck-Neumann and co-workers also demonstrated that the pentadienyl iron tricarbonyl motif was not a requirement for this cyclization-fluorination process to proceed, as treatment of the ω -pentenyl benzylic alcohol 381 under analogous conditions resulted in the formation of fluorinated products, although in this case a complex mixture of 382–385 and elimination products 386 was the result (Scheme 97).²⁰⁹ Use of

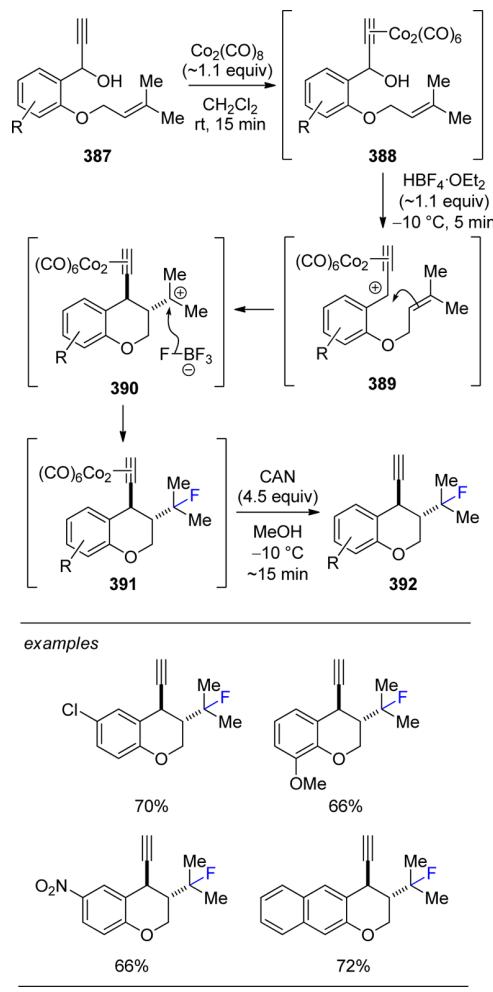
Scheme 97. Cyclization-Fluorination of ω -Pentenyl Benzylic Alcohol 380

3.0 equiv of $\text{BF}_3\cdot\text{OEt}_2$ in this reaction merely promoted the formation of cyclohexenes 386 at the expense of fluorides 382–385, presumably due to fluoride abstraction from initially formed fluorides by excess $\text{BF}_3\cdot\text{OEt}_2$.²¹⁰

Related cyclization-fluorination processes have also been realized with dicobalt hexacarbonyl alkynyl stabilized (Nicholas) cations as initiators for the cyclization of pendant alkenes. In the first ever study of cyclizations of unactivated alkenes onto Nicholas cations, Tyrell et al. developed a one-pot procedure involving the treatment of in situ generated dicobalt hexacarbonyl alkyne complexes 388 with $\text{HBF}_4\cdot\text{OEt}_2$, followed by oxidative decomplexation with ceric ammonium nitrate (CAN), which gave *anti*-fluorinated benzopyrans 392²¹² in good yield (ten examples, 59–72% yield).²¹¹ Mechanistically,

cyclization of the alkene moiety onto Nicholas cation **389** was proposed to give a carbocation **390**, which underwent nucleophilic trapping by fluoride transfer from a BF_4^- anion to give **391**. Interestingly, the amount of $\text{HBF}_4 \cdot \text{OEt}_2$ could be lowered to 0.25 equiv without a significant impact on the yield of **392** ($\text{R} = 6\text{-Br}$), and the authors concluded that as many as three of the fluorine atoms within $\text{HBF}_4 \cdot \text{OEt}_2$ may be transferable. The reaction was also shown to be equally efficient with $\text{BF}_3 \cdot \text{OEt}_2$ in place of $\text{HBF}_4 \cdot \text{OEt}_2$ (Scheme 98).

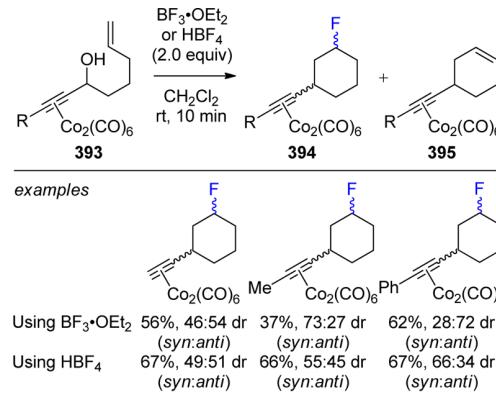
Scheme 98. Cyclization-Fluorination of Dicobalt Hexacarbonyl Alkyne Complexes 388



Bertrand and co-workers have demonstrated the *6-endo* cyclization-fluorination of (ω -pentenyl)alkynyl dicobalt hexacarbonyl complexes **393** under the agency of 2.0 equiv of $\text{BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 at room temperature to give diastereoisomeric mixtures of fluorinated cyclohexanes **394** (three examples, 37–62% yield), in addition to alkenes **395** resulting from a competing elimination reaction. In one example ($\text{R} = \text{Ph}$), lowering the reaction temperature to 0 °C was found to increase the ratio of fluorides **394** to alkene **395**, such that **394** was isolated in 86% yield and **395** was isolated in 10% yield. The cyclization-fluorination reactions could also be conducted with HBF_4 in place of $\text{BF}_3 \cdot \text{OEt}_2$, affording fluorides **394** in generally higher yields (five examples, 34–67% yield). The authors noted that the diastereoselectivity of the reaction was

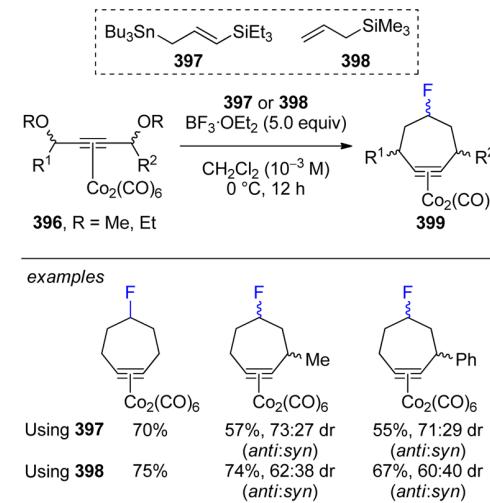
highly sensitive to the substituent on the alkyne, but did not rationalize the results (Scheme 99).²¹³

Scheme 99. Cyclization-Fluorination of (ω -Pentenyl)alkynyl Dicobalt Hexacarbonyl Complexes 393



Patel and Green have reported that $\text{BF}_3 \cdot \text{OEt}_2$ -mediated [4+3]-cycloadditions of alkyne 1,4-diether dicobalt complexes **396** with allyldimetal equivalents **397** result in the formation of fluorinated carbocycles **399** (four examples, 55–80% yield). It was found that a slow rate of addition of 5.0 equiv of $\text{BF}_3 \cdot \text{OEt}_2$ over 12 h to a highly dilute (10^{-3} M) solution of **396** and **397** in CH_2Cl_2 at 0 °C delivered the highest yields of fluorides **399** with minimal competing elimination (Scheme 100).²¹⁴

Scheme 100. Cycloaddition-Fluorination of Alkyne 1,4-Diether Dicobalt Complexes 396

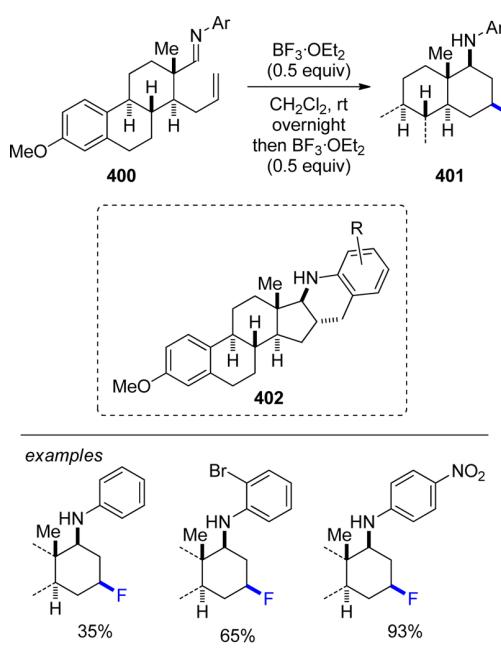


Subsequent work revealed that allyltrimethylsilane **398** could be used in place of allyldimetal equivalents **397** for this transformation, allowing the conversion of alkyne 1,4-diether dicobalt complexes **396** to fluorides **399** in superior yields, albeit with lower diastereoselectivities (Scheme 100).²¹⁵

In addition to cyclization-fluorination reactions involving metal-stabilized carbocations, similar processes have also been reported with oxo- and azacarbenium ion species. For example, during studies into the preparation of novel analogues of steroidal alkaloids via a $\text{BF}_3 \cdot \text{OEt}_2$ -mediated intramolecular hetero-Diels–Alder reaction of estrone-derived imines **400**,

Tietze, Schneider, and co-workers found that electronic tuning of the *N*-Ar group on the imine could bias reaction in favor of production of $17\alpha\alpha$ -(*N*-arylaminoo)- 16β -fluoro-*D*-homoestrone derivatives **401**, via an aza-Prins cyclization-fluorination reaction (Scheme 101).²¹⁶ Specifically, electron-withdrawing

Scheme 101. Cyclization-Fluorination of Estrone-Derived Imines 400



N-Ar groups promoted the formation of fluorinated compounds **401** at the expense of (formal) Diels–Alder products **402**, whereas the reverse was true when electron-releasing *N*-Ar groups were employed. Similar results were subsequently disclosed for an analogous $\text{BF}_3\cdot\text{OEt}_2$ -mediated oxa-Prins-fluorination process to access 16β -fluoro-*D*-homosteroid derivatives.^{217,218}

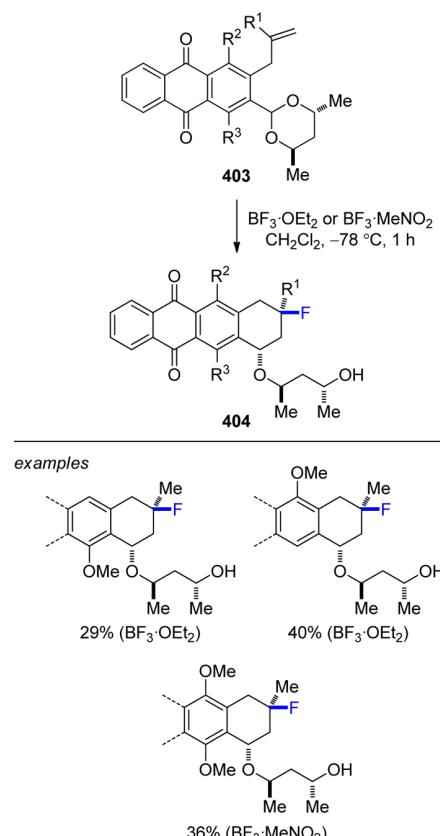
A $\text{BF}_3\cdot\text{OEt}_2$ -mediated oxa-Prins cyclization-fluorination strategy using dioxane acetals as chiral auxiliaries has been developed by Cambie and co-workers to access C(9)-fluorinated anthracyclinones. Treating enantiopure *ortho*-methallyl-substituted anthraquinonyl dioxanes **403** with $\text{BF}_3\cdot\text{OEt}_2$ or $\text{BF}_3\cdot\text{MeNO}_2$ resulted in, *inter alia*, diastereoselective formation of 9-fluoro-9-methyl anthracyclinones **404** in low to moderate yield (Scheme 102).^{219,220}

In addition to alkenes, a few reports of alkynes as competent π -nucleophiles in cation– π cyclization-fluorinations are also on record. For example, the reaction of cyclodec-5-ynols **405** with $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 gave the corresponding bicyclic alkenyl fluorides **406** in excellent yields (Scheme 103).²²¹

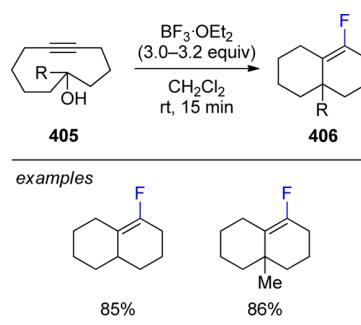
Similarly, during the study of polyolefin cyclizations initiated by the Lewis acid-mediated decomposition of α -diazo ketones, Smith and Dieter noted the reaction of enyne **407** with excess $\text{BF}_3\cdot\text{OEt}_2$ resulted in the formation of alkenyl fluorides **408** as the major products, in 35% combined yield. Several other unidentified products incorporating fluorine or chlorine were also obtained, with the latter presumably arising via chloride transfer from CH_2Cl_2 (Scheme 104).²²²

More recently, Yeh and co-workers have described the formation of interesting spirocyclic alkenyl fluoride products

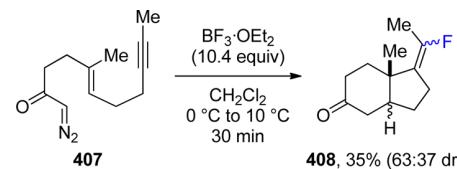
Scheme 102. Cyclization-Fluorination of Anthraquinonyl Dioxanes 403



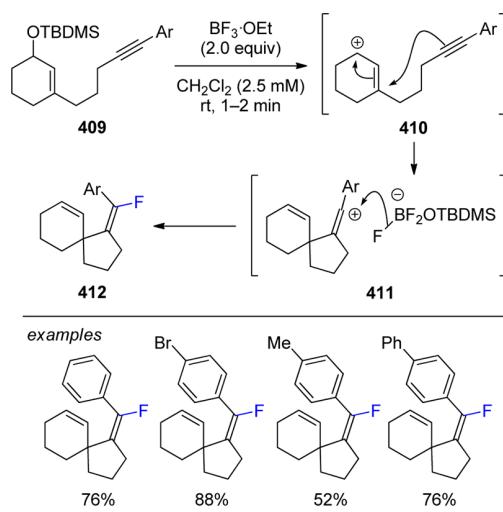
Scheme 103. Cyclization-Fluorination of Cyclodec-5-ynols 405



Scheme 104. Cyclization-Fluorination of Enyne 405



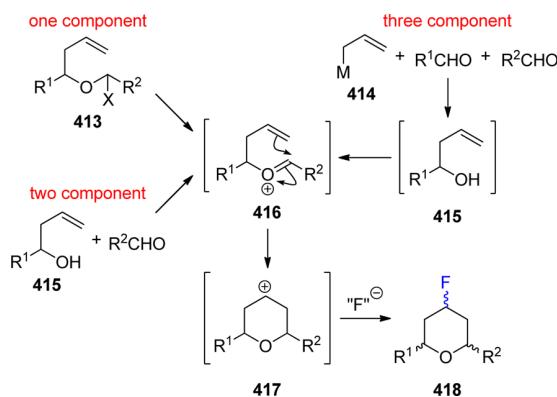
from the treatment of TBDSMS-protected, cyclic enynols **409** with $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 (four examples, 52–88% yield, single diastereoisomers) (Scheme 105).²²³ The reactions are believed to proceed via the initial formation of an allylic carbocation **410** (by BF_3 -assisted departure of the silyloxy group), followed by sequential cyclization of the tethered

Scheme 105. Cyclization-Fluorination of Enyne 409

alkyne and trapping of the resultant alkenyl cation 411 by fluoride from the putative $\text{BF}_3(\text{OTBDMS})^-$ ion.

