Review

The Chemistry of Propargylic and Allylic Fluorides

M. Carmen Pacheco, Sophie Purser, and Ve#ronique Gouverneur

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The Chemistry of Propargylic and Allylic Fluorides

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Contents

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1. Introduction

The presence of fluorine is very often highly advantageous in pharmaceutical and agrochemical compounds as well as in performance materials. In response to a growing demand for complex fluorinated molecules, chemists are continuously seeking ingenious methods for their preparation. Molecular fluorine and inorganic fluoride sources are reagents available for fluorination and are used for the synthesis of large quantities of "primary" fluorinated building blocks. The development of various nucleophilic and electrophilic fluorinating reagents of tuned reactivity has allowed for the production of a larger portfolio of fluorinated building blocks used for further functional group manipulation and for the fluorination to be programmed as a key step in the synthetic sequence of complex fluorinated targets. Chiral, nonracemic fine chemicals featuring a fluorinated stereogenic center are more often prepared, relying on a key C−F bond-forming process, as very few chiral fluorinated building blocks are commercially available to date. Two building blocks that may feature a fluorinated stereogenic center are propargylic and allylic monofluorides. The importance of these compounds in racemic or enantioenriched form as key functional groups cannot be underestimated and is possibly best compared with the long-established value of the corresponding propargylic and allylic alcohols in natural and non-natural product synthesis. Propargylic and allylic fluorides are structural motifs found in important life science compounds such as insecticides, herbicides, and fungicides or fluorinated Vitamin D and prostanoid analogues. In addition, they are potentially amenable to countless functional manipulations (Chart 1).

In the context of asymmetric synthesis, these compounds could serve as valuable mechanistic probes to assess the stereodirecting effect of allylic polar functional groups. This is because an allylic fluorine substituent can be responsible for strong stereoelectronic effects but is sterically undemanding and reluctant to act as a hydrogen-bond acceptor. These properties were used to probe the origin of stereocontrol for the Rh complex catalyzed hydrogenation of α-hydroxyalkyl-*N*-methoxyacrylamide upon comparison with the Ru complex catalyzed hydrogenation of an α-(fluoroalkyl)acrylate.[1] Propargylic and allylic fluorides have attracted the attention of physical organic chemists interested in using both experimental and theoretical methods to determine their preferential conformation in the gas phase. The conformational behavior of 3-fluoro-2-methylpropene has been investigated through MP2 and/or B3LYP levels of theory.[2,3] 3-Fluoro-2-methylpropene occurs as a mixture of the s-cis and gauche rotamers

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After graduating with honors in Chemistry at the University of Alicante, Mª Carmen Pacheco carried out her Ph.D. in the development of oxime-derived palladacycles and the study of their reactivity, under the supervision of Professor Carmen Nájera and Dr. Diego Alonso. In November 2003 she joined the group of Dr. Véronique Gouverneur at the University of Oxford, where she worked as a postdoctoral fellow for three years in the field of electrophilic fluorodesilylation of various organosilanes. Afterward she returned to work with Professor Carmen Nájera, where she has since been working as a Juan de la Cierva fellow.

Sophie Purser graduated with an MChem (honors) degree from Jesus College Oxford in 2004, completing her Part II research project with Dr. John M. Brown, FRS. She is currently carrying out her D.Phil at the University of Oxford under the supervision of Dr. Véronique Gouverneur, where her research is focused on the synthesis of enantioenriched allylic fluorides and their application in the synthesis of fluorinated carbohydrate analogues.

in nearly equal proportions. B3LYP/6-31G(d,p) calculations indicate that the s-cis rotamer, with the allylic fluorine eclipsing the alkene, is more stable than the gauche form (allylic hydrogen eclipsing the alkene) by an energy difference of only 0.3 kcal mol^{-1} (Chart 2). These findings are in agreement with experimental data for methallyl fluoride in the vapor phase. 3-Hydroxy-2-methylpropene displayed a similar conformational behavior. In contrast, if the 3-position is occupied by a Cl, Br, I, OMe, or OEt moiety, the gauche form is the most stable. For 3-fluoropropene, both experimental and theoretical data revealed that the s-cis conformer is the most stable.

Ab initio, MM3, microwave, and NMR structural studies were also performed on propargyl fluoride. The $C_{sp}-C_{sp^3}-F$ angle was found to be 110.8°.[4] These data corroborate microwave studies carried out by Wiedenmann et al.[5] The characteristic experimental vibrational frequencies for propargylic fluorides are found at 2148 cm^{-1} (C≡C stretching) and at 1040 cm^{-1} (C−F stretching). Propargylic fluorides typically have ^{19}F NMR spectra with δ_F −170 ppm, and ^1H NMR spectra with δ_H(C*H*F) 5.10 ppm and $^2J_{H-F} = 48.8$ Hz. Characteristic NMR data for allylic fluorides are found to be for ^{19}F NMR δ_F −185 ppm, with ^1H NMR spectra having δ_H(C*H*F) 5.06 ppm and $^2J_{H-F} = 47$ Hz. In view of the value of both propargylic and allylic mono fluorides, we have undertaken to review the known synthetic routes to these compounds and their reactivity, up to January 2008. An overview on the synthesis of these functional groups is provided in ref 6.

Véronique Gouverneur received her undergraduate degree in chemistry at the Université Catholique de Louvain (Belgium), where she worked with Professor L. Ghosez. She stayed in the group of Professor L. Ghosez for her doctoral studies. In 1992, she moved to a postdoctoral position with Professor R. Lerner at the Scripps Research Institute (USA). She returned to Europe in 1994, where she accepted a position of Maître de Conférence at the University Louis Pasteur in Strasbourg (France). She worked with Dr. Charles Mioskowski during this period. She started her independent research career as a member of the chemistry faculty at the University of Oxford in 1998, where her group's research interests are centered on fluorine chemistry. Since her appointment in Oxford, she also holds a tutorial fellowship at Merton College Oxford, where she teaches organic and biological chemistry. To date, she has published 80 papers, patents, and book chapters. Véronique's research has recently been recognized by the AstraZeneca Award for organic chemistry 2005. In 2007, she joined the Editorial Board of *Organic & Biomolecular Chemistry*.

2. Propargylic Fluorides

2.1. Synthesis

The most commonly used methods for the preparation of propargyl monofluorides involve the use of nucleophilic sources of fluorine. Electrophilic sources of fluorine have been used far less frequently, however this strategy shows potential for the expansion of the availability of propargyl monofluorides.

2.1.1. Nucleophilic Fluorination

2.1.1.1. Dehydroxyfluorination. *2.1.1.1.1. Diethylaminosulfur Trifluoride (DAST).* DAST is by far the most commonly used reagent for the dehydroxyfluorination of propargylic alcohols. The reaction was first performed by Middleton in 1975, whereby the propargylic alcohol **5** was converted to the corresponding propargylic fluoride by treatment with DAST at low temperature (Scheme 1).[7]

The generally accepted mechanism for dehydroxyfluorination consists of two steps. Initial nucleophilic attack of the propargylic hydroxyl at sulfur forms intermediate **9**, where the hydroxyl is activated as a leaving group. The fluoride ion, which has been released, can then displace this group by either an S_N2 or S_N1 pathway. The mechanistic

Chart 1. Selected Propargylic and Allylic Fluorides of Importance in Life Sciences

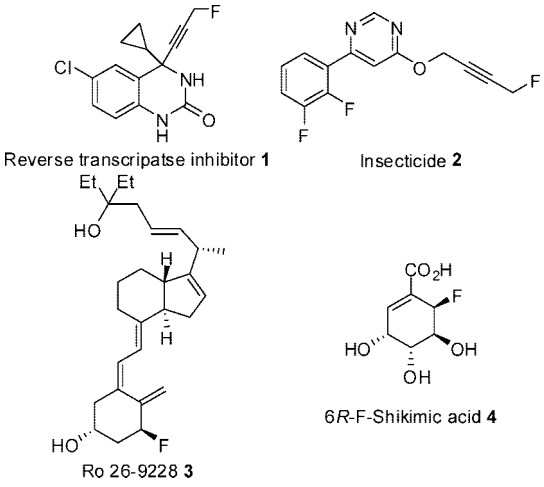
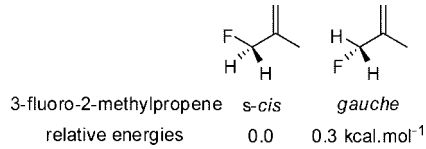
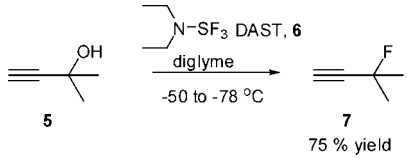