5.2. Synthesis of Fluorinated Oxacycles: The Prins Cyclization-Fluorination

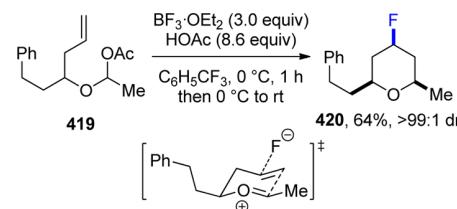
The 6-*endo* π -cyclization of an alkene onto an oxocarbenium ion intermediate 416 followed by nucleophilic trapping of the resultant carbocation 417 to generate a tetrahydropyran product is frequently termed a Prins cyclization.²²⁴ When the terminating nucleophile is fluoride, a 4-fluorotetrahydropyran 418 is produced, and the reaction can be designated a Prins cyclization-fluorination.²²⁵ As with all such Prins cyclizations, these reactions can be classified according to the number of components used to generate the key oxocarbenium ion intermediate 416 (Scheme 106).²²⁴ One-component Prins

Scheme 106. Prins Cyclization-Fluorination

cyclizations involve the generation of the oxocarbenium ion intermediate 416 from a preformed homoallylic alcohol derivative 413 featuring a “masked aldehyde”. On the other hand, two-component Prins cyclizations typically feature the condensation of a homoallylic alcohol 415 with an aldehyde under acidic conditions to generate the oxocarbenium species 416. Finally, three-component (or “tandem”) Prins cyclizations are similar to two-component processes except that the homoallylic alcohol 415 is generated in situ by the initial reaction of an allylmetal reagent 414 with an equivalent of

aldehyde. Most frequently, Prins cyclization-fluorinations have utilized $\text{BF}_3\cdot\text{OEt}_2$ as both the Lewis acid promoter and the source of nucleophilic fluoride, but examples of fluoride transfer from a BF_4^- ion (e.g., from a supporting electrolyte) are also known.

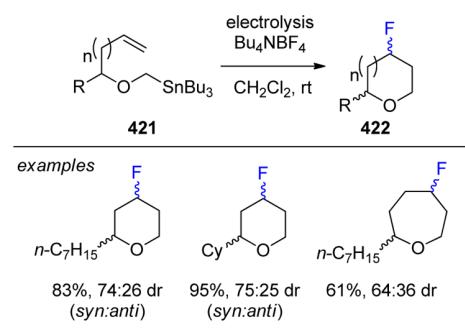
5.2.1. One-Component Prins Cyclization-Fluorinations. Rychnovsky and co-workers divulged a single example of 4-fluorotetrahydropyran formation with $\text{BF}_3\cdot\text{OEt}_2$ as a Lewis acid promoter during studies into the segment-coupling Prins cyclization utilizing α -acetoxy ethers in place of mixed acetal intermediates.²²⁶ Thus, treatment of α -acetoxy ether 419 in α,α,α -trifluorotoluene with a premixed solution of 3.0 equiv of $\text{BF}_3\cdot\text{OEt}_2$ and 8.6 equiv of AcOH in α,α,α -trifluorotoluene at 0 °C for 1 h gave 4-fluorotetrahydropyran 420 in 64% yield as a single diastereoisomer. The high diastereoselectivity in this reaction was proposed to result from cyclization of the alkene onto the (*E*)-configured oxocarbenium ion via a chairlike transition state, with concerted formation of the C–C and C–F bonds in an antiperiplanar manner (Scheme 107). It was

Scheme 107. Prins Cyclization-Fluorination of 419

noticed that acetoxy incorporation was generally favored over fluorine incorporation when the reaction was conducted in a nonpolar solvent such as hexane and a precooled (0 °C) mixture of $\text{BF}_3\cdot\text{OEt}_2$ and AcOH was added to the substrate at 0 °C. Similar examples of fluorine incorporation during $\text{BF}_3\cdot\text{OEt}_2$ -mediated Prins cyclizations of homoallylic acetals or α -acetoxy ethers have also been observed.²²⁷

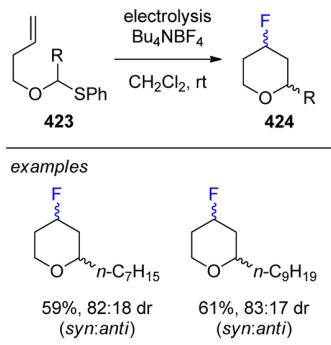
In a distinctly different approach, Yoshida and co-workers have performed one-component Prins cyclization-fluorination reactions via the anodic oxidation of α -stannyl ethers 421 in the presence of Bu_4NBF_4 as the supporting electrolyte and nucleophilic fluoride source, affording fluorinated oxacycles 422 in good yields and with modest levels of diastereoselectivity (Scheme 108).²²⁸

This reaction was subsequently extended to include α -phenylthio ethers 423 as substrates, which provided 4-fluorotetrahydropyrans 424 with improved levels of *syn*-diastereoselectivity, although in lower isolated yields (Scheme

Scheme 108. Prins Cyclization-Fluorination of 421

109).²²⁹ To account for the fact that the diastereoselectivity depends on the nature of the electroauxiliary (i.e., SnBu_3 vs

Scheme 109. Prins Cyclization-Fluorination of 423



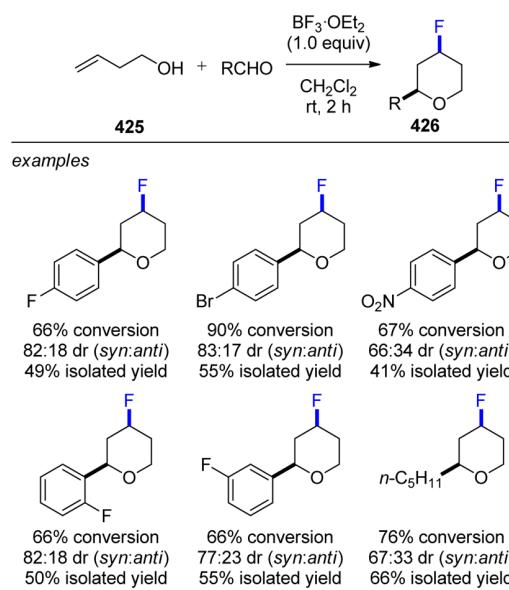
SPh), the authors suggested that, after a one-electron oxidation of the electroauxiliary (EA), formation of the C–C and C–F bonds may proceed in concert with C–EA bond cleavage. However, an alternative explanation may be that the closer match in oxidation potentials of the starting material **423** and product **424** when using phenylthio electroauxiliaries may lead to undesired overoxidation processes, which could selectively drain the *anti* diastereoisomer of **424**.

5.2.2. Two-Component Prins Cyclization-Fluorinations. Building upon earlier literature precedent,²³⁰ the scope of two-component Prins cyclization-fluorinations using $\text{BF}_3\cdot\text{OEt}_2$ as the Lewis acid and nucleophilic fluoride source has been recently investigated in detail by O'Hagan and co-workers.²³¹ With but-3-en-1-ol **425** as the nucleophilic partner, reaction with a variety of aldehydes in the presence of $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 at room temperature gave the corresponding 4-fluorotetrahydropyrans **426**. Electron-rich benzaldehydes and 2-methylcinnamaldehyde proved to be poor substrates and gave <20% conversion, although good conversions were observed for electron-poor benzaldehydes [seven examples, 65–90% conversion, 66:34 dr (*syn:anti*) up to 83:17 dr (*syn:anti*)] and *n*-hexanal [76% conversion, 67:33 dr (*syn:anti*)]. The *syn*- and *anti*-diastereoisomers proved separable by chromatography in all cases, allowing isolation of the major *syn*-diastereoisomers in modest to good yield (Scheme 110). Low diastereoselectivities of ~67:33 dr (*syn:anti*) could be increased to 91:9 dr (*syn:anti*) in several cases (three examples, 59–61% conversion) on lowering the temperature to -20°C , but this necessitated an extended reaction time of 5 h. The authors also demonstrated that the use of microwave conditions afforded improved conversions with greatly reduced reaction times, although the diastereoselectivities remained modest.

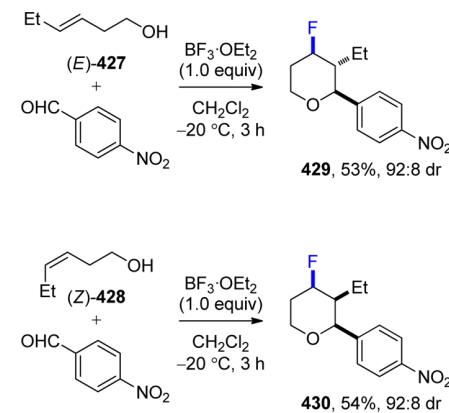
With the diastereoisomeric hex-3-en-1-ols (*E*)-**427** and (*Z*)-**428** as substrates, the reactions with *para*-nitrobenzaldehyde gave two diastereoisomeric products **429** and **430** in 92:8 dr (epimeric at the fluorinated center) in both cases, which were isolated in moderate yield (Scheme 111).²³¹ These results demonstrate that C–C bond formation is stereospecific with respect to the alkene configuration, a result consistent with the expected chairlike transition state of the Prins cyclization, in which the C(2) substituent is placed in a pseudoequatorial position.

The reaction also proved successful with 2-vinylcyclohexanol **431**, giving bicyclic fluorides **432** in good *syn*-diastereoselectiv-

Scheme 110. Prins Cyclization-Fluorination of 425



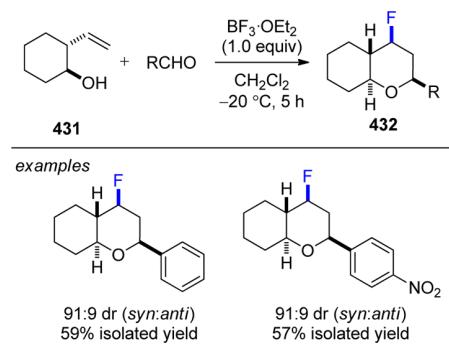
Scheme 111. Prins Cyclization-Fluorination of 427 and 428



ities, from which the major products could be isolated as single diastereoisomers in moderate yield (Scheme 112).²³¹

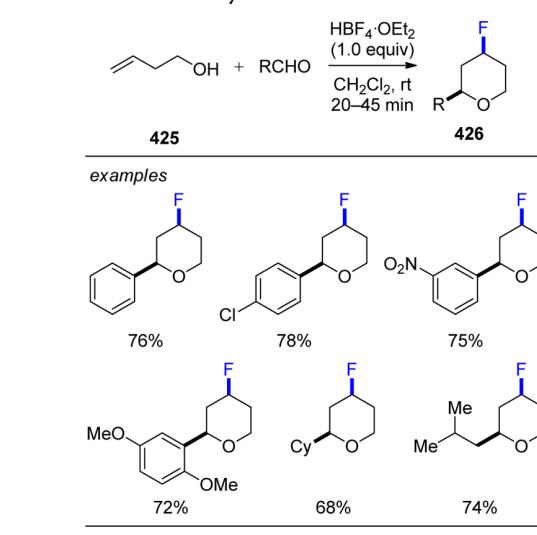
Yadav and co-workers have shown that use of $\text{HBF}_4\cdot\text{OEt}_2$ as the acid promoter and nucleophilic fluoride source for reaction of but-3-en-1-ol **425** with a variety of aromatic (both electron-poor and electron-rich) and aliphatic aldehydes gives the corresponding *syn*-configured 4-fluorotetrahydropyrans **426** as

Scheme 112. Prins Cyclization-Fluorination of 431



single diastereoisomers in good yield (seven examples, 65–78% yield).²³² Considering the modest *syn* selectivities reported by O'Hagan et al. employing $\text{BF}_3\cdot\text{OEt}_2$ as the fluorinating agent in this reaction,²³¹ the formation of the 4-fluorotetrahydropyran products **426** as single diastereoisomers when using $\text{HBF}_4\cdot\text{OEt}_2$ is surprising, and the origin of this effect is currently unclear (Scheme 113).

Scheme 113. Prins Cyclization-Fluorination of **425**

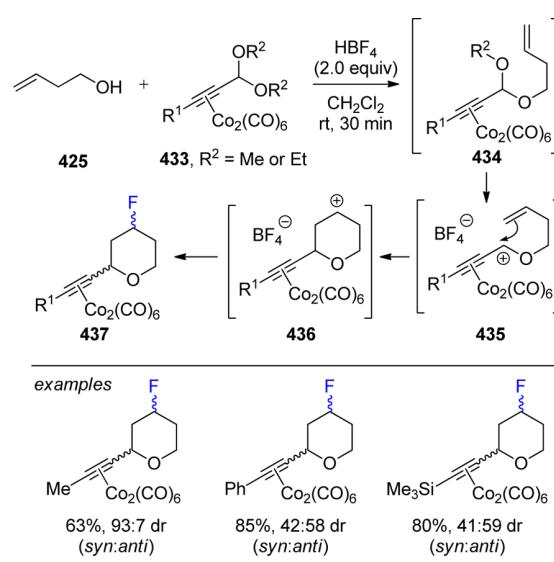


In a complementary procedure, Bertrand et al. have developed a Nicholas–Prins-fluorination reaction involving the treatment of a mixture of homoallylic alcohol **425** and dicobalt hexacarbonyl complexes of propargylic acetals **433** with either HBF_4 or $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 to give 2-alkynyl-4-fluorotetrahydropyran $\text{Co}_2(\text{CO})_6$ -complexes **437** [five examples, 52–85% yield, 41:59 dr (*syn:anti*) to 93:7 dr (*syn:anti*)].²³³ In the absence of $\text{Co}_2(\text{CO})_6$ -complexation of the propargylic acetals, the corresponding 2-alkynyl-4-fluorotetrahydropyrans were isolated in much lower yields and with reduced diastereoselectivities. Possible epimerization at C(2) by a reversible Nicholas reaction was suggested to be responsible for the significant proportion of the *anti*-diastereoisomer which was observed in some cases (Scheme 114).