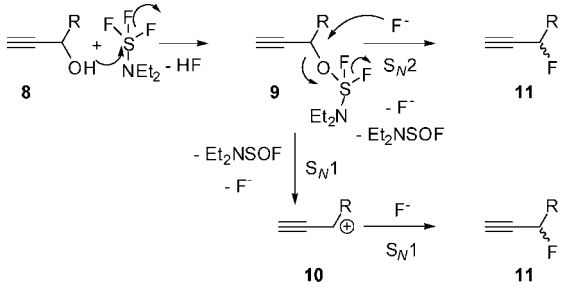
Chart 2. Rotamers of 3-Fluoro-2-methylpropene



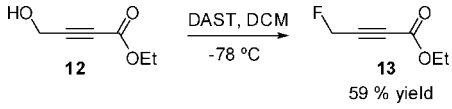
Scheme 1. DAST-Mediated Fluorination Reported by Middleton



Scheme 2. Mechanism of Dehydroxyfluorination using DAST



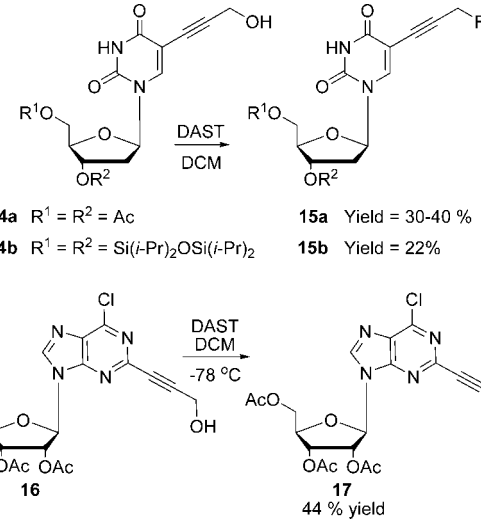
Scheme 3. DAST-Mediated Fluorination Reported by Poulter and Co-Workers



course of the second substitution step is strongly dependent upon the reaction conditions. Side reactions can occasionally occur: for example, carbonium type rearrangements or dehydration of the alcohol (Scheme 2).[7] Poulter and co-workers utilized this methodology toward the synthesis of fluorinated geraniol. The propargyl alcohol **12** was transformed into propargylic fluoride **13** upon treatment with DAST at low temperature (Scheme 3).[8]

The substitution of the propargylic hydroxyl group by fluorine is a key step for the synthesis of fluorinated nucleoside analogues bearing the fluorine substituent on the

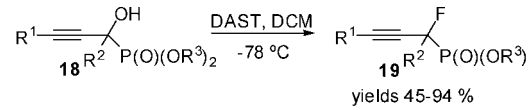
Scheme 4. Preparation of Fluorinated Nucleoside Analogues



14a $R^1 = R^2 = Ac$ **15a** Yield = 30-40 %

14b $R^1 = R^2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$ **15b** Yield = 22%

Scheme 5. Preparation of (α-Fluoropropargyl)phosphonate Esters Reported by Hammond and Co-Workers



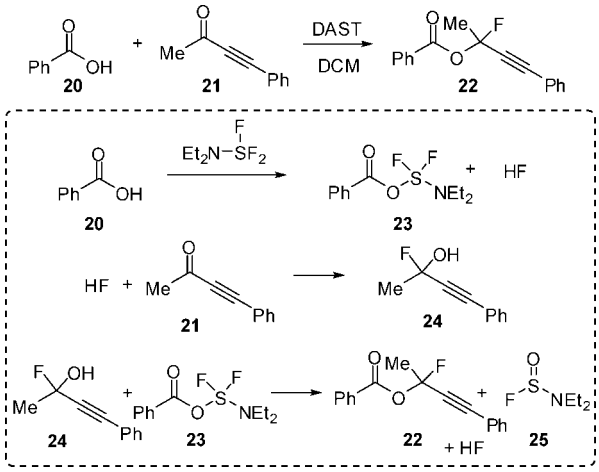
a R^1 = Me, R^2 = H, R^3 = Et
b $R^1 = SiMe_3$, R^2 = H, R^3 = Et
c $R^1 = Si^iPr_3$, R^2 = H, R^3 = Et
d $R^1 = SiMe_2{}^t\text{Bu}$, R^2 = H, R^3 = Et
e R^1 = Ph, R^2 = H, R^3 = Et
f R^1 = Me, R^2 = Et, R^3 = Et
g R^1 = Et, R^2 = Me, R^3 = Et
h R^1 = Ph, R^2 = Me, R^3 = Et
i $R^1 = n\text{-}C_5H_{11}$, R^2 = H, R^3 = Et
j R^1 = Ph, R^2 = H, R^3 = Bu
k R^1 = Ph, R^2 = H, $R^3 = CH_2CH(Et)C_4H_9$
l $R^1 = n\text{-}C_5H_{11}$, R^2 = H, $R^3 = CH_2CH(Et)C_4H_9$

nitrogen-containing base. Kalman and co-workers prepared the propargylic monofluorides **15** as intermediates in the synthesis of a series of 5-fluoropropynyldeoxyuridylates,[9,10] which are compounds displaying anticancer activity. The fluorination was found to be sensitive to the nature of the protecting group. Nair et al. prepared fluorinated purine nucleoside analogues featuring propargylic fluorides using similar chemistry. These compounds may be potential antiviral agents (Scheme 4).[11]

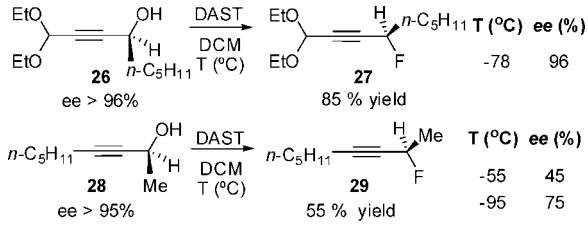
(α-Fluoropropargyl)phosphonate esters **19**, with the fluorine on a stereogenic center, were synthesized by Hammond and co-workers by substitution of α-hydroxyphosphonates.[12–15] The use of DAST in DCM at low temperature led to the corresponding fluorophosphonates **19** with moderate to high yields. When tertiary alcohols **18f**,**g** were used, the yield of the reaction decreased due to the formation of phosphonate enynes resulting from a competitive elimination process (Scheme 5).

Rye et al. synthesized the nonterminal racemic propargylic fluoride **22** as part of an investigation into its suitability as a synthetic substrate for esterases and lipases. The compound was synthesized in moderate to good yield by reacting the appropriate acid and ketone (or aldehyde) with DAST. On the basis of the observation that no reaction took place between benzoyl fluoride and acetone (with or without DAST) or between 1,1-difluorocyclohexane and benzoic acid, the authors postulated a mechanism occurring via intermediate **23**. This intermediate, formed upon initial attack of the carboxylic acid with DAST, may subsequently react with the α-fluoro alcohol **24**, generated by reaction of the ketone with HF (Scheme 6).[16]

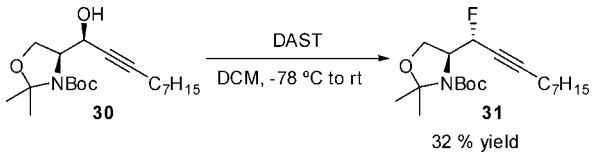
Scheme 6. Postulated Mechanism for the Synthesis of Fluorinated Benzoates Starting From Acids and Ketones, Reported by Rye and Co-Workers



Scheme 7. Preparation of Non-Terminal Enantioenriched Propargylic Fluorides Reported by Grée and Co-Workers



Scheme 8. Fluorination of an Enantiopure Propargylic Alcohol using DAST Reported by Herdewijn and Co-Workers

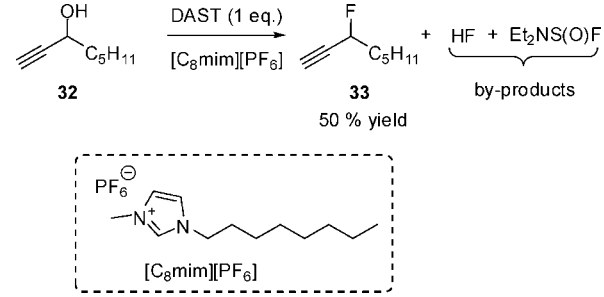


Grée and co-workers synthesized nonterminal enantioenriched propargylic alcohols to probe the stereochemical outcome of these fluorinations. Low-temperature fluorinations of propargylic alcohols **26** and **28** yielded propargylic fluorides **27** and **29** in good yields. For compound **26**, no loss in ee was observed when the fluorination was conducted at −78 °C. The stereochemical integrity of **28** was found to be dependent on temperature. At −55 °C the ee fell from 95% to 45%. The propargylic fluoride was formed with a 75% ee when the reaction was conducted at −95 °C. This suggests that, at higher temperatures, the S_N2 process is not the sole pathway in operation (Scheme 7).[17,18]

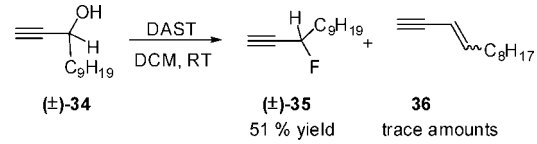
In an attempt to synthesize a fluorinated analogue of the signaling lipid sphinganine, Herdewijn et al. performed a direct fluorination of the enantiopure propargylic alcohol **30**, to furnish the desired propargylic fluoride **31** in 32% yield. Subsequent catalytic hydrogenation did not yield the desired saturated compound; hence, the intermediate **31** was not used in the final synthesis (Scheme 8).[19]

Chandrasekhar and Grée used ionic liquids as recyclable solvents for DAST-mediated dehydroxyfluorinations. The pure propargylic fluoride could be distilled from the high-boiling ionic liquid or extracted with pentane, allowing for the ionic liquid to be recycled after drying under vacuum (Scheme 9).[20]

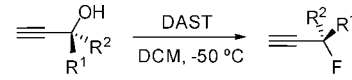
Scheme 9. Ionic Liquids as Recyclable Solvents for DAST-Mediated Dehydroxyfluorinations Reported by Grée and Co-Workers



Scheme 10. Dehydroxyfluorination of a Terminal Alkyne Reported by Grée and Co-Workers



Scheme 11. Enantioenriched Terminal Propargylic Fluorides Reported by Grée and Co-Workers



(+)-34 R^1 = H, R^2 = n-C_9H_{19} *ee* = 90 % **(-)-35** *ee* = 88 %, 51 % yield
(-)-37 R^1 = $(CH_2)_4OTBDMS$, R^2 = H *ee* > 98 % **(+)-38** *ee* > 95 %, 59 % yield

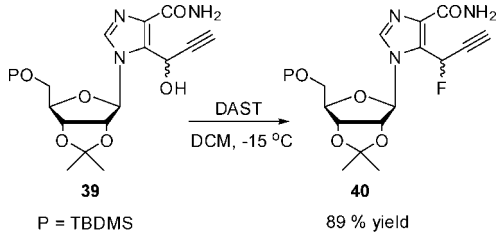
Grée and co-workers investigated the stereoselectivity of dehydroxyfluorination reactions of terminal alkynes using DAST.[17,18,21–25] Initial studies aimed at establishing the feasibility of the fluorination process were conducted using the racemic terminal alkyne **34**, which upon treatment with DAST at room temperature afforded the propargylic fluoride **35** in 51% yield. In addition to the desired fluorinated product, a trace amount of the corresponding enyne was also detected (Scheme 10).[21]

The authors prepared a series of enantioenriched alcohols by asymmetric reduction of the corresponding alkynones, affording compounds (+)-**34** and (−)-**37** with an enantiomeric excess (ee) of 90%[23] and >98%,[24] respectively. At low temperature (−50 °C) the dehydroxyfluorination reactions proceeded with no significant erosion of ee. It is notoriously difficult to measure the enantiomeric excess of propargylic fluorides; Grée and co-workers used an NMR technique based on chiral liquid crystals. The technique resolves the two enantiomers in the ^{13}C spectra when the NMR spectra are recorded in the PBLG liquid crystal.[23,24] Although it was not unambiguously demonstrated, the authors suggested that the reaction proceeded with inversion of configuration (Scheme 11).

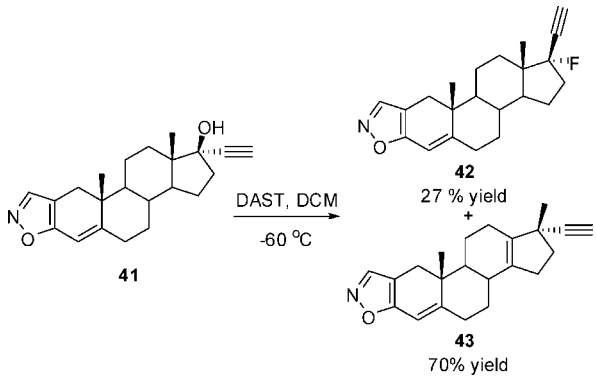
Matsuda et al. reported the synthesis of the propargylic fluoride **40**, a key intermediate in the synthesis of 3-fluoropurine ribonucleosides. Regardless of whether the starting alcohol **39** was used as a single diastereomer or as a 1:1 diastereomeric mixture, upon treatment with DAST in CH_2Cl_2 at −15 °C, compound **40** was isolated as an approximately 3:2 mixture of diastereomers. To account for these results, the authors proposed that the reaction proceeds via a cationic intermediate (Scheme 12).[26]

Kumar and co-workers synthesized a series of C-17 fluorinated derivatives of Danazol **41**, a gonadotropin inhibi-

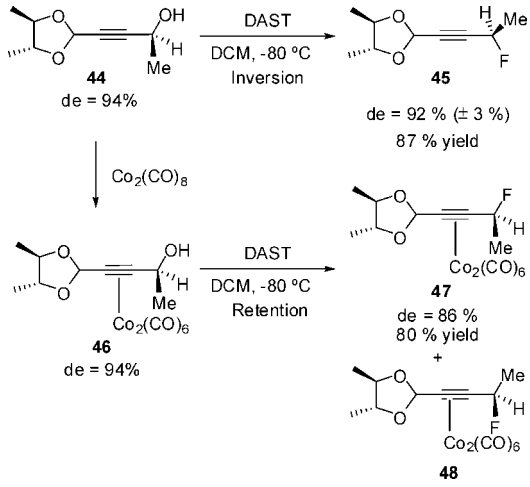
Scheme 12. Fluorinated Ribonucleosides Reported by Matsuda and Co-Workers



Scheme 13. Fluorinated Danazol Derivatives Reported by Kumar and Co-Workers



Scheme 14. Dehydroxyfluorination of Co Complexes Reported by Grée and Co-Workers

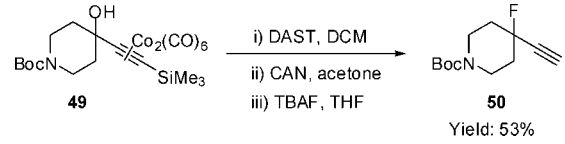


tor used for the treatment of endometriosis. The reaction of Danazol and three of its derivatives with DAST furnished the desired propargylic fluorides in low yields. The major product was derived from a competing Wagner−Meerwein type rearrangement of the carbocationic intermediate (Scheme 13).[27]

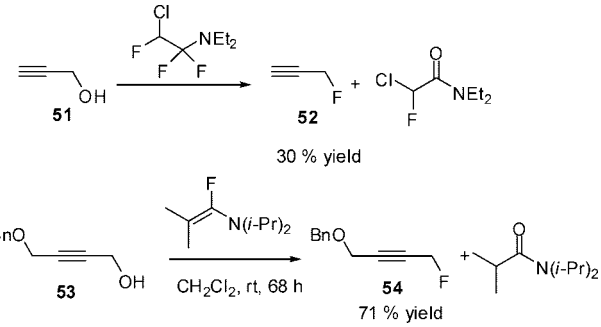
Grée and co-workers performed a selective dehydroxyfluorination reaction with retention of configuration, using a cobalt carbonyl complex of the triple bond. Using DAST, the substitution reaction of the uncomplexed propargylic alcohol **44** proceeded with inversion of configuration, with the diastereomeric ratio of the fluorinated product mirroring that of the starting material. When the corresponding cobalt carbonyl complex was used, the major stereoisomer was the fluorinated product **47**, resulting from retention of configuration (Scheme 14).[25]

Van Niel et al. synthesized a series of fluorinated piperazines and piperidines in order to investigate their potency as human 5-HT_{1D} receptor ligands. For this study they

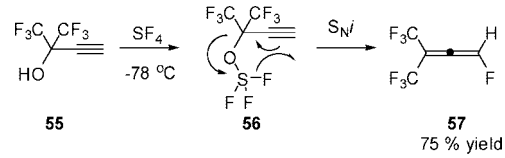
Scheme 15. Fluorinated Piperidines by Dehydroxyfluorination of Co-Complexes Reported by Van Niel and Co-Workers



Scheme 16. Dehydroxyfluorination using Yarovenko's Reagent



Scheme 17. Postulated Mechanism of Allene Formation Reported by Dear and Gilbert



performed a dehydroxyfluorination of the cobalt protected propargyl alcohol **49**. Deprotection of the triple bond using ceric(IV) ammonium nitrate (CAN) and tetrabutylammonium fluoride (TBAF) gave the propargylic fluoride **50** in an overall 53% yield (Scheme 15).[28]