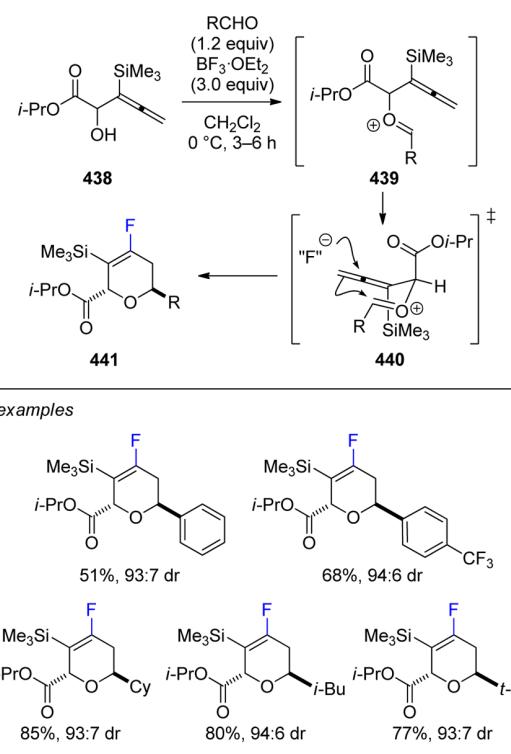
In an extension of the Prins cyclization-fluorination protocol, Loh and co-workers have disclosed a method for the synthesis of 2,6-*anti*-substituted 4-fluoro-3,4-dihydropyrans **441**: treatment of allenic alcohols **438** with a range of aliphatic and aromatic aldehydes and 3.0 equiv of $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 at 0 °C gave 2,6-*anti*-substituted 4-fluoro-3,4-dihydropyrans **441** in high yields and good diastereoselectivities (eleven examples, 43–85% yield, 89:11 to 94:6 dr). To account for the *anti*-diastereoselectivity of the reaction, a chairlike transition state **440** was proposed in which the oxocarbenium ion is stabilized by interaction with one of the carbonyl lone pairs of the axially disposed ester moiety (Scheme 115).

5.2.3. Three-Component Prins Cyclization-Fluorinations. The first reported example of a three-component Prins cyclization-fluorination, disclosed in 1989 by Chan and co-workers, was also the earliest recorded instance of fluorine incorporation in a Prins reaction using $\text{BF}_3\cdot\text{OEt}_2$ as the Lewis acid.²³⁵ During the attempted execution of an asymmetric variant of the Hosomi–Sakurai reaction²³⁶ of aliphatic aldehydes using (−)-menthol-derived allylsilanol ether **442** in

Scheme 114. Nicholas–Prins Cyclization-Fluorination of **425** and **433**

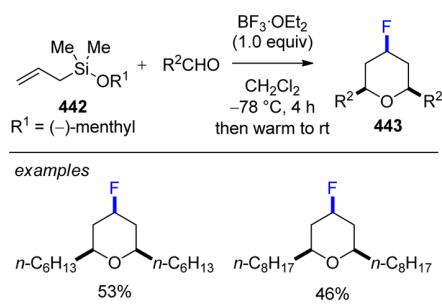


Scheme 115. Prins Cyclization-Fluorination of **438**

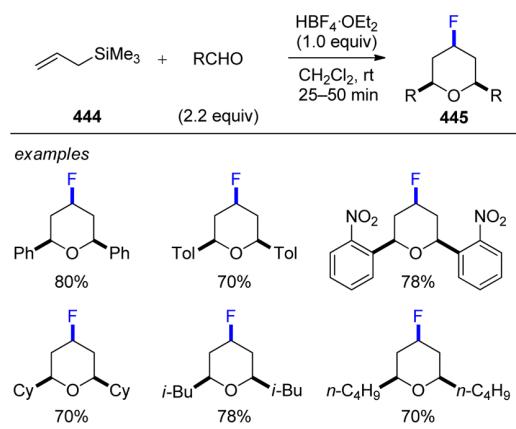


combination with $\text{BF}_3\cdot\text{OEt}_2$, 2,4,6-*syn*-4-fluorotetrahydropyran **443** were unexpectedly obtained in moderate yield and as single diastereoisomers, although ee values were not reported (Scheme 116). Similar results were also obtained using a mandelic acid-derived allylsilanol ether reagent, although in this case the 4-fluorotetrahydropyrans were isolated in low yields (25–35%) due to the competitive formation of 4-alkoxytetrahydropyran products.

More recently, Yadav and co-workers have probed the generality of this reaction using $\text{HBF}_4\cdot\text{OEt}_2$ as both a Brønsted acid promoter and a nucleophilic fluoride source.²³² Thus, the

Scheme 116. Prins Cyclization-Fluorination of 442

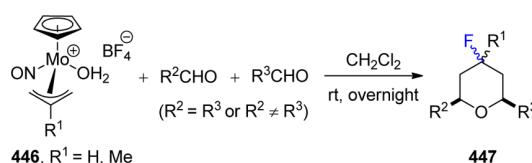
reaction of allyltrimethylsilane **444** with a variety of aldehydes (2.2 equiv) in the presence of HBF₄·OEt₂ (1.0 equiv) gave 2,4,6-*syn*-4-fluorotetrahydropyrans **445** (fourteen examples, 70–85% yield) as single diastereoisomers in all cases (Scheme 117).

Scheme 117. Prins Cyclization-Fluorination of 444

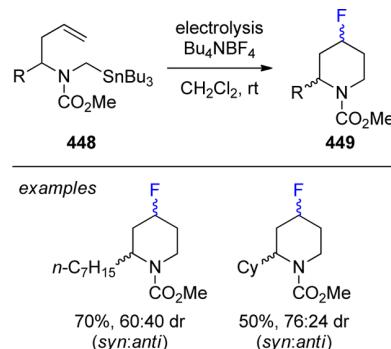
An interesting variant of the three-component Prins cyclization-fluorination process has been advanced by Faller and Linebarrier, entailing the use of molybdenum π -allyl tetrafluoroborate complexes **446** as the allylmetal component, with the BF₄[−] ion serving as a source of nucleophilic fluoride.²³⁷ Thus, treatment of [CpMo(NO)(η^3 -2-methylallyl)]⁺BF₄[−] complex **446** with 2.0 equiv of an aldehyde in CH₂Cl₂ at room temperature gave the corresponding symmetrical 2,6-*syn*-disubstituted 4-fluorotetrahydropyrans **447**, which were isolated in good yield (five examples, 54–73% yield). Impressively, when a 1:1 mixture of benzaldehyde and 4-methoxybenzaldehyde was employed, an unsymmetrical 2,6-*syn*-disubstituted 4-fluorotetrahydropyran product **447** ($R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R^3 = 4$ -methoxyphenyl) could also be prepared in 75% yield, albeit with minor amounts of the corresponding symmetrical products present as contaminants (Scheme 118). The preference for axial attack of fluoride when $R^1 = \text{Me}$ is in agreement with similar Prins cyclizations proceeding via tertiary carbocation intermediates.²²⁴

5.3. Synthesis of Fluorinated Azacycles

In addition to oxa-Prins cyclization-fluorination processes, analogous BF₃·OEt₂- or HBF₄·OEt₂-mediated aza-Prins reactions have also been reported, enabling the direct synthesis of medicinally important 4-fluoropiperidines. In an extension of their work on electro-oxidative oxa-Prins cyclizations (section

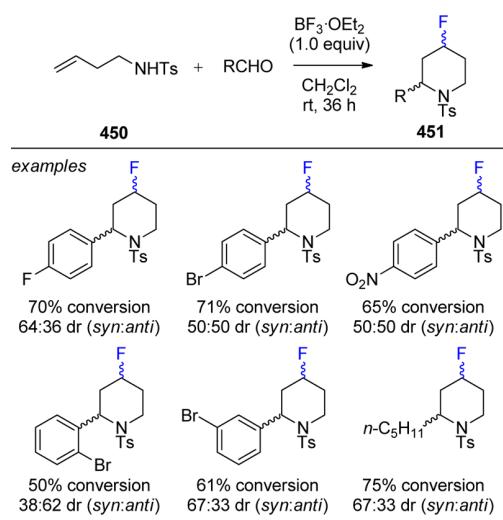
Scheme 118. Prins Cyclization-Fluorination of 446

5.2), Yoshida and co-workers performed an anodic oxidation of α -stannyl amides **448** in the presence of Bu₄NBF₄ as the supporting electrolyte and nucleophilic fluoride source, giving two examples of the formation of N-CO₂Me 4-fluoropiperidines **449** in good yields and with modest levels of *anti*-diastereoselectivity [60:40 to 76:24 dr (*anti:syn*)] (Scheme 119).²²⁸

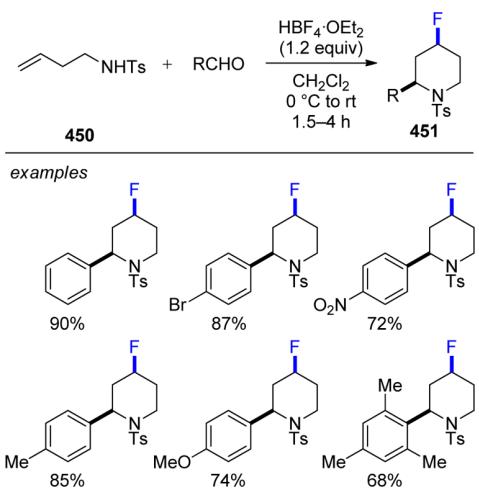
Scheme 119. Aza-Prins Cyclization-Fluorination of 448

O'Hagan et al. have studied the generality of the aza-Prins cyclization-fluorination process using *N*-Ts homoallylic amine **450** with BF₃·OEt₂ as the Lewis acid mediator and nucleophilic fluoride source to give *N*-Ts 4-fluoropiperidines **451** (ten examples, 23–82% yield).²³¹ Although the yields for the *N*-Ts 4-fluoropiperidines **451** were comparable to those obtained for 4-fluorotetrahydropyrans in the analogous oxa-Prins reaction (section 5.2), longer reaction times (typically 36 h) were required, although microwave conditions allowed shortening of the reaction time to 30 min. As for the oxa-Prins method, reaction with 4-methoxybenzaldehyde (as a representative electron-rich aromatic aldehyde) gave only 23% conversion, and no reaction occurred at all with 2-methylcinnamaldehyde, although good conversions were observed for electron-poor benzaldehydes and aliphatic aldehydes (nine examples, 50–82% conversion). The diastereoselectivities of these reactions proved highly variable, but were at best modest [between 38:62 dr (*syn:anti*) and 71:29 dr (*syn:anti*)], although the *syn*- and *anti*-diastereoisomers generally proved separable by chromatography, and were isolated in low to modest yield (Scheme 120). The poor diastereoselectivities were not improved by lowering the reaction temperature to −20 °C.

Yadav, Grée, and co-workers have studied the generality of this aza-Prins cyclization-fluorination process using HBF₄·OEt₂ as both a Brønsted acid activator and a nucleophilic fluoride

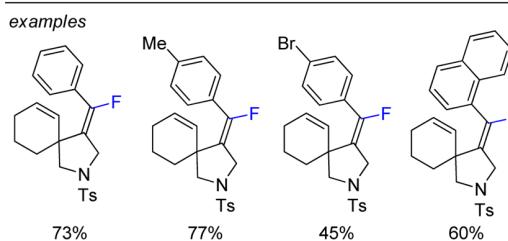
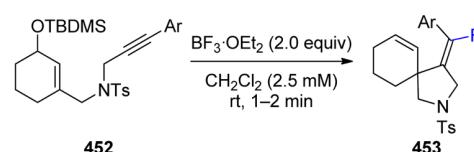
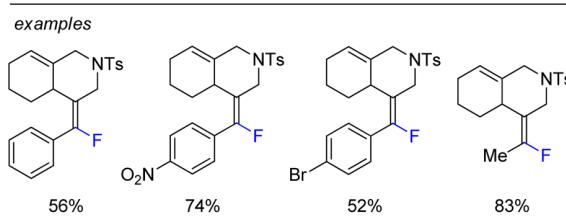
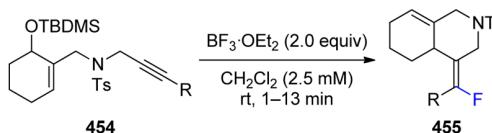
Scheme 120. Aza-Prins Cyclization-Fluorination of 450

source.²³⁸ Thus, treatment of *N*-Ts homoallylic amine **450** with a range of aliphatic and aromatic aldehydes and $\text{HBF}_4\cdot\text{OEt}_2$ in CH_2Cl_2 gave *N*-Ts 4-fluoropiperidines **451** in excellent yields and good *syn*-diastereoselectivities (12 examples, 68–93% yield). Notably, electron-rich aromatic aldehydes and α,β -unsaturated aldehydes were well tolerated under these conditions (Scheme 121).

Scheme 121. Aza-Prins Cyclization-Fluorination of 450

Besides aza-Prins reactions, cation– π cyclizations in which the substrate bears a spectator nitrogen atom in the tether between the cation and π -nucleophile can also deliver azacyclic products. In a recent example of this approach using alkyne nucleophiles, Yeh et al. showed that the treatment of *O*-TBDMS-protected, *N*-containing, cyclic enynols **452** with 2.0 equiv of $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 gave rise to spiro, azabicyclic alkenyl fluorides **453** (four examples, 45–77% yield) as single diastereoisomers (Scheme 122).²²³

Similarly, the reaction of regioisomeric *O*-TBDMS-protected, *N*-containing, cyclic enynols **487** with 2.0 equiv of $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 gave fused, azabicyclic alkenyl fluorides **488** (ten examples, 40–83% yield), again as single diastereoisomers in all cases (Scheme 123).²²³ As the product yield was significantly

Scheme 122. Cyclization-Fluorination of 452**Scheme 123. Cyclization-Fluorination of 454**

lower when only 1.0 equiv of $\text{BF}_3\cdot\text{OEt}_2$ was employed, the authors suggested that the BF_4^- ion [generated by fluoride abstraction from the $\text{BF}_3(\text{OTBDMS})^-$ ion by the second equivalent of BF_3] may be the active terminating nucleophile in these reactions. However, it is also possible that competitive complexation of BF_3 with the NTs moiety may inhibit the reaction when only 1.0 equiv of $\text{BF}_3\cdot\text{OEt}_2$ is employed.

6. SUMMARY AND OUTLOOK

In a field that has become almost synonymous with costly or hazardous reagents, typically inexpensive and easily handled fluoroborates (e.g., $\text{HBF}_4\cdot\text{OEt}_2$) and boron fluorides (e.g., $\text{BF}_3\cdot\text{OEt}_2$) are clearly valuable members of the existing arsenal of nucleophilic fluorinating agents. Obvious advantages of these reagents include their low cost, atom economy (low molecular weight, high active fluoride content), low volatility, and the fact that they do not etch standard borosilicate glassware. However, the real power of these reagents arises from their Brønsted or Lewis acidic character, which can be harnessed to promote reactions of a cationic nature, reactions that are frequently orthogonal to, or difficult with, more Brønsted basic sources of nucleophilic fluoride. This is best exemplified by the nucleophilic fluorination of α -diazo β -keto esters (section 2.6), the ring-opening fluorination of epoxides, aziridines, and cyclopropanes (sections 3.1–3.3), the ammonium-directed hydroxyfluorination of allylic amines (section 4.3), and fluorinative cation– π cyclizations (section 5), all of which require (or are at least strongly assisted by) Brønsted or Lewis acidic conditions. In many cases, the reactions proceed at

ambient temperature and with short reaction times (sometimes only a few minutes), and functional group tolerance can often be broad. Although stereoselectivity during C–F bond formation for reactions proceeding via (putative) carbocation intermediates can be highly variable, the ring-opening of strained rings (e.g., epoxides, aziridines) or -iranium intermediates (e.g., thiiranium ions, haliranum ions) via fluoride transfer from fluoroborate ions typically proceeds with high stereoselectivity. Moreover, several of the reactions described in this Review have been conducted on gram scales, which bodes well for their application to large-scale preparations of valuable fluorinated building blocks, without the issue of prohibitively high reagent costs.