2.1.1.1.2. Other Reagents. There are only limited examples of dehydroxyfluorination using a nucleophilic source of fluorine other than DAST. The Yarovenko reagent was found to be suitable for the fluorination of 2-propyn-1-ol (**51**) furnishing the propargylic fluoride **52** in 30% yield (Scheme 16).[3] Tietze et al. reported the fluorination of the propargylic alcohol **53** with *N*,*N*-diisopropyl-1-fluoro-2-methylpropenamine, a reaction proceeding in 71% yield (Scheme 16).[29]

The difference in product outcome upon fluorination with SF_4 of propargylic alcohols and their perfluorinated counterparts featuring two CF_3 groups on the hydroxylated propargylic carbon is of interest. The CF_3-substituted substrates were found to react with sulfur trifluoride to form fluorinated allenes, with no trace of the corresponding propargylic fluoride. Dear and Gilbert postulated that the mechanism of allene formation involves an initial reaction between the hydroxy group and SF_4 with concomitant loss of HF, followed by an intramolecular S_Ni rearrangement. The authors suggested that the two trifluoromethyl groups withdraw electron density from the triple bond, hence making it more susceptible to nucleophilic attack (Scheme 17).[30]

2.1.1.2. Fluorination of a Silyl Ether Group

The nucleophilic fluorination of a propargylic (trimethylsilyl)oxy group is an alternative to dehydroxyfluorination, the advantage being the formation of trimethylsilyl fluoride as a side product rather than hydrogen fluoride.

The use of sulfur tetrafluoride to perform this transformation was described by Kornilov and co-workers, furnishing

Scheme 18. Propargylic Fluorides using SF_4 Reported by Kornilov and Co-Workers

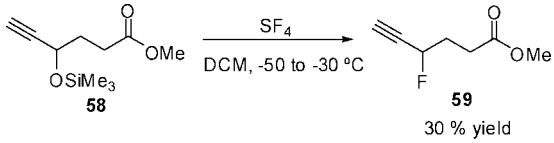
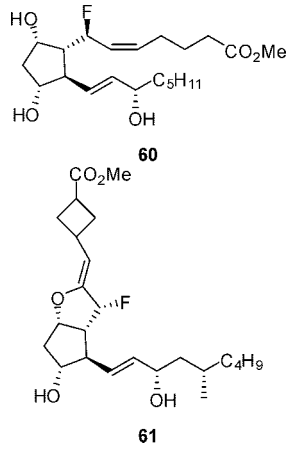
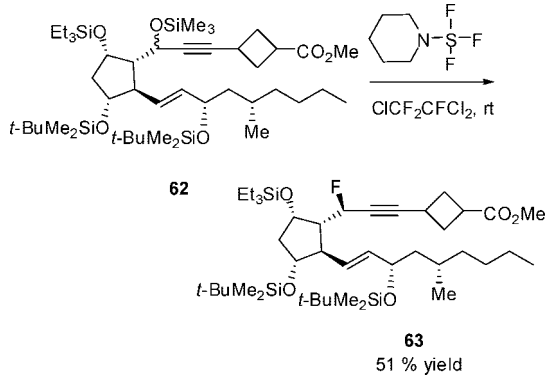


Chart 3. Fluorinated Prostacyclin Analogues



Scheme 19. Fluorinated Prostacyclin Analogues using Piperidinosulfur Trifluoride Reported by Matsumura



the propargylic fluoride **59** in 30% yield. The fluorinating reagent SF_4 is a gas requiring specialist apparatus for handling (Scheme 18).[13,31]

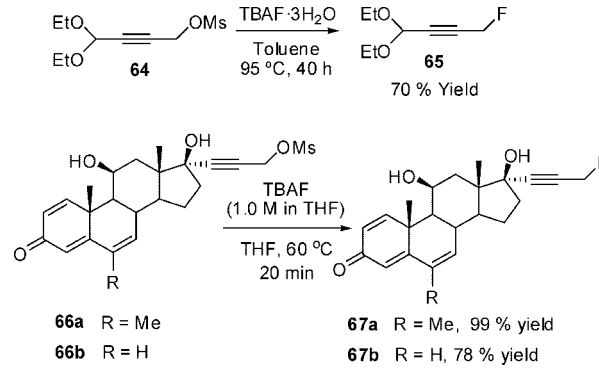
Matsumura and co-workers showed that piperidinosulfur trifluoride was a suitable reagent for the stereocontrolled fluorination of propargylic trimethylsilyl ethers.[32–35] They prepared various fluorinated alkynes that were subsequently used as intermediates in the synthesis of the antianginal fluorinated prostacyclin analogues **60** and **61** (Chart 3).

Initial attempts to fluorinate the unprotected propargylic alcohol resulted mainly in dehydration. Optimization studies using a model substrate showed that fluorination of the corresponding trimethylsilyl ether **62** with piperidinosulfur trifluoride gave the best yields. The fluorination of 7-(*S*)-**62** or 7-(*R*)-**62** led to the same product 7-(*R*)-**63**, indicating that the reaction proceeds via a common carbocationic intermediate, with the fluoride nucleophile approaching preferentially anti with respect to the bulky triethylsiloxy group (Scheme 19).[32–35]

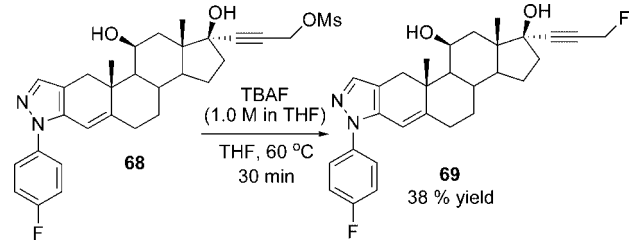
2.1.1.3. Fluorination of Activated Alcohols

The activation of hydroxyl groups is necessary when the fluorination is performed with fluoride sources other than DAST. To date, only few propargylic fluorides have been prepared using this method, an early example being the fluorination of a propargylic tosylate using potassium fluoride.[36]

Scheme 20. Fluorination of Propargylic Mesylates using TBAF



Scheme 21. Synthesis of a Fluoroarylpyrazolo Steroid using TBAF



Tetrabutylammonium fluoride (TBAF) has been used as an alternative fluoride source: for example, in the synthesis of the propargylic fluoride **65** from the corresponding mesylate derivative.[37] Katzenellenbogen[38] and Crouzel[39] studied the potential of fluorine-substituted corticosteroids **67** as selective ligands for type II corticosteroid receptors in the hippocampus. In this study, the substitution reactions of the propargylic mesylates **66a**,**b**, using TBAF, furnished the propargylic fluorides **67a**,**b** in excellent yields (Scheme 20).[38] Compound **67a** was also prepared successfully by Crouzel et al. from the corresponding bromide.[39]

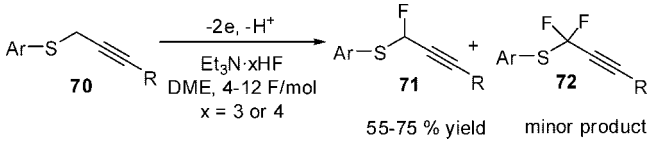
The fluoroarylpyrazolo steroid **69** was synthesized as a novel ligand for glucocorticoid receptors and prepared by treatment of the mesylate **68** with TBAF. For positron emission tomography (PET) studies, the corresponding ^{18}F-labeled compound was also successfully prepared using [^{18}F]KF, albeit with a low radiochemical yield of 9% (Scheme 21).[40]

2.1.1.4. Electrochemical Methods

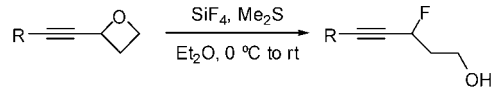
A major limitation with electrochemical methods for the preparation of monofluorinated compounds is the propensity for overfluorination under the reaction conditions.[41] The electrochemical synthesis of propargylic fluorides has been performed using aryl propargyl sulfides as starting materials.

The anodic fluorination of aryl propargyl sulfides **70** proceeded with a range of both aromatic and heteroaromatic aryl substituents to give the α-monofluorinated compounds **71** in moderate to good yields.[42–44] Fluorination occurred chemoselectively α to the sulfur, except when the 4-phenylthiazolyl substrate was used. In this case, fluorination occurred exclusively on the aromatic ring. In most cases, the α,α-difluorinated compounds were also detected[45] (Scheme 22).

Scheme 22. Electrochemical Synthesis of Fluorinated Propargylic Sulfides Reported by Riyadh and Co-Workers

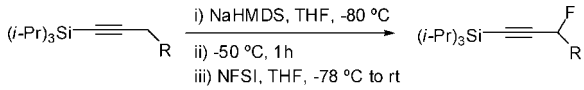


Scheme 23. Ring Opening of Oxetanes using SiF_4 Reported by Shimizu and Co-Workers

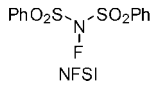


73a R = Ph **74a** 52% yield
73b R = n-C_6H_{13} **74b** 65% yield

Scheme 24. Electrophilic Fluorination of Alkynes using NFSI Reported by Hammond and Co-Workers



75a R = $P(O)(OEt)_2$ **19c** R = $P(O)(OEt)_2$ 63% yield
75b R = TIPS **76** R = TIPS 50% yield



2.1.1.5. Ring Opening of Oxetanes

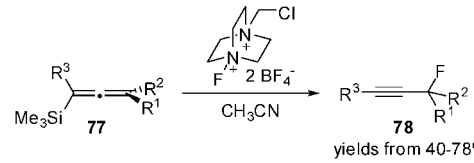
Upon ring opening of oxetanes with silicon tetrafluoride, two regioselective fluorinations were performed, leading to hydroxylated propargylic fluorides.[46] Alkynyloxetanes **73** underwent fluorination in the presence of SiF_4, affording the γ-fluoroalkynols **74** in 52% and 65% yields, respectively, with the fluorine substituent positioned exclusively at the most substituted carbon (Scheme 23).

2.1.2. Electrophilic Fluorination

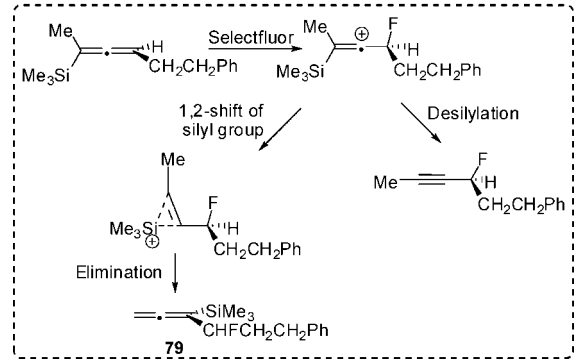
The use of an electrophilic source of fluorine for the synthesis of propargylic fluorides is rare, with only two methods known to date. Hammond et al. described the preparation of propargylic fluorides **19c** and **76** by deprotonation of **75a**,**b** and quenching of the resulting anion with *N*-fluorobenzenesulfonimide (NFSI). This electrophilic route to compound **19c** proved to be more efficient than the corresponding dehydroxyfluorination (Scheme 24).[14,15]

More recently, Gouverneur et al. reported the use of allenylsilanes as precursors for the synthesis of both terminal and nonterminal secondary propargyl fluorides. Treatment of allenylsilanes with the electrophilic fluorinating reagent Selectfluor furnished the desired propargylic fluorides in moderate to good yields. Propargylic fluorides bearing a quaternary fluorinated center could not be isolated, due to their propensity to eliminate HF under the reaction conditions. The authors propose that the C−Si bond oriented cis coplanar with the allylic π-bond conferred stability to the transition state resulting from C−F bond formation. This event leads to a stabilized vinyl cation, which can undergo desilylation to afford the corresponding propargylic fluoride. Small amounts of the side product **79** were observed in some cases, which was rationalized by a 1,2-silyl shift of the silyl group, thereby testifying to the existence of a cationic intermediate (Scheme 25).[47]

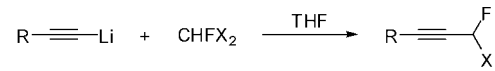
Scheme 25. Electrophilic Fluorodesilylation of Silylated Allenes Reported by Gouverneur and Co-Workers



R^1 = $PhCH_2CH_2$, C_6H_{11}, $(CH_2)_5OTBDMS$, $(CH_2)_8CH{=}CH_2$, H
R^2 = H or $R^1 = R^2 = -(CH_2)_5$
R^3 = Me, Bu, *t*-Bu, Bn, H

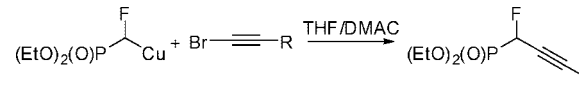


Scheme 26. Synthesis of Propargylic Fluorides from Fluorodihalomethane



80 X = Cl R = n-C_5H_{11}, n-C_6H_{13}, TMS, $THPOCH_2$, $THPOCH(CH_3)$, Ph, $TBSO(CH_2)_3CH(OTHP)$, $THPO(CH_2)_3CH(OTBS)$, TIPS **82** 30-70% yield
81 X = Br R = $THPOCH_2$, TIPS **83** 32-64% yield

Scheme 27. Synthesis of Propargylic Fluorophosphonates from Fluorinated Cuprates Reported by Burton and Co-Workers



84a R = Ph **19e** 74% yield
84b R = n-C_6H_{13} **85b** 71% yield

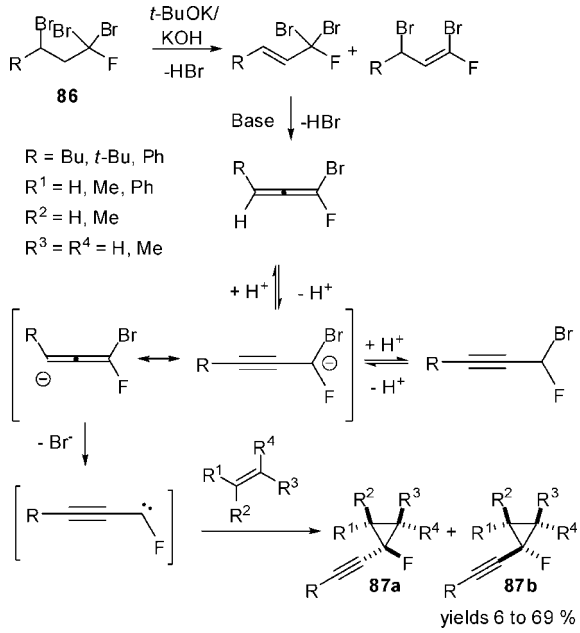
2.1.3. Fluorinated Building Blocks

The most common fluorine-containing building blocks for the synthesis of propargylic fluorides are fluorodihalomethanes. Fluoro halo compounds **82** and **83** were prepared by alkylation of terminal alkynes with fluorodihalomethane (Scheme 26).[48−51] Upon deprotonation with *n*-butyllithium, the acetylides **80** and **81** reacted with dichlorofluoro- or dibromofluoromethane at low temperature to give the desired propargylic fluorides **82** and **83** (Scheme 26).

Burton and co-workers utilized a fluorine-containing building block approach for the synthesis of propargylic fluorophosphonates, using a cross-coupling reaction with an organocuprate derived from α-fluorophosphonate alkynyl bromides **84** (Scheme 27).[52]

Unusual alkynyl fluorocyclopropanes are accessible from 1,1,3-tribromo-1-fluoroalkane derivatives **86**. Upon treatment with a strong base (KOH or *t*-BuOK), these building blocks generated the corresponding alkyne-substituted fluorocarbenes by sequential elimination of three molecules of HBr. These carbenes were trapped in situ with different alkenes,

Scheme 28. Synthesis and Proposed Mechanism of Alkynylfluorocyclopropanes Reported by Shavrin



giving alkynylfluorocyclopropanes **87** in poor to good yields. When unsymmetrical alkenes were used, the cyclopropanes were obtained as a mixture of diastereomers (Scheme 28).[53–55]

2.2. Reactivity

2.2.1. Hydrogenation

Partial hydrogenation of propargylic fluorides is one of the most convenient methodologies for the preparation of (*Z*)-allylic fluorides. Hammond and co-workers found that the semihydrogenation of (α-fluoropropargyl)phosphonate esters, leading to the corresponding (*Z*)-allylic fluorides, was substrate specific. Partial hydrogenation of secondary propargyl fluoride **88** in the presence of Lindlar's catalyst supported on alumina yielded the desired fluorinated compound **89** in 89% yield. However, this methodology could not be extended to other substrates, and an alternative quinoline-poisoned $Pd/BaSO_4$ catalyst was utilized. Under these conditions, aromatic and nonaromatic (α-fluoropropargyl)phosphonate esters were partially reduced in excellent yields. The authors noted that increasing substitution at the propargylic center increased reaction times from several hours to 2 days. Substitution of the terminal position of the triple bond with a TMS group prevented hydrogenation (Scheme 29).[12,56]

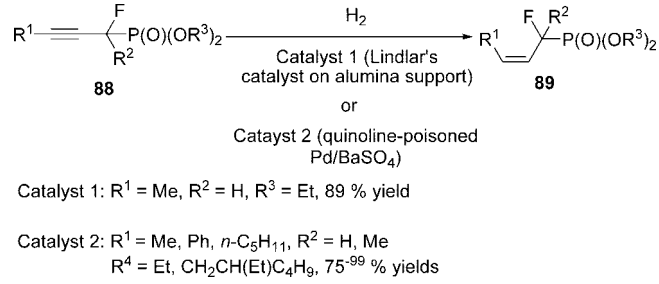
Lindlar's catalyst has also been used successfully in the partial hydrogenation of propargylic fluorides for the synthesis of analogues of fatty acid metabolites **90**,[17,57] fluorine-containing prostacyclin precursors **91**[32–35] and 3-fluoropurine ribonucleosides **92**[26] (Scheme 30).