A general requirement for success in these fluorinations is the absence of other competent nucleophiles, including other anions, certain functional groups, or nucleophilic solvents. Chlorinated solvents (commonly CH_2Cl_2) have usually been the reaction media of choice, although Et_2O can be superior in some reactions with $\text{BF}_3\cdot\text{OEt}_2$, and aromatic solvents (e.g., benzene) have also been used in some instances.

Clearly, not all classes of fluorination reactions can be effected with fluoroborate or boron fluoride reagents, a limitation that is largely due to the characteristically low nucleophilicity of BF_4^- (or BF_3X^-) ions. Deoxofluorination reactions, for example (e.g., alcohols to alkyl fluorides, carbonyl compounds to *gem*-difluorides), or the $\text{S}_{\text{N}}2$ -type nucleophilic displacement of halides/sulfonates with fluoride ion sources are both popular fluorination methods for which reagents like $\text{BF}_3\cdot\text{OEt}_2$ or $\text{HBF}_4\cdot\text{OEt}_2$ appear to be wholly unsuited. Despite this caveat, the sheer breadth of different transformations documented in this Review should serve as ample testimony to the utility of fluoroborate or boron fluoride reagents in the synthesis of fluorinated compounds. In several cases, it is evident that these reagents can succeed where the traditional alternatives fail, and there are a growing number of examples of their use in the synthesis of fluorinated natural product analogues (e.g., steroids, sphingoid bases, carbohydrates, anthacyclines) as well as other pharmacologically important compounds. Clearly there is still ample opportunity for further development of fluorination methods based on fluoroborates and boron fluorides, and it is hoped that this Review will go at least some way to inspiring those future advances.

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Notes

The authors declare no competing financial interest.

Biographies



Alex Cresswell was born in Bradford, West Yorkshire, in 1985. He obtained an M.Chem. at the University of Oxford in 2008, and subsequently received his D.Phil. from the same institution in 2011, under the supervision of Professor Stephen G. Davies. His research focused on the use of boron fluorides and tetrafluoroborates as nucleophilic fluorinating agents. Following a two year postdoctoral stay with Professor Scott E. Denmark at the University of Illinois at Urbana–Champaign, he is currently undertaking a second postdoctoral appointment with Professor Guy C. Lloyd-Jones FRS at the University of Edinburgh. His current research interests include stereoselective halogenation as well as iron- and gold-catalyzed cross-coupling reactions.



Steve Davies is the Waynflete Professor of Chemistry at the University of Oxford. He has been the recipient of numerous prizes, including the Hickinbottom Fellowship, Corday Morgan Medal and Prize, Award for Organometallic Chemistry, Bader Award, Tilden Lectureship, Award for Stereochemistry, and Perkin Prize for Organic Chemistry from the Royal Society of Chemistry, and was recently conferred the degree of Dr Honoris Causa by the University of Salamanca. He has published more than 500 papers and has research interests ranging from organometallic chemistry, asymmetric synthesis, and natural product chemistry to medicinal chemistry and drug discovery.



Paul Roberts graduated with an M.Chem. from the University of Oxford in 2000, which was followed by a D.Phil. with Professor Steve Davies in the area of the asymmetric synthesis of piperidine alkaloids employing a ring-closing metathesis approach. He subsequently took up a postdoctoral position with Professor Davies at Oxford, where his research interests center upon natural product synthesis and the development of new stereoselective methodologies, for example, to effect the chemo- and stereoselective functionalization of allylic amines with a range of electrophilic reagents.



Jim Thomson studied chemistry at the University of Oxford where he gained an M.Chem. (2003) and then D.Phil. (2007), working with Professor Steve Davies in the area of β -amino acid organocatalysis. He then took up a postdoctoral position with Professor Davies, as a Junior Research Fellow, and in 2010 was appointed to a Research Fellowship in association with St. Catherine's College, Oxford. His current research interests center upon the development of novel asymmetric transformations and the total synthesis of natural products.

ABBREVIATIONS

$^{\circ}\text{C}$	degrees Celcius
\AA	angstroms
Ac	acetyl
AIBN	azobis(isobutyronitrile)
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bs	benzenesulfonyl
Bu	<i>n</i> -butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cy	cyclohexyl
DCE	1,2-dichloroethane

DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DFT	density functional theory
DMF	<i>N,N</i> -dimethylformamide
DMM	dimethoxymethane
DMSO	dimethyl sulfoxide
dr	diastereoisomeric ratio
E^{\ominus}	standard electrode potential
ee	enantiomeric excess
emim	1-ethyl-3-methylimidazolium tetrafluoroborate
equiv	equivalents
Et	ethyl
GC	gas chromatography
<i>gem</i>	geminal
h	hours
Hz	Hertz
<i>i</i> -Bu	isobutyl
IBX	2-iodoxybenzoic acid
<i>i</i> -Pr	isopropyl
kcal	kilocalories
kJ	kilojoules
<i>m</i>	meta
<i>m</i> -CPBA	<i>m</i> -chloroperbenzoic acid
Me	methyl
min	minutes
Ms	methanesulfonyl
MS	molecular sieves
NBSA	4'-nitrobenzenesulfenanilide
NMR	nuclear magnetic resonance
Ns	<i>p</i> -nitrobenzenesulfonyl
<i>n</i> -Pr	<i>n</i> -propyl
<i>o</i>	ortho
<i>p</i>	para
PCB	<i>p</i> -chlorobenzyl
Ph	phenyl
PNBz	<i>p</i> -nitrobenzoyl
Py	pyridine
quant	quantitative
rt	room temperature
S _N 1	substitution nucleophilic unimolecular
S _N 2	substitution nucleophilic bimolecular
S _N Ar	substitution nucleophilic aromatic
S _N <i>i</i>	substitution nucleophilic internal return
S _N V	substitution nucleophilic vinylic
<i>t</i> _{1/2}	half-life
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tol	<i>p</i> -tolyl
Ts	<i>p</i> -toluenesulfonyl
UHP	urea hydrogen peroxide complex
V	volts
wrt	with respect to
χ	electronegativity

REFERENCES

- (a) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100*, 127.
- (b) Murphy, C. D.; Schaffrath, C.; O'Hagan, D. *Chemosphere* **2003**, *52*, 455.
- (2) Gribble, G. W. *Chemosphere* **2003**, *52*, 289.

- (3) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004.
- (4) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
- (5) Allred, A. L. *J. Inorg. Nucl. Chem.* **1961**, *17*, 215.
- (6) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
- (7) Heidelberger, C.; Chaudhuri, N. K.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, R. J. *Nature* **1957**, *179*, 663.
- (8) Takeuchi, Y.; Shiragami, T.; Kimura, K.; Suzuki, E.; Shibata, N. *Org. Lett.* **1999**, *1*, 1571.
- (9) (a) Holmgren, S. K.; Taylor, K. M.; Bretscher, L. E.; Raines, R. T. *Nature* **1998**, *392*, 666. (b) Bretscher, L. E.; Jenkins, C. L.; Taylor, K. M.; DeRider, M. L.; Raines, R. T. *J. Am. Chem. Soc.* **2001**, *123*, 777. (c) Hodges, J. A.; Raines, R. T. *J. Am. Chem. Soc.* **2003**, *125*, 9262. (d) Hodges, J. A.; Raines, R. T. *J. Am. Chem. Soc.* **2005**, *127*, 15923.
- (10) (a) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27. (b) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (c) Isanobor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (d) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013. (e) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem* **2007**, *2*, 1100. (f) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (g) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (h) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (i) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (j) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.
- (11) Hunter, L. *Beilstein J. Org. Chem.* **2010**, *6*, 38.
- (12) Buissonneaud, D. Y.; van Mourik, T.; O'Hagan, D. *Tetrahedron* **2010**, *66*, 2196.
- (13) (a) Schlosser, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1496. (b) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer-Verlag: Berlin, 2000. (c) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. (d) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing Ltd./CRC Press: Boca Raton, FL, 2004. (e) Soloshonok, V. A. *Fluorine-Containing Synthons*; ACS Symposium Series 911; Oxford University Press: Washington, DC, 2005. (f) Uneyama, K. *Organofluorine Chemistry*; Blackwell Publishing: Oxford, 2006. (g) Bégué, J.-P.; Bonnet-Delpont, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Weinheim, 2008.
- (14) Jeschke, P. *ChemBioChem* **2004**, *5*, 570.
- (15) (a) Kirsch, P.; Bremer, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4217. (b) Johns, K.; Stead, G. J. *J. Fluorine Chem.* **2000**, *104*, 5. (c) Smart, B. E. *J. Fluorine Chem.* **2003**, *122*, 1. (d) Pagliaro, M.; Ciriminna, R. *J. Mater. Chem.* **2005**, *15*, 4981. (e) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003.
- (16) Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11860.
- (17) For selected examples, see: (a) Goekjian, P. G.; Wu, G.-Z.; Chen, S.; Zhou, L.; Jirousek, M. R.; Gillig, J. R.; Ballas, L. M.; Dixon, J. T. *J. Org. Chem.* **1999**, *64*, 4238. (b) Moumné, R.; Pasco, M.; Prost, E.; Lecourt, T.; Micouin, L.; Tisné, C. *J. Am. Chem. Soc.* **2010**, *132*, 13111.
- (18) For reviews of the use of ¹⁹F NMR spectroscopy in chemical biology, see: (a) Cobb, S. L.; Murphy, C. D. *J. Fluorine Chem.* **2009**, *130*, 132. (b) Chen, H.; Viel, S.; Ziarelli, F.; Peng, L. *Chem. Soc. Rev.* **2013**, *42*, 7971.
- (19) (a) Ametamey, S. A.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501. (b) *Fluorine and Health: Molecular Imaging, Biomedical Materials and Pharmaceuticals*; Tressaud, A.; Haufe, G., Eds.; Elsevier: Amsterdam, 2008.
- (20) Lal, G. S.; Pez, G. P.; Syvert, R. G. *Chem. Rev.* **1996**, *96*, 1737.
- (21) Mascaretti, O. A. *Aldrichimica Acta* **1993**, *26*, 47.
- (22) (a) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 647. (b) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505. (c) *Science of Synthesis*; Percy, J., Ed.; Thieme: Stuttgart, 2006; Vol. 34: Fluorine. (d) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803. (e) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.
- (23) For recent developments in the catalysis of fluorination reactions, see: (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. For reviews on catalytic, enantioselective fluorination, see: (b) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065. (c) Brunet, V. A.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1179. (d) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (e) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708.
- (24) For selected examples of recently developed nucleophilic fluorinating agents, see: (a) Kim, D. W.; Jeong, H.-J.; Lim, S. T.; Sohn, M.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 8404. (b) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401. (c) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, *132*, 18199. (d) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482. (e) Zhao, H.; Gabbaï, F. P. *Org. Lett.* **2011**, *13*, 1444.
- (25) Farooq, O.; Tiers, G. V. D. *J. Org. Chem.* **1994**, *59*, 2122 and refs cited therein.
- (26) Balz, G.; Schiemann, G. *Ber. Deutsch. Chem. Ges.* **1927**, *60*, 1186.
- (27) *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, 2008.
- (28) For the BF₃-catalyzed hydrofluorination of halogenated olefins with HF, see: (a) Henne, A. L.; Arnold, R. C. *J. Am. Chem. Soc.* **1948**, *70*, 758. For the BF₃·OEt₂-catalyzed decarboxylative conversion of alkyl fluoroformates to alkyl fluorides, see: (b) Nakanishi, S.; Myers, T. C.; Jensen, E. V. *J. Am. Chem. Soc.* **1955**, *77*, 5033. For the BF₃·OEt₂-promoted desulfonylative conversion of alkyl fluorosulfinate esters to alkyl fluorides, see: (c) Zappel, A. *Chem. Ber.* **1961**, *94*, 873. For the BF₃-catalyzed conversion of carbonyl compounds to gem-difluorides with SF₄ or MoF₆, see: (d) Smith, W. C. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 467. (e) Mathey, F.; Bensoam, J. *Tetrahedron* **1971**, *27*, 3965. For the BF₃·OEt₂-promoted ring-opening fluorination of α,β -epoxy nitriles with HF, see: (f) Cantacuzène, J.; Atlani, M.; Aniébié, J. *Tetrahedron Lett.* **1968**, *9*, 2335. (g) Cantacuzène, J.; Atlani, M. *Tetrahedron* **1970**, *26*, 2447. (h) Cantacuzène, J.; Leroy, J. *Tetrahedron Lett.* **1970**, *11*, 3277. For the BF₃·OEt₂-catalyzed isomerization of α -fluorooxiranes to α -fluoroketones, see: (i) Elkik, E.; Le Blanc, M. *Bull. Soc. Chim. Fr.* **1971**, *870*. For the BF₃·OEt₂-catalyzed/initiated difluorination of carbon-carbon double bonds with XeF₂, see: (j) Shackelford, S. A.; McGuire, R. R.; Pflug, J. L. *Tetrahedron Lett.* **1977**, *18*, 363. (k) Stavber, S.; Zupan, M. *J. Chem. Soc., Chem. Commun.* **1978**, 969. (l) Shackelford, S. A. *J. Org. Chem.* **1979**, *44*, 3485. For the BF₃·OEt₂-catalyzed fluorination of aromatics with CsSO₄F, see: (m) Stavber, S.; Zupan, M. *J. Org. Chem.* **1985**, *50*, 3609. (n) Patrick, T. B.; Darling, D. L. *J. Org. Chem.* **1986**, *51*, 3242. For the BF₃·OEt₂-promoted ring-opening fluorination of α,β -epoxy sulfoxides with KHF₂, see: (o) Satoh, T.; Shishikura, J.; Yamakawa, K. *Chem. Pharm. Bull.* **1990**, *38*, 1798. For the BF₃·OEt₂-catalyzed iodofluorination of perfluoroalkenes with HF, see: (p) Petrov, V. A.; Krespan, C. G. *J. Org. Chem.* **1996**, *61*, 9605. For the BF₃·OEt₂-catalyzed ring-opening fluorination of epoxides with Et₃N·3HF, see: (q) Goj, O.; Haufe, G. *Liebigs Ann.* **1996**, 1289.
- (29) With BF₃·OEt₂: (a) Kelly, D. R.; Roberts, S. M. *Synth. Commun.* **1979**, *9*, 295. (b) Jansson, K.; Frejd, T.; Kihlberg, J.; Magnusson, G. *Tetrahedron Lett.* **1986**, *27*, 753. (c) Mori, Y.; Sawada, T.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 731. With BF₄⁻ sources: (d) Metcalf, B. W.; Burkhardt, J. P.; Jund, K. *Tetrahedron Lett.* **1980**, *21*, 35. (e) Lipshutz, B. H.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* **1981**, *22*, 4603. (f) Uenishi, J.; Tanaka, Y.; Kawai, N. *Tetrahedron Lett.* **2006**, *47*, 5553.
- (30) Farooq, O. *J. Fluorine Chem.* **1995**, *70*, 225.
- (31) Jorapur, Y. R.; Shimada, T. *Synlett* **2012**, 1064 and refs cited therein.
- (32) (a) Farooq, O. *J. Chem. Soc., Perkin Trans. 1* **1998**, 839. (b) Bienewald, F.; Tran Huy, N. H.; Mathey, C. R. *Acad. Sci. Paris, t.2, Série IIc* **1999**, 701. (c) Farooq, O. *Inorg. Chim. Acta* **2000**, *303*, 124. (d) Farooq, O. *New J. Chem.* **2000**, *24*, 81. (e) Mathew, N.; Jagirdar, B. R.; Gopalan, R. S.; Kulkarni, G. U. *Organometallics* **2000**, *19*, 4506.