Complete hydrogenation to the saturated compound is also possible. The fluorinated 4-phenylpiperidine **94**, a precursor of antimigraine drugs, was prepared in a moderate 43% yield via hydrogenation of **93** in the presence of 10 mol % of Pd−C (Scheme 31).[28]

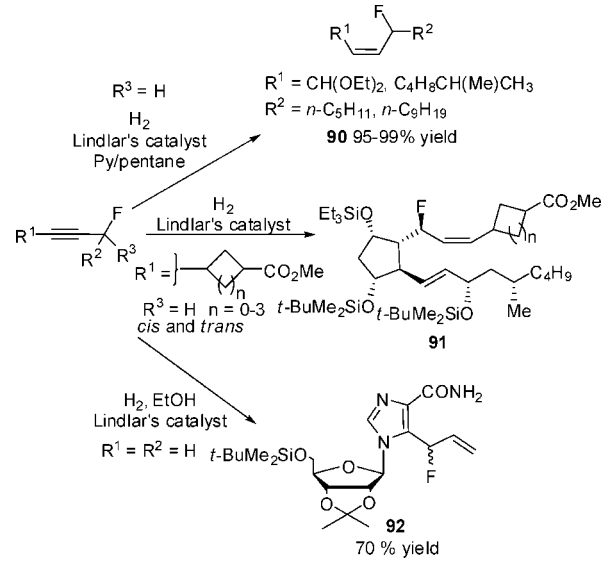
2.2.2. Hydrostannylation

Hydrostannylation of propargyl fluorides allows for the preparation of fluorinated vinyl stannanes, a class of highly

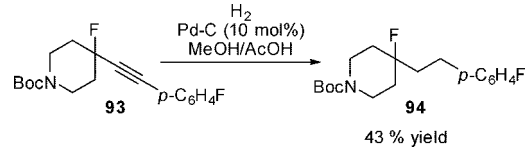
Scheme 29. Partial Hydrogenation of (Fluoropropargyl)phosphonate Esters Reported by Hammond



Scheme 30. Partial Hydrogenation of Propargylic Fluorides using Lindlar's Catalyst



Scheme 31. Complete Hydrogenation of Propargylic Fluorides Reported by Van Niel

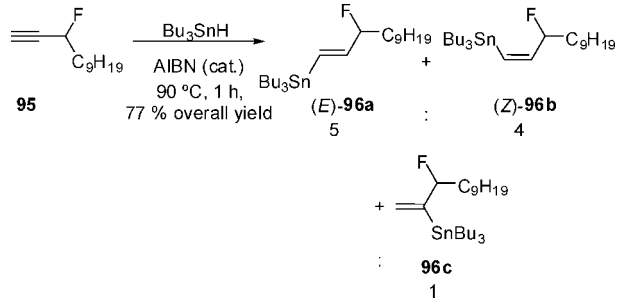


versatile fluorinated building blocks which could undergo further functional group manipulations. Madiot et al. showed that the hydrostannylation of propargylic fluorides was feasible, but poor control of regioselectivity and *E*:*Z* geometry was obtained. The reaction of the racemic propargylic fluoride **95** with tributyltin hydride under radical conditions yielded **96** in 77% yield as a mixture of three compounds (Scheme 32).[22]

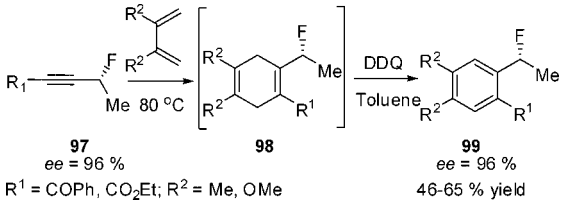
2.2.3. Cycloadditions

Grée et al. recently reported the cycloadditions of enantioenriched propargylic monofluorides, followed by aromatization of the primary adduct, for the synthesis of enantioenriched benzylic fluorides. These compounds are challenging to prepare by either direct nucleophilic or electrophilic fluorination. Diels−Alder reactions with the enantioenriched propargylic fluorides **97** furnished intermediates **98**, which could aromatize upon treatment with DDQ to afford the benzylic fluorides **99** with no loss in ee throughout the synthetic process (Scheme 33).[58]

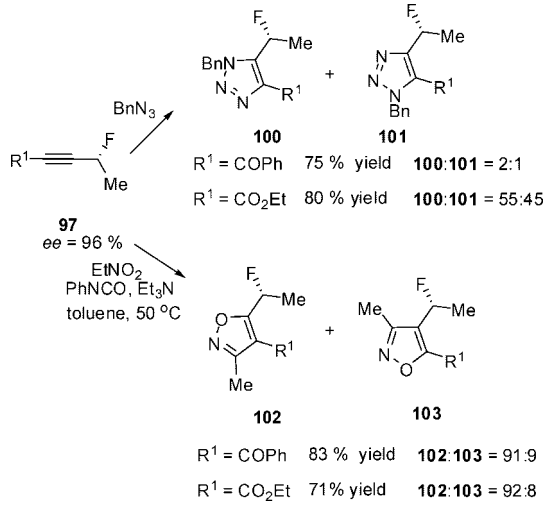
Scheme 32. Hydrostannylation of Propargylic Fluorides Reported by Madiot and Co-Workers



Scheme 33. Cycloadditions of Enantioenriched Propargylic Fluorides Reported by Grée and Co-Workers



Scheme 34. 1,3-Dipolar Cycloadditions of Enantioenriched Propargylic Fluorides Reported by Grée and Co-Workers

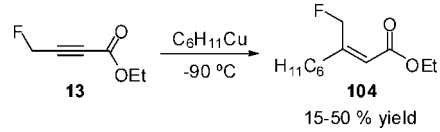


The authors expanded their methodology to the preparation of fluorinated heteroaromatics. In this study, the propargylic fluorides were used as dipolarophiles to lead to fluorinated triazoles and isoxazoles **100**−**103** upon 1,3-dipolar cycloadditions with azide and nitrile oxides, respectively (Scheme 34).[58]

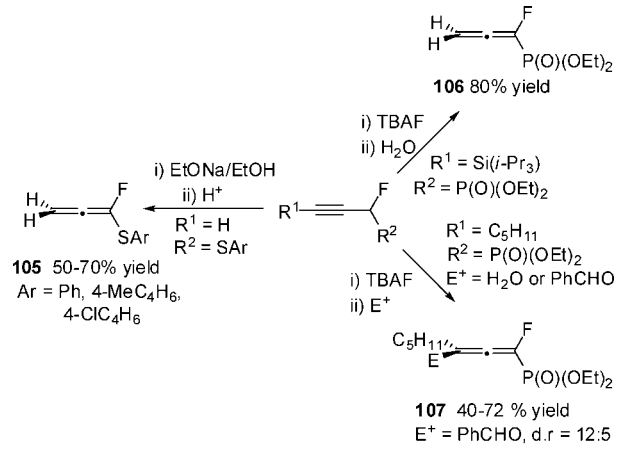
2.2.4. Conjugated Additions

The Michael addition of an organocuprate to 4-fluoro-2-butynoate **13** has been reported by Poulter et al. as part of synthetic studies toward the synthesis of a fluorinated geraniol derivative. The conjugate addition leading to the α,β-unsaturated allylic fluoride **104** was found to be a challenging transformation, with yields ranging from 15 to 50%.[8] The involvement of a Michael addition to 5-fluoropropynyl-2′-deoxyuridine-5′-phosphate has also been postulated in the mechanism of inactivation of the enzyme thymidylate synthase (Scheme 35).[9,10] Grée et al. recently reported the enantioselective synthesis of monofluorinated pyridines, using a Bohlman−Rahtz reaction of a propargylic fluoride as the key step.[59]

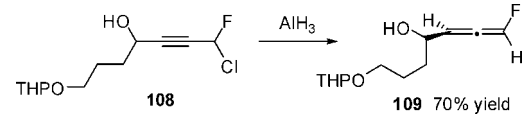
Scheme 35. Michael Addition to a Propargylic Fluoride Reported by Poulter and Co-Workers



Scheme 36. Synthesis of Fluorinated Allenes Reported by Fuchigami and Hammond



Scheme 37. Reductive Elimination of Propargylic Fluorides Reported by Castelhano and Krantz