- (33) For reviews, see: (a) Reedijk, J. *Comments Inorg. Chem.* **1982**, *1*, 379. (b) Doherty, N. M.; Hoffman, N. W. *Chem. Rev.* **1991**, *91*, 553. (c) Murphy, E. F.; Murugavel, R.; Roesky, H. W. *Chem. Rev.* **1997**, *97*, 3425. For selected examples, see: (d) Winter, C. H.; Zhou, X.-X.; Heeg, M. J. *Inorg. Chem.* **1992**, *31*, 1808. (e) Almeida, S. S. P. R.; Pombeiro, J. L. *Organometallics* **1997**, *16*, 4469. (f) Yamamoto, J. H.; Enright, G. D.; Carty, A. J. *J. Organomet. Chem.* **1999**, *577*, 126. (g) Uhl, W.; Breher, F.; Neumüller, B.; Lützen, A.; Saak, W.; Grunenberg, J. *Organometallics* **2001**, *20*, 5478. (h) Li, H.; Lee, G.-H.; Peng, S.-M. *J. Mol. Struct.* **2004**, *707*, 179. (i) Qian, X.; Huang, J.; Qian, Y. *J. Organomet. Chem.* **2004**, *689*, 1503. (j) Kannan, S.; Moody, M. A.; Barnes, C. L.; Duval, P. B. *Inorg. Chem.* **2006**, *45*, 9206. (k) Reger, D. L.; Watson, R. P.; Gardinier, J. R.; Smith, M. D.; Pellechia, P. J. *Inorg. Chem.* **2006**, *45*, 10088. (l) Tomat, E.; Cuesta, L.; Lynch, V. M.; Sessler, J. L. *Inorg. Chem.* **2007**, *46*, 6224.
- (34) (a) Roe, A. *Org. React.* **1949**, *5*, 193. (b) Suschitzky, H. *Adv. Fluorine Chem.* **1965**, *4*, 1. (c) Langlois, B. In *Introduction of Fluorine via Diazonium Compounds (Fluorodediazoniation)*; Baasner, B., Hagemann, H., Tatlow, J. C., Eds.; Houben-Weyl, Methods of Organic Chemistry; Thieme: Stuttgart, 1999; Vol. E10a, Organo-Fluorine Compounds, pp 686–740.
- (35) Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, *28*, 225.
- (36) (a) Bunnett, J. H.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273. (b) Richey, H. G.; Richey, J. M. In *Carbenium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley: New York, 1970; Vol. 2. (c) Burri, P.; Loewenschuss, H.; Zollinger, H.; Zwolinski, G. K. *Helv. Chim. Acta* **1974**, *57*, 395. (d) Swain, C. G.; Sheats, J. E.; Harbison, K. G. *J. Am. Chem. Soc.* **1975**, *97*, 783. (e) Swain, C. G.; Rogers, R. J. *J. Am. Chem. Soc.* **1975**, *97*, 799. (f) Bergstrom, R. G.; Landells, R. G. M.; Wahl, G. H., Jr.; Zollinger, H. *J. Am. Chem. Soc.* **1976**, *98*, 3301. (g) Ambroz, H. B.; Kemp, T. J. *Chem. Soc. Rev.* **1979**, *8*, 353. (h) Bernasconi, C. F. *Chimia* **1980**, *34*, 1. (i) Laali, K.; Szele, I.; Yoshida, K. *Helv. Chim. Acta* **1983**, *66*, 1710.
- (37) Sellers, C.; Suschitzky, H. *J. Chem. Soc. C* **1968**, 2317.
- (38) (a) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572. (b) Garel, L.; Saint-Jalmes, L. *Tetrahedron Lett.* **2006**, *47*, 5705.
- (39) Milner, D. J. *Synth. Commun.* **1992**, *22*, 73.
- (40) Laali, K. K.; Gettwert, V. J. *J. Fluorine Chem.* **2001**, *107*, 31.
- (41) Van der Puy, M. J. *Fluorine Chem.* **1982**, *21*, 385.
- (42) Umemoto, T.; Adachi, K.; Ishihara, S. *J. Org. Chem.* **2007**, *72*, 6905.
- (43) Taylor, E. C.; Bigham, E. C.; Johnson, D. K.; McKillop, A. *J. Org. Chem.* **1977**, *42*, 362.
- (44) (a) De Meio, G. V.; Pinhey, J. T. *J. Chem. Soc., Chem. Commun.* **1990**, 1065. (b) De Meio, G.; Morgan, J.; Pinhey, J. T. *Tetrahedron* **1993**, *49*, 8129.
- (45) (a) Wang, K.-P.; Yun, S. Y.; Mamidipalli, P.; Lee, D. *Chem. Sci.* **2013**, *4*, 3205. (b) Saito, M.; Miyamoto, K.; Ochiai, M. *Chem. Commun.* **2011**, *47*, 3410.
- (46) (a) Bott, K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 259. (b) Glaser, R. *J. Phys. Chem.* **1989**, *93*, 7993. (c) Hanack, M.; Subramanian, L. R. *J. Phys. Org. Chem.* **1993**, *6*, 44.
- (47) Okuyama, T.; Lodder, G. *Adv. Phys. Org. Chem.* **2002**, *37*, 1.
- (48) (a) Okuyama, T.; Fujita, M.; Gronheid, R.; Lodder, G. *Tetrahedron Lett.* **2000**, *41*, 5125. For the formation of alkenyl fluorides as products of the photochemical decomposition of alkenyl(phenyl)iodonium tetrafluoroborates in CH_2Cl_2 , see: (b) Gronheid, R.; Lodder, G.; Okuyama, T. *J. Org. Chem.* **2002**, *67*, 693.
- (49) (a) Hammen, G.; Hanack, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 614. (b) Hanack, M.; Harder, I.; Bofinger, K.-R. *Tetrahedron Lett.* **1981**, *22*, 553. (c) Kitamura, T.; Kobayashi, S.; Taniguchi, H.; Rappoport, Z. *J. Org. Chem.* **1982**, *47*, 5003. (d) Spraul, M.; Griesbaum, K. *Chem. Ber.* **1983**, *116*, 2641. For the formation of alkenyl fluorides in low yield from the treatment of α -diazo- β -hydroxy esters with $\text{BF}_3\text{-OEt}_2$, see: (e) Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marrazzi, M.; Synder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A. *J. Am. Chem. Soc.* **1996**, *118*, 1.

- (50) The production of methyl fluoride from methylamine by diazotization with NOBF_4 has been achieved, see: Wannagat, U.; Hohlstein, G. *Chem. Ber.* **1955**, *88*, 1839.
- (51) For selected examples of the nucleophilic trapping of alkyl carbocations by fluoride transfer from the BF_4^- ion, see refs 49a, b and: (a) Beak, P.; Trancik, J.; Mooberry, J. B.; Johnson, P. Y. *J. Am. Chem. Soc.* **1966**, *88*, 4288. (b) Beak, P.; Trancik, R. J.; Simpson, D. A. *J. Am. Chem. Soc.* **1969**, *91*, 5073. (c) Hittich, R.; Mach, H.; Griesbaum, K. *Chem. Ber.* **1983**, *116*, 2738. (d) Hemming, K.; Morgan, D. T.; Smalley, R. K. *J. Fluorine Chem.* **2000**, *106*, 83.
- (52) (a) Doyle, M. P.; Whitefleet, J. L.; Bosch, R. J. *J. Org. Chem.* **1979**, *44*, 2923. (b) Doyle, M. P.; Whitefleet, J. L.; Zaleta, M. A. *Tetrahedron Lett.* **1975**, *16*, 4201.
- (53) The intermediacy of nitrilium ions arising from inter- or intramolecular attack of the cyano moiety was discounted on the basis of an absence of amide products on aqueous workup, as well as the fact that earlier studies from Doyle et al. found no evidence that nitrilium ions undergo nucleophilic attack by fluoride transfer from the BF_4^- ion.
- (54) Maeda, H.; Koide, T.; Matsumoto, S.; Ohmori, H. *Chem. Pharm. Bull.* **1996**, *44*, 1480.
- (55) Bloodworth, A. J.; Bower, K. J.; Mitchell, J. C. *Tetrahedron Lett.* **1987**, *28*, 5347.
- (56) Dávila, A.; Escobedo, J. O.; Read, M. W.; Fronczek, F. R.; Strongin, R. M. *Tetrahedron Lett.* **2001**, *42*, 3555.
- (57) Azacarbenium ions are another class of stabilized carbocation that could in principle undergo nucleophilic trapping by fluoride transfer from the BF_4^- ion to give α -fluoro amine products, but only a single example of such a transformation is on record. Specifically, a 4-fluoroazetidinone derivative has been isolated in 40% yield from the decomposition of a secopencillanate sulfonium tetrafluoroborate salt, see: Brennan, J.; Hussain, F. H. S.; Virgili, P. *Tetrahedron Lett.* **1986**, *27*, 3199.
- (58) For other isolated examples of the formation of α -fluoro ether products by fluoride transfer from the BF_4^- ion, see: (a) Griesbaum, K.; Schlindwein, K. *J. Org. Chem.* **1995**, *60*, 8062. (b) Wang, Y.-C.; Lin, Y.-C.; Liu, Y.-H. *Chem.—Asian J.* **2012**, *7*, 2703. On a related note, the in situ generation of acyl fluorides via fluoride transfer from the BF_4^- ion to iodonium-activated aldehydes has also been invoked in the proposed mechanism of IPy_2BF_4 -mediated Friedel-Crafts acylation reactions from the aldehyde oxidation level, see: (c) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3140.
- (59) (a) Shimizu, M.; Togo, H.; Yokoyama, M. *Synthesis* **1998**, 799. (b) Toshima, K. *Carbohydr. Res.* **2000**, *327*, 15. (c) Mukaiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5590.
- (60) Williams, S. J.; Withers, S. G. *Carbohydr. Res.* **2000**, *327*, 27.
- (61) (a) Igarashi, K.; Honma, T.; Irisawa, J. *Carbohydr. Res.* **1969**, *11*, 577. (b) Igarashi, K.; Honma, T.; Irisawa, J. *Carbohydr. Res.* **1970**, *13*, 49.
- (62) Kunz, H.; Sager, W. *Helv. Chim. Acta* **1985**, *68*, 283.
- (63) Maeda, H.; Matsumoto, S.; Koide, T.; Ohmori, H. *Chem. Pharm. Bull.* **1998**, *46*, 939.
- (64) (a) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 319. (b) Barluenga, J. *Pure Appl. Chem.* **1999**, *71*, 431.
- (65) (a) López, J. C.; Uriel, C.; Guillamón-Martín, A.; Valverde, S.; Gómez, A. M. *Org. Lett.* **2007**, *9*, 2759. (b) Huang, K.-T.; Winssinger, N. *Eur. J. Org. Chem.* **2007**, 1887.
- (66) Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *J. Chem. Soc., Chem. Commun.* **1988**, 823.
- (67) López, J. C.; Bernal-Albert, P.; Uriel, C.; Valverde, S.; Gómez, A. M. *J. Org. Chem.* **2007**, *72*, 10268.
- (68) Blomberg, L.; Norberg, T. *J. Carbohydr. Chem.* **1992**, *11*, 751.
- (69) Tsegay, S.; Williams, S. J.; Williams, S. J. *Carbohydr. Res.* **2012**, *357*, 16.
- (70) (a) Meyer, G.; Yvelin, F.; Jutand, A.; Amatore, C.; Sinaÿ, P. *Carbohydr. Res.* **1993**, *244*, 237. (b) Suzuki, S.; Matsumoto, K.; Kawamura, K.; Suga, S.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3755. (c) Saito,

- K.; Ueoka, K.; Matsumoto, K.; Suga, S.; Nokami, T.; Yoshida, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5153.
- (71) (a) Okamoto, K.; Kondo, T.; Goto, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 631. (b) Pearson, A. G.; Kiefel, M. J.; Ferro, V.; von Itzstein, M. *Carbohydr. Res.* **2005**, *340*, 2077. (c) Filali, H.; Danel, M.; Ballereau, S.; Baltas, M. *Carbohydr. Res.* **2010**, *345*, 2421.
- (72) Fry, A. J.; Migron, Y. *Tetrahedron Lett.* **1979**, *20*, 3357.
- (73) Pasceri, R.; Bartrum, H. E.; Hayes, C. J.; Moody, C. J. *Chem. Commun.* **2012**, *48*, 12077.
- (74) For the nucleophilic fluorination of ethyl 3-(1'-adamantanyl)-2-diazo-3-oxopropanoate with $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 , see: Ohno, M.; Itoh, M.; Ohashi, T.; Eguchi, S. *Synthesis* **1993**, 793.
- (75) (a) Sheffer, H. E.; Moore, J. A. *J. Org. Chem.* **1963**, *28*, 129. (b) Brunovlenskaya, I. I.; Kolontsov, A. A.; Skvarchenko, V. R. *Zh. Org. Khim.* **1979**, *15*, 1499. (c) Benati, L.; Calestani, G.; Monteverecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2637.
- (76) For a representative example, see: Kakuchi, T.; Satoh, T.; Umeda, S.; Hashimoto, H.; Yokota, K. *Macromolecules* **1995**, *28*, 4062.
- (77) For a representative example that employs $\text{BF}_3\cdot\text{OEt}_2$ as a catalyst for the ring-opening fluorination of epoxides with $\text{Et}_3\text{N}\cdot 3\text{HF}$, see ref 28q.
- (78) For a representative example, see: Kita, Y.; Kitagaki, S.; Yoshida, Y.; Mihara, S.; Fang, D.-F.; Kondo, M.; Okamoto, S.; Imai, R.; Akai, S.; Fujioka, H. *J. Org. Chem.* **1997**, *62*, 4991.
- (79) For a representative example, see: Vankar, Y. D.; Chaudhuri, N. C.; Vankar, P. S. *J. Chem. Res.* **1989**, 178.
- (80) Whilst the ring-opening fluorination of oxetanes with $\text{BF}_3\cdot\text{OEt}_2$ as the nucleophilic fluorine source is unknown as a synthetic method, fluorohydrin byproducts have been observed during the cyclic oligomerization of oxetanes with $\text{BF}_3\cdot\text{OEt}_2$, see: Dale, J.; Fredriksen, S. B. *Pure Appl. Chem.* **1989**, *61*, 1587.
- (81) Notably, the Lewis acid silicon tetrafluoride, SiF_4 , has also been described as a reagent for the ring-opening fluorination of epoxides; see: (a) Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1988**, *29*, 4101. (b) Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1989**, *30*, 967. For the ring-opening fluorination of oxetanes with SiF_4 , see: (c) Shimizu, M.; Kanemoto, S.; Nakahara, Y. *Heterocycles* **2000**, *52*, 117.
- (82) (a) Knunyants, I. L. *C. R. (Dokl.) Acad. Sci. URSS* **1947**, *55*, 223. (b) Knunyants, I. L.; Kil'disheva, O. V.; Petrov, I. P. *Zh. Obshch. Khim.* **1949**, *19*, 95. (c) Knunyants, I. L.; Kil'disheva, O. V.; Bykhovskaya, E. Zh. Obshch. Khim. **1949**, *19*, 101.
- (83) Henbest, H. B.; Wrigley, T. I. *J. Chem. Soc.* **1957**, 4765.
- (84) (a) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 779. (b) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872.
- (85) By analogy to substituted cyclopropanes, a donor-substituted epoxide can be defined as one that bears a *p*- or π -donor substituent, which is able to enter into conjugation with an adjacent carbocation formed by cleavage of the oxirane C–O bond. This includes aryl, alkenyl, alkynyl substituents as well as heteroatoms bearing lone electron pairs (e.g., O, N).
- (86) For reviews of the nucleophilic ring-opening of epoxides with retention of configuration, see: (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (b) Akrem, A. A.; Morseenkov, A. M.; Dobrynin, V. N. *Russ. Chem. Rev.* **1968**, *37*, 448. For an instructive discussion on the effect of solvent and steric inhibition of resonance on the stereoselectivity of the ring-opening of aryl epoxides under acidic conditions, see: (c) Balsamo, A.; Crotti, P.; Macchia, F. *Tetrahedron* **1973**, *29*, 199.
- (87) For selected examples, see: (a) Blunt, J. W.; Hartshorn, M. P.; Kirk, D. N. *Tetrahedron* **1965**, *21*, 559. (b) Hinoue, K.; Nojima, M.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3096. (c) Butke, G. P.; Jimenz, F.; Michalik, J.; Gorski, R. A.; Rossi, N. F.; Wemple, J. *J. Org. Chem.* **1978**, *43*, 954. (d) Bach, R. D.; Klix, R. C. *J. Org. Chem.* **1985**, *50*, 5438. (e) Bach, R. D.; Klix, R. C. *Tetrahedron Lett.* **1985**, *26*, 985. (f) Klix, R. C.; Bach, R. D. *J. Org. Chem.* **1987**, *52*, 580. (g) Fujimoto, Y.; Kanzawa, Y.; Ikuina, Y.; Kakinuma, K.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* **1989**, 1107.
- (88) (a) Bowers, A.; Ringold, H. J. *Tetrahedron* **1958**, *3*, 14. (b) Bowers, A.; Cuéllar Ibáñez, L.; Ringold, H. J. *Tetrahedron* **1959**, *7*, 138. (c) Blunt, J. W.; Hartshorn, M. P.; Kirk, D. N. *Tetrahedron* **1966**, *22*, 3195. (d) Coxon, J. M.; Hartshorn, M. P.; Muir, C. N.; Richards, K. E. *Tetrahedron Lett.* **1967**, *8*, 3725. (e) Bull, J. R. *Tetrahedron Lett.* **1968**, *9*, 5959. (f) Guest, I. G.; Marples, B. A. *Tetrahedron Lett.* **1969**, *10*, 1947. (g) Coxon, J. M.; Hartshorn, M. P.; Muir, C. N. *Tetrahedron* **1969**, *25*, 3925. (h) Blackett, B. N.; Coxon, J. M.; Hartshorn, M. P.; Richards, K. E. *Tetrahedron* **1969**, *25*, 4999. (i) Coxon, J. M.; Hartshorn, M. P.; Sutherland, B. L. S. *Tetrahedron Lett.* **1969**, *10*, 4029. (j) Guest, I. G.; Marples, B. A. *J. Chem. Soc. C* **1970**, 1626. (k) Guest, I. G.; Marples, B. A. *J. Chem. Soc. C* **1971**, 576. (l) Guest, I. G.; Marples, B. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 900. (m) Mastalerz, H.; Morand, P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 154.
- (89) (a) Coxon, J. M.; Hartshorn, M. P.; Kirk, D. N. *Tetrahedron* **1964**, *20*, 2531. (b) Coxon, J. M.; Hartshorn, M. P.; Kirk, D. N. *Tetrahedron* **1964**, *20*, 2547. (c) Morrison, G. A.; Wilkinson, J. B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 345. (d) Zhao, K.; Wang, Y.; Han, L. *Steroids* **2007**, *72*, 95.
- (90) (a) Ruelas, J. P.; Iriarte, J.; Kincl, F.; Djerassi, C. *J. Org. Chem.* **1958**, *23*, 1744. (b) Zderic, J. A.; Limon, D. C.; Ringold, H. J.; Djerassi, C. *J. Am. Chem. Soc.* **1959**, *81*, 3120.
- (91) (a) Bowers, A.; Ringold, H. J. *J. Am. Chem. Soc.* **1958**, *80*, 4423. (b) Edwards, J. A.; Zaffaroni, A.; Ringold, H. J.; Djerassi, C. *Proc. Chem. Soc.* **1959**, 87. (c) Mills, J. S.; Bowers, A.; Campillo, C. C.; Djerassi, C.; Ringold, H. J. *J. Am. Chem. Soc.* **1959**, *81*, 1264. (d) Bowers, A.; Ibáñez, L. C.; Ringold, H. J. *J. Am. Chem. Soc.* **1959**, *81*, 5991. (e) Bowers, A.; Denot, E.; Sanchez, M. B.; Ringold, H. J. *Tetrahedron* **1959**, *7*, 153. (f) Knox, L. H.; Zderic, J. A.; Ruelas, J. P.; Djerassi, C.; Ringold, H. J. *J. Am. Chem. Soc.* **1960**, *82*, 1230. (g) Edwards, J. A.; Ringold, H. J.; Djerassi, C. *J. Am. Chem. Soc.* **1960**, *82*, 2318. (h) Mills, J. S.; Bowers, A.; Djerassi, C.; Ringold, H. J. *J. Am. Chem. Soc.* **1960**, *82*, 3399. (i) Mills, J.; Candiani, O.; Djerassi, C. *J. Org. Chem.* **1960**, *25*, 1056. (j) Ramírez, J. A.; Gros, E. G.; Galagovsky, L. R. *Tetrahedron* **2000**, *56*, 6171.
- (92) Slavíková, B.; Kasal, A.; Chodounská, H.; Křištofíková, Z. *Collect. Czech. Chem. Commun.* **2002**, *67*, 30.
- (93) Kasch, H.; Liedtke, B. U.S. Patent 89340, 2006.
- (94) May, P. J.; Nice, F. A.; Phillipps, G. H. *J. Chem. Soc. C* **1966**, 2210.
- (95) Reshetova, I. G.; Akhrem, A. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1965**, *79*. For English translation, see: Reshetova, I. G.; Akhrem, A. A. *Russ. Chem. Bull., Int. Ed.* **1965**, *14*, 68.
- (96) (a) Murai, A.; Sasamori, H.; Masamune, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 437. (b) Murai, A.; Sasamori, H.; Masamune, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 254.
- (97) Coxon, J. M.; Hartshorn, M. P.; Kirk, D. N. *Tetrahedron* **1965**, *21*, 2489.
- (98) Yoshida, K. *Tetrahedron* **1969**, *25*, 1367.
- (99) Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 1.
- (100) Other investigators have demonstrated if the reaction of epoxide 77 with $\text{BF}_3\cdot\text{OEt}_2$ in benzene is quenched after only 25 s, fluorohydrin 80 can be isolated in 8% yield; see ref 88d.
- (101) Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275.
- (102) An alternative explanation based on dipole–dipole repulsions between the BF_3 -coordinated axial 3α -OAc group and the $\text{C}(5\alpha)$ - OBF_3^- moiety during fluorohydrin formation has also been advanced; see ref 88d.
- (103) Bowers, A.; Ringold, H. J. U.S. Patent 3115492, 1963.
- (104) It has been suggested that coordination of one molecule of BF_3 with the less-hindered 3β -oxygen atom of the ketal group may be more likely, thus magnifying the $\text{C}(3\beta)$ -O rather than the $\text{C}(5\alpha)$ -O dipole and not opposing fluorohydrin formation by dipolar repulsion; see ref 88d.
- (105) House, H. O.; Reif, D. J. *J. Am. Chem. Soc.* **1955**, *77*, 6525.
- (106) For reviews of the synthesis of vicinal fluorohydriins, see: (a) Haufe, G. *J. Fluorine Chem.* **2004**, *125*, 875. (b) Haufe, G. Product Subclass 9: β -Fluoro Alcohols. In *Science of Synthesis*; Percy, J., Ed.; Thieme: Stuttgart, 2006; Vol. 34: Fluorine, p 345.

- (107) For reviews of amine–HF reagents, see: (a) Yoneda, N. *Tetrahedron* **1991**, *47*, 5329. (b) McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31.
- (108) Shahak, I.; Manor, S.; Bergmann, E. D. *J. Chem. Soc. C* **1968**, 2129.
- (109) Alvernhe, G.; Laurent, A.; Haufe, G. *J. Fluorine Chem.* **1986**, *34*, 147.
- (110) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 733–775.
- (111) Wilton, J. H.; Doskotch, R. W. *J. Org. Chem.* **1983**, *48*, 4251.
- (112) St. Enev, V.; Tsankova, E. T. *Tetrahedron* **1991**, *47*, 6399.
- (113) For other examples of terpenoid-derived epoxides giving rise to fluorohydrins in low (or unreported) yields upon treatment with $\text{BF}_3\cdot\text{OEt}_2$, see: (a) Hikino, H.; Suzuki, N.; Takemoto, T. *Chem. Pharm. Bull.* **1967**, 1395. (b) Reusch, W.; Anderson, D. F.; Johnson, C. K. *J. Am. Chem. Soc.* **1968**, *90*, 4988. (c) Nakano, T.; Haces, A.; Martin, A.; Rojas, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2075. (d) Fischer, N. H.; Wu-Shih, Y.-F.; Chiari, G.; Fronczek, F. R.; Watkins, S. F. *J. Nat. Prod.* **1981**, *44*, 104. (e) Ramage, R.; Southwell, I. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1323. (f) Begley, M. J.; Jackson, C. B.; Pattenden, G. *Tetrahedron* **1990**, *46*, 4907. (g) Hwu, J. R.; Wetzel, J. M.; Lee, J. S.; Butcher, R. J. *J. Organomet. Chem.* **1993**, *453*, 21.
- (114) Goldsmith, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 3913.
- (115) (a) House, H. O. *J. Am. Chem. Soc.* **1956**, *78*, 2298. (b) House, H. O.; Wasson, R. L. *J. Am. Chem. Soc.* **1956**, *78*, 4394. (c) House, H. O.; Ryerson, G. D. *J. Am. Chem. Soc.* **1961**, *83*, 979. (d) Berti, G.; Macchia, B.; Macchia, F.; Monti, L. *J. Chem. Soc. C* **1971**, 3371.
- (116) (a) Canonica, L.; Ferrari, M.; Pagnoni, U. M.; Pelizzoni, F.; Maroni, S.; Salvatori, T. *Tetrahedron* **1969**, *25*, 1. (b) Taylor, S. K.; Bischoff, D. S.; Blanksespoor, C. L.; Deck, P. A.; Harvey, S. M.; Johnson, P. L.; Marolewski, A. E.; Mork, S. W.; Motry, D. H.; Van Eenenaam, R. *J. Org. Chem.* **1990**, *55*, 4202. (c) Pettersson, L.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 789.
- (117) Maruoka, K.; Murase, N.; Bureau, R.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3663.
- (118) Alarcón, P.; Pardo, M.; Soto, J. L. *J. Heterocycl. Chem.* **1985**, *22*, 273.
- (119) Coxon, J. M.; Hartshorn, M. P.; Lewis, A. J.; Richards, K. E.; Swallow, W. H. *Tetrahedron* **1969**, *25*, 4445.
- (120) Coxon, J. M.; Thorpe, A. J. *J. Org. Chem.* **2000**, *65*, 8421.
- (121) Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *J. Org. Chem.* **1974**, *39*, 1142.
- (122) Coxon, J. M.; Morokuma, K.; Thorpe, A. J.; Whalen, D. J. *J. Org. Chem.* **1998**, *63*, 3875.
- (123) Nowak, I. *J. Fluorine Chem.* **2000**, *104*, 201.
- (124) Takaishi, N.; Takahashi, H.; Inamoto, Y. *Tetrahedron Lett.* **1985**, *26*, 2361.
- (125) Stork, G.; Worrall, W. S.; Pappas, J. *J. Am. Chem. Soc.* **1960**, *82*, 4315.
- (126) Ashwell, M.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron* **1990**, *46*, 7429.
- (127) α -Fluoro ketones have also been isolated as minor products from the reaction of 2-methyl- and 2-phenyl-substituted 2-nitro-3-phenyloxirane with $\text{BF}_3\cdot\text{OEt}_2$ in benzene; see: Newan, H.; Angier, R. B. *Tetrahedron* **1970**, *26*, 825.
- (128) For reviews on the synthesis and biological activity of fluorinated anthracyclines, see: (a) Giannini, G. *Curr. Med. Chem.* **2002**, *9*, 687. (b) Giannini, G. *Med. Chem. Rev. Online* **2004**, *1*, 47.
- (129) Giannini, G. *Gazz. Chim. Ital.* **1996**, *126*, 771.
- (130) Lombardi, P.; Animati, F.; Cipollone, A.; Giannini, G.; Monteagudo, E.; Arcamone, F. *Acta Biochim. Polym.* **1995**, *42*, 433.
- (131) Del Nero, S.; Lombardi, P. *Gazz. Chim. Ital.* **1984**, *114*, 517.
- (132) Ruland, Y.; Zedde, C.; Baltas, M.; Gorrichon, L. *Tetrahedron Lett.* **1999**, *40*, 7323.
- (133) (a) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3751. (b) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762. (c) Bond, C. W.; Cresswell, A. J.; Davies, S. G.; Kurosawa, W.; Lee, J. A.; Fletcher, A. M.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *J. Org. Chem.* **2009**, *74*, 6735. (d) Davies, S. G.; Fletcher, A. M.; Kurosawa, W.; Lee, J. A.; Poce, G.; Roberts, P. M.; Thomson, J. E.; Williamson, D. M. *J. Org. Chem.* **2010**, *75*, 7745. (e) Kurosawa, W.; Roberts, P. M.; Davies, S. G. *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.)* **2010**, *68*, 1295. (f) Brennan, M. B.; Claridge, T. D. W.; Compton, R. G.; Davies, S. G.; Fletcher, A. M.; Henstridge, M. C.; Hewings, D. S.; Kurosawa, W.; Lee, J. A.; Roberts, P. M.; Schoonen, A. K.; Thomson, J. E. *J. Org. Chem.* **2012**, *77*, 7241.
- (134) Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Morris, M. J.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2011**, *76*, 4617.
- (135) Although there is no consensus on the pK_a of aqueous HBF_4^- , measurements indicate that 72.9% aqueous HBF_4^- is slightly more acidic than 100% H_2SO_4 , and is thus classified as a “superacid”, see: Fărăciu, D.; Hâncu, D. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 2161.
- (136) (a) Wolinsky, J.; Thorstenson, J. H.; Killinger, T. A. *J. Org. Chem.* **1978**, *43*, 875. (b) Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tetrahedron* **1994**, *50*, 12999.
- (137) For the cationic polymerization of cyclohexene oxide during attempted ring-opening fluorination with anhydrous HF, see: Shahak, I.; Manor, S.; Bergmann, E. D. *J. Chem. Soc.* **1968**, 2129.
- (138) The cationic polymerization of (*R,R*)-*trans*-2,3-epoxybutane has been shown to proceed with inversion of configuration at the oxirane carbons to generate an optically inactive polyether, indicative of an $\text{S}_{\text{N}}2$ -type attack of epoxide monomers onto oxiranium ion intermediates, see: Vandenburg, E. *J. Am. Chem. Soc.* **1961**, *83*, 3538.
- (139) For selected examples of this phenomenon, see: (a) Drucker, A.; Morawetz, H. *J. Am. Chem. Soc.* **1956**, *78*, 346. (b) Bovey, F. A. *J. Polym. Sci., Polym. Chem.* **1963**, *1*, 843. (c) Ponratnam, S.; Kapur, S. L. *Macromol. Chem.* **1977**, *178*, 1029. (d) Hamid, S. M.; Sherrington, D. C. *Polymer* **1987**, *28*, 332. (e) Huang, P. C.; Reichert, K.-H. *Angew. Makromol. Chem.* **1988**, *162*, 19. (f) van de Grampel, H. T.; Tan, Y. Y.; Challa, G. *Macromolecules* **1990**, *23*, 5209. (g) Baldy, C. J.; Morrison, D. L.; Elliot, C. M. *Langmuir* **1991**, *7*, 2376. (h) Anseth, K. S.; Scott, R. A.; Peppas, N. A. *Macromolecules* **1996**, *29*, 8308.
- (140) The strong inductive-withdrawal effect of the ammonium group may also serve to decrease the nucleophilicity of the oxirane lone pairs and further contribute to a rate decrease for polymerization.
- (141) For a review on the rearrangement of β -amino alcohols via aziridinium ions, see: Metro, T. X.; Duthion, B.; Pardo, D. G.; Cossy, J. *Chem. Soc. Rev.* **2010**, *39*, 89.
- (142) House, H. O. *J. Org. Chem.* **1956**, *21*, 1306.
- (143) Stomberg, R.; Li, S.; Lundquist, K. *Acta Crystallogr.* **1994**, *C50*, 1145.
- (144) Weber, F. G.; Giese, H.; Koeppel, H.; Reinhold, M.; Strobel, R.; Radeglia, R.; Storek, W. *J. Prakt. Chem.* **1985**, *327*, 133.
- (145) (a) Tanaka, H.; Hiroo, M.; Ichino, K.; Ito, K. *Chem. Pharm. Bull.* **1989**, *37*, 1441. (b) Ralph, J.; Ede, R. M.; Robinson, N. P.; Main, L. *J. Wood Chem. Technol.* **1987**, *7*, 133.
- (146) Tung, C. C.; Speziale, A. *J. Org. Chem.* **1963**, *28*, 2009.
- (147) Barili, P. L.; Bellucci, G.; Berti, G.; Macchia, B.; Macchia, F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 477.
- (148) Islas-González, G.; Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Riera, A.; Pericàs, M. A. *Tetrahedron Lett.* **2004**, *45*, 6337.
- (149) See the correction (Rodríguez-Escrich, S.; Popa, D.; Jimeno, C.; Vidal-Ferran, A.; Pericàs, M. A. *Org. Lett.* **2010**, *12*, 3116) to: Rodríguez-Escrich, S.; Popa, D.; Jimeno, C.; Vidal-Ferran, A.; Pericàs, M. A. *Org. Lett.* **2005**, *7*, 3829.
- (150) Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Tyte, M. J. *Org. Lett.* **2010**, *12*, 2936.
- (151) For other ring-opening fluorinations of aryl epoxides, which proceed with retention of configuration, see ref 81a and: (a) Tamura, M.; Shibakami, M.; Arimura, T.; Kurosawa, S.; Sekiya, A. *J. Fluorine Chem.* **1995**, *70*, 1. (b) Shimizu, M.; Nakahara, Y. *J. Fluorine Chem.* **1999**, *99*, 95. (c) Akiyama, Y.; Fukuhara, T.; Hara, S. *Synlett* **2003**, 1530. For ring-opening chlorinations or brominations of aryl epoxides which proceed with retention of configuration, see ref 146 and: (d) Reichel, L.; Neubauer, A. *Liebigs Ann.* **1975**, *7–8*, 1538. (e) Bach,