2.2.5. Synthesis of Fluorinated Allenes

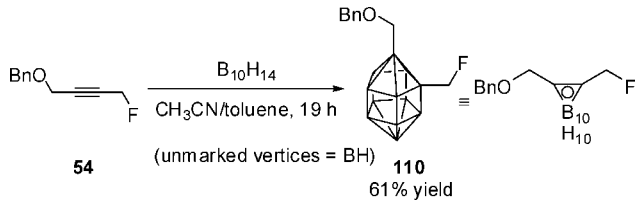
Fluorinated allenes can be prepared from activated propargylic fluorides either by isomerization under basic conditions or by reductive elimination of a chlorinated derivative. Fuchigami and co-workers reported the preparation of α-fluoroallenyl sulfides **105** by deprotonation of the corresponding propargylic fluoride with sodium ethoxide.[43,44] Deprotonation of the terminal alkyne forms a propargylic carbanion which rearranges to give the allenyl carbanion, leading to the terminal allene upon protonation. α-Fluoroallenylphosphonate **106** was obtained by treatment of the corresponding silylated propargylic fluoride with TBAF. Desilylation leaves a terminal alkynyl anion, which rearranges to the allenyl carbanion. When an alkyl-substituted analogue was treated with TBAF in the presence of an electrophile, internal allenes **107** were formed in moderate to good yields (Scheme 36).[14]

Castelhano and Krantz reported the reductive elimination of fluorine-containing propargylic chlorides using AlH_3. Allene **109** was prepared in 70% yield by relying on this methodology (Scheme 37).[49]

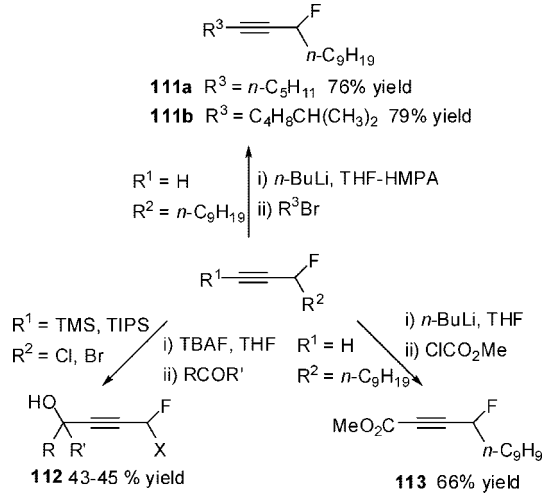
2.2.6. Complexation with Metals

Cobalt carbonyl complexes of propargylic fluorides have been prepared by Grée et al. and discussed in section 2.1.1.1.1.[25] Tietze et al. have reported the complexation of propargylic fluorides with carboranes. The fluorinated carborane **110** was synthesized as a precursor of fluorinated *o*-carboranyl lactosides and glucosides for the treatment of cancer by boron neutron capture therapy (BNCT) (Scheme 38).[29]

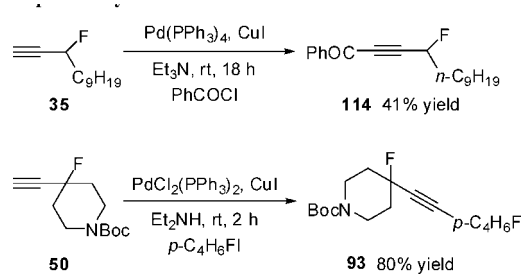
Scheme 38. Fluorinated Carboranes Reported by Tietze and Co-Workers



Scheme 39. Alkylation of Terminal Propargylic Fluorides by Grée, Hammond and Co-Workers



Scheme 40. Pd-Mediated Cross-Coupling Reactions of Propargylic Fluorides Reported by Grée and by van Niel

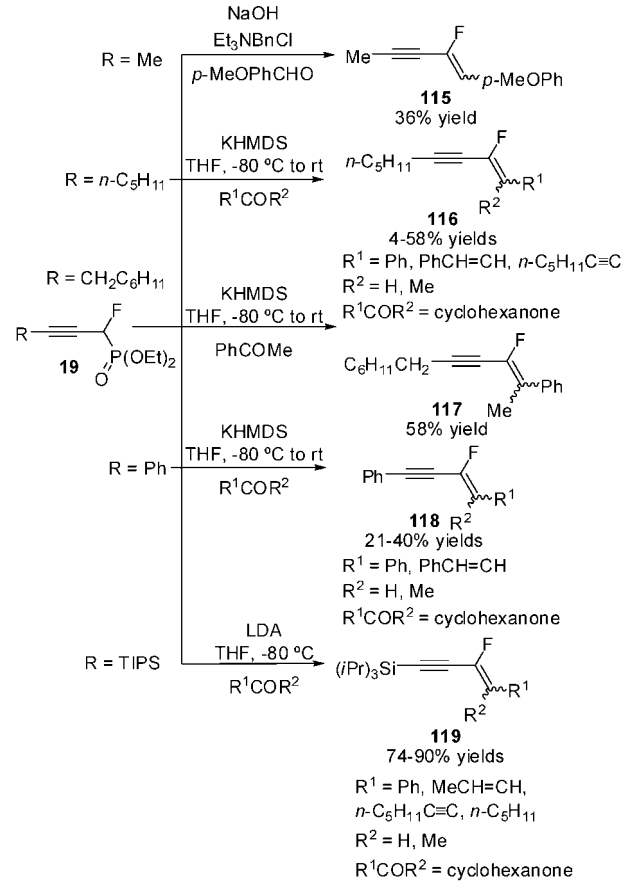


2.2.7. Addition and Coupling

Grée and co-workers functionalized terminal propargylic fluorides via deprotonation with *n*-BuLi and alkylation of the resulting anion, leading to functionalized compounds **111**. Deprotonation followed by reaction with a carbonyl electrophile led to compounds **113**. No elimination of HF was observed under these conditions.[22,57] When a trialkylsilyl group was occupying the terminal position (R^1 = TMS, TIPS), a desilylative process was necessary to carry out further functionalization. The treatment of silylated alkynes with TBAF in the presence of a carbonyl electrophile allowed the formation of the fluorinated propargylic alcohols **112** in only moderate yield (Scheme 39).[48,50]

Some of the most useful methods for the synthesis of internal propargylic fluorides are palladium-mediated cross-coupling reactions.[60] Grée and co-workers utilized a palladium-mediated cross-coupling reaction for the synthesis of the internal propargylic fluoride **114**,[22] and van Niel et al. performed a Sonogashira−Hagihara reaction for the preparation of **93** (Scheme 40).[28]

Scheme 41. Horner−Wadsworth−Emmons Reactions of (α-Fluoropropargyl)phosphonate Esters Reported by Hammond



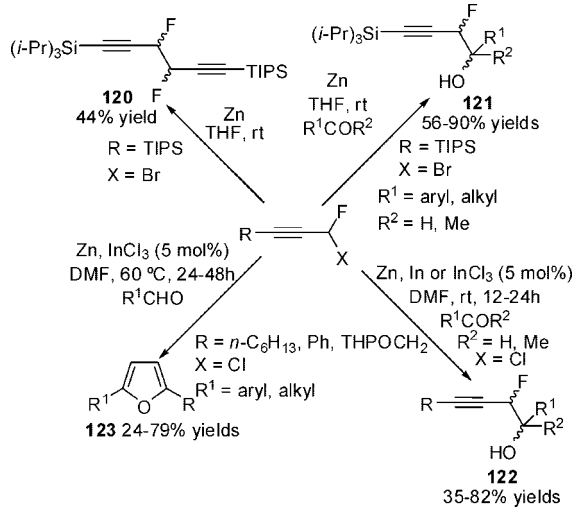
2.2.8. Wittig-Type Reactions

Hammond and co-workers investigated the reactivity of a series of (α-fluoropropargyl)phosphonate esters **19** toward Horner−Wadsworth−Emmons (HWE) olefinations.[14,56,61] When R was an alkyl or aryl group, the corresponding fluoroenynes **115**−**118** were obtained in poor to moderate yields with *E*:*Z* ratios of approximately 1:1. The authors attributed the low yields to the instability of the fluoropropargylic carbanionic intermediate formed upon deprotonation (see section 2.2.1.5). No fluorinated enynes were formed when saturated aldehydes such as pentanal were used, as products of self-aldol condensations were isolated instead. The silylated fluoropropargylphosphonate ester **19** (R = Si(*i*-Pr_3)) reacted with both saturated and unsaturated aldehydes or ketones to give enynes **119** in good to excellent yields. The authors suggested that this significant improvement in yields may be due to additional stabilization of the α-carbanion, via a cumulene-type resonance with the silicon atom[14] (Scheme 41).