- R. D.; Domagala, J. M. *J. Org. Chem.* **1984**, *49*, 4181. (f) Einhorn, C.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1986**, 1368. (g) Litkei, G.; Tökés, A. L. *Synth. Commun.* **1991**, *21*, 1597. (h) Thijs, L.; Cillissen, P. J. M.; Zwanenburg, B. *Tetrahedron* **1992**, *48*, 9985. (i) Ghelfi, F.; Grandi, R.; Pagnoni, U. M. *Gazz. Chim. Ital.* **1995**, *125*, 215. (j) Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; McCague, R.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, *3501*. (k) Bickley, J. F.; Gillmore, A. T.; Roberts, S. M.; Skidmore, J.; Steiner, A. J. *Chem. Soc., Perkin Trans. 1* **2001**, *1109*. (l) Zhou, Z.; Mei, X.; Chang, J.; Feng, D. *Synth. Commun.* **2001**, *31*, 3609. (m) Khanjin, N. A.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 2028. (n) Gillmore, A.; Lauret, C.; Roberts, S. M. *Tetrahedron* **2003**, *59*, 4363. (o) Marques, C. S.; Moura, N.; Burke, A. J. *Tetrahedron Lett.* **2006**, *47*, 6049. (p) Das, B.; Venkateswarlu, K.; Krishnaiah, M. *Helv. Chim. Acta* **2007**, *90*, 149. (q) Lu, Z.; Wu, W.; Peng, L.; Wu, L. *Can. J. Chem.* **2008**, *86*, 142. For ring-opening of aryl epoxides with alkoxy and aryloxy nucleophiles, which proceed with retention of configuration, see ref 151o and: (r) Durham, D.; Kingsbury, C. A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 923. (s) Pineschi, M.; Bertolini, F.; Haak, R. M.; Crotti, P.; Macchia, F. *Chem. Commun.* **2005**, 1426. (t) Bertolini, F.; Crotti, P.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **2006**, *47*, 61.
- (152) Blunt, J. W.; Coxon, J. M.; Lim, C.-E.; Schuyt, H. A. *Aust. J. Chem.* **1983**, *36*, 97.
- (153) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.
- (154) García Ruano, J. L.; Parra, A.; Alonso, I.; Fuster, S.; del Pozo, C.; Arroyo, Y.; Sanz-Tejedor, A. *Chem.—Eur. J.* **2011**, *17*, 6142.
- (155) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462.
- (156) Huang, S.; Xiao, Z.; Wang, F.; Zhou, J.; Yuan, G.; Zhang, S.; Chen, Z.; Thiel, W.; von Ragué Schleyer, P.; Zhang, X.; Hu, X.; Chen, B.; Gan, L. *Chem.—Eur. J.* **2005**, *11*, 5449.
- (157) Samata, K.; Some, S.; Kim, Y.; Yoon, Y.; Min, M.; Lee, S. M.; Park, Y.; Lee, H. *Chem. Commun.* **2013**, *49*, 8991.
- (158) (a) Hudlicky, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907. (b) Brandänge, S.; Bäckvall, J.-E.; Leijonmarck, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2051. (c) Nagumo, S.; Miyoshi, I.; Akita, H.; Kawahara, N. *Tetrahedron Lett.* **2002**, *43*, 2223. (d) Méndez, P. S.; Cachau, R. E.; Seoane, G.; Ventura, O. N. *J. Mol. Struct. (THEOCHEM)* **2009**, *904*, 21.
- (159) Lie Ken Jie, M. S. F.; Lau, M. M. L.; Lam, C. N. W.; Alam, M. S.; Metzger, J. O.; Biermann, U. *Chem. Phys. Lipids* **2003**, *125*, 93.
- (160) (a) Duhamel, P.; Leblond, B.; Poirier, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 476. (b) Duhamel, P.; Leblond, B.; Bidois-Séry, L.; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2265.
- (161) The use of 0.33 equiv of $\text{BF}_3\cdot\text{OEt}_2$ gave incomplete conversion, prompting the authors to propose that only two fluorine atoms within $\text{BF}_3\cdot\text{OEt}_2$ were transferable under the reaction conditions. They suggested that the (putative) $\text{BF}(\text{OR})_2$ intermediate may not be sufficiently Lewis acidic to react further with epoxide starting material.
- (162) Donnelly, J. A.; Keegan, J. R.; Quigley, K. *Tetrahedron* **1980**, *36*, 1671.
- (163) (a) Griesbaum, K.; Keul, H.; Kibar, R.; Pfeffer, B.; Spraul, M. *Chem. Ber.* **1981**, *114*, 1858. (b) Griesbaum, K.; Lie, G. O.; Raupp, E. *Chem. Ber.* **1981**, *114*, 3273. (c) Keul, H.; Pfeffer, B.; Griesbaum, K. *Chem. Ber.* **1984**, *117*, 2193.
- (164) Voronkov, M. G.; Fedotova, L. A. *Khim. Geterotsikl. Soedin.* **1966**, 545. For English translation, see: Voronkov, M. G.; Fedotova, L. A. *Chem. Heterocycl. Compd.* **1967**, 408.
- (165) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Synlett* **2004**, 2218.
- (166) Sugihara, Y.; Iimura, S.; Nakayama, J. *Chem. Commun.* **2002**, 134.
- (167) Legters, J.; Willem, J. G. H.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59.
- (168) Reddy, R.; Jaquith, J. B.; Neelagiri, V. R.; Saleh-Hanna, S.; Durst, T. *Org. Lett.* **2002**, *4*, 695.
- (169) Hu, X. E. *Tetrahedron Lett.* **2002**, *43*, 5315.
- (170) Duréault, A.; Tranchepain, I.; Depezy, J.-C. *J. Org. Chem.* **1989**, *54*, 5324.
- (171) Prasad, B. A. B.; Pandey, G.; Singh, V. K. *Tetrahedron Lett.* **2004**, *45*, 1137.
- (172) Desjardins, M.; Lallemand, M.-C.; Freeman, S.; Hudlicky, T.; Abbound, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 621.
- (173) (a) Berner, H.; Vypel, H.; Schulz, G. *Tetrahedron* **1987**, *43*, 765. (b) Kanemoto, S.; Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1987**, *28*, 663. (c) Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1987**, *28*, 3119. (d) Kanemoto, S.; Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1987**, *28*, 6313. (e) Kanemoto, S.; Shimizu, M.; Yoshioka, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2024. (f) Finch, H.; Highcock, R. M.; Roberts, S. M.; Short, K. M.; Sik, V. *J. Chem. Soc., Chem. Commun.* **1989**, 670. (g) Kanemoto, S.; Shimizu, M.; Yoshioka, H. *J. Chem. Soc., Chem. Commun.* **1989**, 690. (h) Fletcher, C. A.; Hilpert, H.; Myers, P. L.; Roberts, S. M.; Storer, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1707. (i) Tamura, M.; Shibasaki, M.; Kurosawa, S.; Arimura, T.; Sekiya, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1891. (j) Kirihara, M.; Kambayashi, T.; Momose, T. *Chem. Commun.* **1996**, 1103. (k) Hell, Z.; Finta, Z.; Dmowski, W.; Faigl, F.; Pustovit, Y. M.; Töke, L.; Harmat, V. *J. Fluorine Chem.* **2000**, *104*, 297. (l) Kirihara, M.; Kakuda, H.; Tsunooka, M.; Shimajiri, A.; Takuwa, T.; Hatano, A. *Tetrahedron Lett.* **2003**, *44*, 8513. (m) Bose, G.; Langer, P. *Tetrahedron Lett.* **2004**, *45*, 3861. (n) Adam, J.-M.; Foricher, J.; Hanlon, S.; Lohri, B.; Moine, G.; Schmid, R.; Stahr, H.; Weber, M.; Wirz, B.; Zutter, U. *Org. Process Res. Dev.* **2011**, *15*, 515.
- (174) Fokin, A. A.; Gunchenko, P. A.; Yaroshinsky, A. I.; Yurchenko, A. G.; Krasutsky, P. A. *Tetrahedron Lett.* **1995**, *36*, 4479.
- (175) Gassman, P. G.; Riehle, R. J. *Tetrahedron Lett.* **1989**, *30*, 3275.
- (176) Löfström, C. M. G.; Bäckvall, J.-E. *Tetrahedron Lett.* **1996**, *37*, 3371.
- (177) (a) Heasley, V. L.; Shellhamer, D. F.; Gipe, R. K.; Wiese, H. C.; Oakes, M. L.; Heasley, G. E. *Tetrahedron Lett.* **1980**, *21*, 4133. (b) Heasley, V. L.; Gipe, R. K.; Martin, J. L.; Wiese, H. C.; Oakes, M. L.; Shellhamer, D. F.; Heasley, G. E.; Robinson, B. L. *J. Org. Chem. Interfacial Electrochem.* **1973**, *43*, 318.
- (178) For an earlier report of fluoride transfer from a BF_4^- ion to the chloriranium ion derived from cyclohexene, see: Koch, V. R.; Miller, L. L.; Clark, D. B.; Fleischmann, M.; Joslin, T.; Pletcher, D. *J. Electroanal. Chem. Interfacial Electrochem.* **1973**, *43*, 318.
- (179) Heasley, G. L.; Janes, J. M.; Stark, S. R.; Robinson, B. L.; Heasley, V. L.; Shellhamer, D. F. *Tetrahedron Lett.* **1985**, *26*, 1811.
- (180) (a) Barluenga, J.; Campos, P. J.; González, J. M.; Suárez, J. L.; Asensio, G. J. *Org. Chem.* **1991**, *S6*, 2234. For earlier isolated examples of the formation of iodofluorinated products during the iodiranium ion-initiated cation- π cyclization of alkenes, see: (b) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1546.
- (181) Evans, R. D.; Schauble, J. H. *Synthesis* **1987**, 551.
- (182) Vorob'eva, É. A.; Krimer, M. Z.; Smit, W. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 2743. For English translation, see: Vorob'eva, É. A.; Krimer, M. Z.; Smit, W. A. *Russ. Chem. Bull., Int. Ed.* **1976**, *25*, 2553.
- (183) The reaction of norbornene with N -[(2-nitrophenyl)thio]piperidine in the presence of $\text{BF}_3\cdot\text{OEt}_2$ has been reported to give a mixture of sulfonylated fluoronorbornanes arising from Wagner-Meerwein rearrangements, see: Sorokin, V. D.; Plokikh, I. G.; Berlin, M. Yu.; Grishin, Yu. K.; Potekhin, K. A.; Koz'min, A. S.; Zefirov, N. S. *Dokl. Akad. Nauk* **1993**, *332*, 730.
- (184) The reaction of norbornene with $[\text{PhS}^+][\text{BF}_4^-]$ (generated in situ from PhSCl and AgBF_4) has been reported to give mainly 2-fluoro-7-(phenylthio)norbornane on warming of the thiiranium ion tetrafluoroborate salt from -30 to 20 °C, see: (a) Smit, W. A.; Krimer, M. Z.; Vorob'eva, É. A. *Tetrahedron Lett.* **1975**, *29*, 2451. For the fluorosulfonylation of a tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene system accompanied by sketal rearrangement, see: (b) Zefirov, N. S.; Koz'min, A. S.; Kirin, V. N.; Zhdankin, V. V.; Caple, R. *J. Org. Chem.* **1981**, *46*, 5264.
- (185) Fujie, S.; Matsumoto, K.; Suga, S.; Yoshida, J. *Chem. Lett.* **2009**, *38*, 1186.

- (186) Benati, L.; Montevercchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1691.
- (187) Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Morris, M. J.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2012**, 77, 7262.
- (188) For other examples of the rate acceleration of the epoxidation of alkenes by peracids in the presence of strong Brønsted acids, see: (a) Bach, R. D.; Canepa, C.; Winter, J. E.; Blanchette, P. E. *J. Org. Chem.* **1997**, 62, 5191. (b) Shi, H.; Zhang, Z.; Wang, Y. *J. Mol. Catal. A* **2005**, 238, 13.
- (189) For reviews, see: (a) Guk, Yu. V.; Ilyushin, M. A.; Golod, E. L.; Gidaspov, B. V. *Russ. Chem. Rev.* **1983**, 52, 284. (b) Smit, W. A. *Sov. Sci. Rev., Sect. B* **1985**, 7, 155. (c) Srepanov, A. V.; Veselovsky, V. V. *Russ. Chem. Rev.* **2003**, 72, 327.
- (190) (a) Mursakulov, I. G.; Guseinov, M. M.; Smit, W. A.; Talibov, A. G.; Zefirov, N. S. *Zh. Org. Khim.* **1977**, 13, 1121. (b) Talibov, A. G.; Mursakulov, I. G. *Azerb. Khim. Zh.* **1978**, 3, 64. (c) Mursakulov, I. G.; Talibov, A. G.; Guseinov, M. M.; Smit, W. A. *Zh. Org. Khim.* **1979**, 15, 95.
- (191) (a) Mursakulov, I. G.; Talibov, A. G.; Smit, W. A.; Movla-Zade, S. A. *Azerb. Khim. Zh.* **1981**, 5, 31. (b) Talibov, A. G.; Mursakulov, I. G.; Guseinov, M. M.; Smit, W. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 654. For English translation, see: Talibov, A. G.; Mursakulov, I. G.; Guseinov, M. M.; Smit, W. A. *Russ. Chem. Bull., Int. Ed.* **1982**, 31, 581.
- (192) Talibov, A. G.; Mursakulov, I. G.; Guliev, A. M. *Azerb. Khim. Zh.* **1982**, 1, 40.
- (193) Mursakulov, I. G.; Talibov, A. G.; Parokhim, S. A.; Smit, W. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 1101. For English translation, see: Mursakulov, I. G.; Talibov, A. G.; Parokhim, S. A.; Smit, W. A. *Russ. Chem. Bull., Int. Ed.* **1982**, 31, 981.
- (194) For the preparation of 1,3-dioxolan-2-ylidium tetrafluoroborate via the treatment of 2-fluoroethyl acetate with BF_3 , see: Meerwein, H.; Bodenbner, K.; Borner, P.; Kunert, F.; Wunderlich, K. *Liebigs Ann.* **1960**, 632, 38.
- (195) Mursakulov, I. G.; Azimzade, A. A.; Talibov, A. G.; Aslanova, M. R. *Zh. Org. Khim.* **1990**, 26, 909.
- (196) For the reaction of acyl fluorides with BF_3 to give acylium tetrafluoroborates, see: Olah, G. A.; Kuhn, S. J.; Tolgyesi, W. S.; Baker, E. B. *J. Am. Chem. Soc.* **1962**, 84, 2733 and refs cited therein.
- (197) For related examples of the serendipitous alkenylfluorination of alkenes, see refs 49a, b.
- (198) Lyubinskaya, O. V.; Smit, W. A.; Semenovskii, A. V.; Kucherov, V. F. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 1803. For English translation, see: Lyubinskaya, O. V.; Smit, W. A.; Semenovskii, A. V.; Kucherov, V. F. *Russ. Chem. Bull., Int. Ed.* **1976**, 25, 1698.
- (199) Anfilogova, S. N.; Frolov, E. B.; Luzikov, Yu. N.; Balenkova, E. S. *Zh. Org. Khim.* **1979**, 15, 1432.
- (200) Although there is general (but not universal) acceptance that C–H bonds are stronger hyperconjugative donors than C–C bonds, such that *t*-Bu would be expected to be less electron-releasing than Me, there is evidence to suggest that the situation may be reversed when electron-demand is high, see: Rozeboom, M. D.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, 104, 1189.
- (201) Balenkova, E. S.; Frolov, E. B.; Anfilogova, S. N. *Zh. Org. Khim.* **1978**, 14, 1109.
- (202) Frolov, E. B.; Anfilogova, S. N.; Pomitkin, I. A.; Luzikov, Yu. N.; Balenkova, E. S. *Zh. Org. Khim.* **1980**, 16, 1839.
- (203) (a) Vasil'ev, A. A.; Balenkova, E. S.; Levashova, T. V.; Grigor'ev, A. A.; Smirnova, N. V.; Luzikov, Yu. N. *Zh. Org. Khim.* **1981**, 17, 2018. (b) Vasil'ev, A. A.; Balenkova, E. S. *Zh. Org. Khim.* **1983**, 19, 288. (c) Vasil'ev, A. A.; Luzikov, Yu. N.; Balenkova, E. S. *Zh. Org. Khim.* **1984**, 20, 1007. (d) Vasil'ev, A. A.; Balenkova, E. S.; Luzikov, Yu. N.; Popkov, A. Y. *Zh. Org. Khim.* **1984**, 20, 1401.
- (204) (a) Shchegolev, A. A.; Smit, W. A.; Khurshudyan, S. A.; Chertkov, V. A.; Kucherov, V. F. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1977**, 1093. For English translation, see: Shchegolev, A. A.; Smit, W. A.; Khurshudyan, S. A.; Chertkov, V. A.; Kucherov, V. F. *Russ. Chem. Bull., Int. Ed.* **1977**, 26, 1001. (b) Kanishchev, M. I.; Smit, W. A.; Shchegolev, A. A.; Caple, R. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 243. For English translation, see: Kanishchev, M. I.; Smit, W. A.; Shchegolev, A. A.; Caple, R. *Russ. Chem. Bull., Int. Ed.* **1978**, 27, 215. (c) Khurshudyan, S. A.; Shchegolev, A. A.; Smit, W. A.; Kucherov, V. F. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 1077. For English translation, see: Khurshudyan, S. A.; Shchegolev, A. A.; Smit, W. A.; Kucherov, V. F. *Russ. Chem. Bull., Int. Ed.* **1978**, 27, 932. (d) Kanishev, M. I.; Shchegolev, A. A.; Smit, W. A.; Caple, R.; Kelner, M. J. *J. Am. Chem. Soc.* **1979**, 101, 5660.
- (205) (a) Shchegolev, A. A.; Kepl, R.; Smit, W. A.; Kucherov, V. F. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 2382. For English translation, see: Shchegolev, A. A.; Kepl, R.; Smit, W. A.; Kucherov, V. F. *Russ. Chem. Bull., Int. Ed.* **1975**, 24, 2274. (b) Kanishchev, M. I.; Smit, W. A.; Shchegolev, A. A.; Caple, R. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1977**, 2175. For English translation, see: Kanishchev, M. I.; Smit, W. A.; Shchegolev, A. A.; Caple, R. *Russ. Chem. Bull., Int. Ed.* **1977**, 26, 2018. (c) Kanishchev, M. I.; Smit, W. A.; Shchegolev, A. A.; Caple, R. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 511. For English translation, see: Kanishchev, M. I.; Smit, W. A.; Shchegolev, A. A.; Caple, R. *Russ. Chem. Bull., Int. Ed.* **1978**, 27, 447. (d) Kanishchev, M. I.; Smit, W. A.; Shchegolev, A. A.; Rodionov, A. P.; Caple, R. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 835. For English translation, see: Kanishchev, M. I.; Smit, W. A.; Shchegolev, A. A.; Rodionov, A. P.; Caple, R. *Russ. Chem. Bull., Int. Ed.* **1979**, 28, 778.
- (206) For a similar acylation of alkynes involving 1,4- or 1,5-bromine shifts followed by fluoride transfer from the BF_4^- ion to give low yields ($\leq 18\%$) of fluorinated products, see: Khurshudyan, S. A.; Shchegolev, A. A.; Smit, W. A.; Kucherov, V. F.; Rodionov, A. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 1559. For English translation, see: Khurshudyan, S. A.; Shchegolev, A. A.; Smit, W. A.; Kucherov, V. F.; Rodionov, A. P. *Russ. Chem. Bull., Int. Ed.* **1978**, 27, 1361.
- (207) Wilson, R. D.; Maya, W.; Pilipovich, D.; Christe, K. O. *Inorg. Chem.* **1983**, 22, 1355.
- (208) (a) Pearson, A. J.; Alimardanov, A.; Pinkerton, A. A.; Fouchard, D. M.; Kirschbaum, K. *Tetrahedron Lett.* **1998**, 39, 5919. (b) Pearson, A. J.; Alimardanov, A. R.; Kerber, W. D. *J. Organomet. Chem.* **2001**, 630, 23.
- (209) Franck-Neumann, M.; Geoffroy, P.; Hanss, D. *Tetrahedron Lett.* **1999**, 40, 8487.
- (210) (a) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, 52, 2769. (b) Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2004**, 45, 2555.
- (211) Mann, A.; Muller, C.; Tyrrell, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1427.
- (212) The biological activity of fluorinated benzopyrans as novel potential potassium channel activators has also been described, see: Tyrell, E.; Tesfa, K. H.; Greenwood, I.; Mann, A. *Bioorg. Med. Chem. Lett.* **2008**, 18, 1237.
- (213) Olier, C.; Gastaldi, S.; Christie, S. D. R.; Bertrand, M. P. *Synlett* **2007**, 423.
- (214) Patel, M. M.; Green, J. R. *Chem. Commun.* **1999**, 509.
- (215) Lu, Y.; Green, J. R. *Synlett* **2001**, 243.
- (216) (a) Wölfing, J.; Frank, É.; Schneider, G.; Tietze, L. F. *Synlett* **1998**, 1205. (b) Wölfing, J.; Frank, É.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **1999**, 3013.
- (217) Wölfing, J.; Frank, E.; Mernyák, E.; Bunkóczki, G.; Seijo, J. A. C.; Schneider, G. *Tetrahedron* **2002**, 58, 6851.
- (218) Other isolated examples of the cyclization of alkenes onto azacarbenium ions to furnish amino-substituted fluorinated carbocycles have also been reported, see: (a) Melnick, M. J.; Freyer, A. J.; Weinreb, S. M. *Tetrahedron Lett.* **1988**, 29, 3891. (b) Johnson, A. P.; Luke, R. W. A.; Boa, A. N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 895. (c) Heaney, H.; Taha, M. O. *Tetrahedron Lett.* **1998**, 39, 3341.
- (219) Cambie, R. C.; Higgs, K. C.; Rustenhoven, J. J.; Rutledge, P. S. *Aust. J. Chem.* **1996**, 49, 751.
- (220) Several other isolated examples of the $\text{BF}_3\text{-OEt}_2$ -promoted cation–π cyclization of alkenes to generate fluorinated carbocycles have also been reported, see: (a) Doyle, M. P.; Trudell, M. L. *J. Org. Chem.* **1984**, 49, 1196. (b) Veselovsky, V. V.; Dragan, V. A;

- Moiseenkov, A. M. *Tetrahedron Lett.* **1990**, *31*, 1187. (c) Petrov, V. A.; Davidson, F.; Smart, B. E. *J. Fluorine Chem.* **2004**, *125*, 1543.
(221) Balf, R. J.; Rao, B.; Weiler, L. *Can. J. Chem.* **1971**, *49*, 3135.
(222) Smith, A. B., III; Dieter, R. K. *J. Am. Chem. Soc.* **1981**, *103*, 2017.
(223) Yeh, M.-C. P.; Liang, C.-J.; Huang, T.-L.; Hsu, H.-J.; Tsau, Y.-S. *J. Org. Chem.* **2013**, *78*, 5521.
(224) For a review of the Prins cyclization reaction, see: Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413.
(225) Although not within the remit of this Review, a method for conducting oxa-, thia-, and aza-Prins cyclizations-fluorinations has been reported by Fugichami and co-workers using ionic liquid HF salts (e.g., Et₄NF-SHF) as the reaction medium, acidic promoter, and fluoride source, see: Kishi, Y.; Inagi, S.; Fuchigami, T. *Eur. J. Org. Chem.* **2009**, *103*.
(226) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679.
(227) (a) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7115. (b) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679. (c) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D.; Simpson, T. J.; Smith, R. W.; Willis, C. L. *Chem. Commun.* **2001**, 835.
(228) Yoshida, J.; Ishichi, Y.; Isoe, S. *J. Am. Chem. Soc.* **1992**, *114*, 7594.
(229) (a) Yoshida, J.; Sugawara, M.; Kise, N. *Tetrahedron Lett.* **1996**, *37*, 3157. (b) Yoshida, J.; Sugawara, M.; Tatsumi, M.; Kise, N. *J. Org. Chem.* **1998**, *63*, 5950.
(230) (a) Yadav, V. K.; Vijaykumar, N. *J. Am. Chem. Soc.* **2004**, *126*, 8652. (b) Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005**, 3727. (c) Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. *Tetrahedron* **2006**, *62*, 2471. (d) Kumar, H. M. S.; Qazi, N. A.; Shafi, S.; Kumar, V. N.; Krishna, A. D.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 7205. (e) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177.
(231) Launay, G. G.; Slawin, A. M. Z.; O'Hagan, D. *Beilstein J. Org. Chem.* **2010**, *6*, 41.
(232) Yadav, J. S.; Subba Reddy, B. V.; Anusha, B.; Subba Reddy, U. V.; Bhadra Reddy, V. V. *Tetrahedron Lett.* **2010**, *51*, 2872.
(233) Olier, C.; Gastaldi, S.; Gil, G.; Bertrand, M. P. *Tetrahedron Lett.* **2007**, *48*, 7801.
(234) Luo, H.-Q.; Hu, X.-H.; Loh, T.-P. *Tetrahedron Lett.* **2010**, *51*, 1041.
(235) Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768.
(236) (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941. (b) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295.
(237) Faller, J. W.; Linebarrier, D. L. *Organometallics* **1990**, *9*, 3182.
(238) Yadav, J. S.; Subba Reddy, B. V.; Ramesh, K.; Narayana Kumar, G. G. K. S.; Grée, R. *Tetrahedron Lett.* **2010**, *51*, 1578.