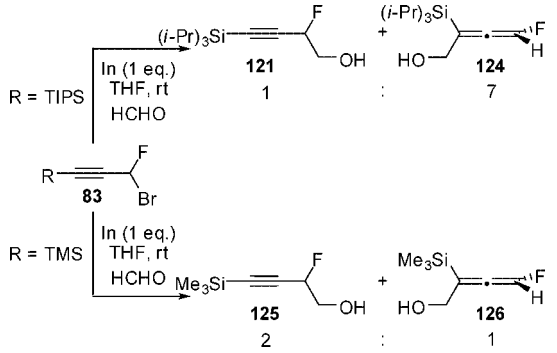
2.2.9. Reactions of Halopropargylic Fluorides

The reactivity of fluorinated propargylic organozinc reagents has been extensively studied by Hammond and co-workers.[50,51] The organozinc derivatives were prepared from fluorohaloacetylenes in the presence of zinc. When a mixture of zinc dust and brominated propargylic fluoride (X = Br, R = TIPS) was stirred in THF at room temperature, the diyne **120** was furnished as a 1:1 mixture of diastereomers.[50] When the reaction occurred in the presence of a carbonyl electrophile, fluorohydrins **121** were isolated as the

Scheme 42. Reactions of Fluoropropargylic Organozinc Derivatives Reported by Hammond and Co-Workers



Scheme 43. In-mediated Synthesis of Fluorinated Allenes Reported by Hammond and Co-Workers



major products along with small amounts of dimer **120**.[62,63] The reaction conditions had to be modified, due to the restricted use of $CHFBr_2$ outlined in the Montreal protocol. In order to perform the reaction with the less reactive fluoropropargyl chlorides, indium metal powder or indium trichloride was used in DMF to afford the desired fluorohydrins **122** at room temperature. When higher temperatures and longer reaction times were applied, nonfluorinated furans **123** were obtained (Scheme 42).[51]

The indium-mediated reaction of triisopropylsilylated alkyne **83** with formaldehyde gave the fluorinated hydroxyallene **124** as the major compound rather than the fluorohydrin **121**. The corresponding trimethylsilylated alkyne afforded the propargylic fluorohydrin **125** as the main product, although a significant amount of hydroxyallene was also isolated (Scheme 43).[64]

2.2.10. Alkylation

Alkylation at the α-position of propargylic fluorides can be achieved with either nucleophiles or electrophiles, depending on the starting materials. Fluorophosphonates **19e**,**c** were deprotonated in the presence of strong bases and subsequently reacted with electrophiles such as methyl acrylate or benzyl bromide to furnish the tetrasubstituted propargylic fluorides **127** and **128** in moderate to good yields (Scheme 44).[13,14] Alternatively, the protected propargyl alcohol **129** was synthesized through a nucleophilic substitution of the bromoalkyne **83** (Scheme 44).[49]

Scheme 44. Alkylation of Nonterminal Propargylic Fluorides

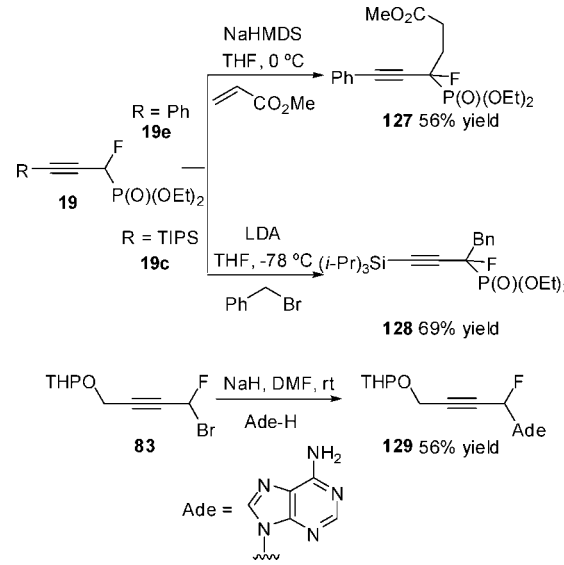
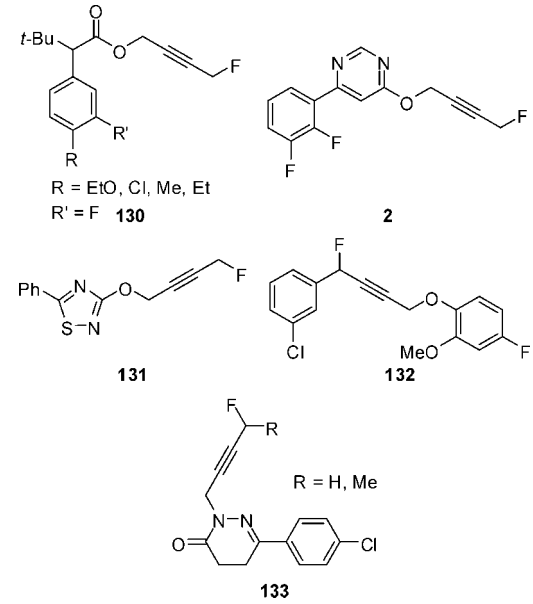


Chart 4. Propargylic Fluorides as Insecticides, Arthropodicides, Herbicides, and Fungicides



2.3. Applications

Propargylic monofluorides have applications in both the agrochemical and pharmaceutical industries. Fluorine-containing compounds represent almost a third of all the halogenated commercially available agrochemicals.[65] There are several examples of propargylic fluorides being used as insecticides, herbicides, and fungicides. A common structural feature of several of these substances is the presence of a heteroatom on the nonfluorinated propargylic position, as exemplified by insecticides **130**[66] and **2**,[67] the arthropodicide **131**,[68] the herbicide **132**,[69] and the fungicides **133**[70–73] (Chart 4).

Phenylacetylenes featuring a fluorine substituent on the propargylic position have applications as fungicides **134**[74] and **136**[75] and pesticides **135**[76] (Chart 5).

Propargylic fluorides flanked by various aromatic and heteroaromatic groups possess interesting agrochemical activity. These include naphthalene derivatives (pesticide and fungicide **137**),[77,78] thiophene derivatives (acaricide and

Chart 5. Propargylic Fluorides as Fungicides and Pesticides

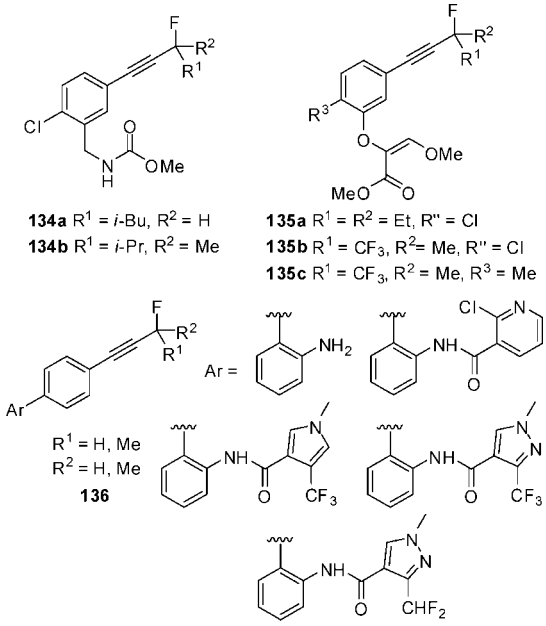
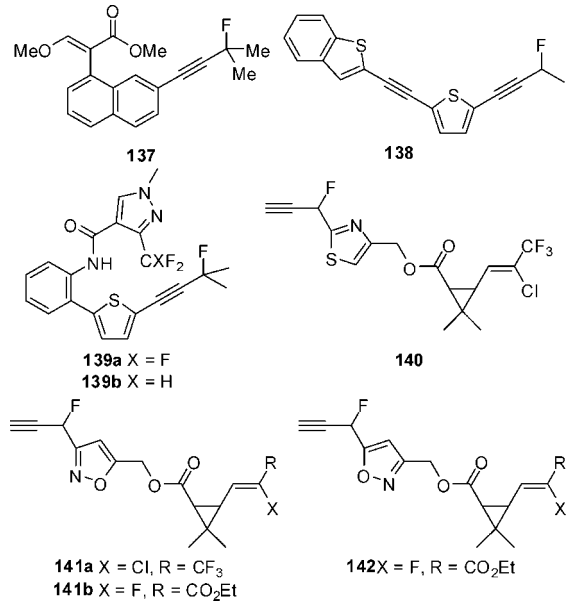


Chart 6. Fluorinated Agrochemicals



insecticide **138**[79] and microbiocides **139**),[80] thiazoles (pesticide **140**),[81] and isoxazoles (insecticides **141** and **142**)[82] (Chart 6).

Propargylic monofluorides also have many applications in the pharmaceutical industry: for example, the fluorinated nucleotide analogue **143** and the quinazoline **1**. The propargylic fluoride **143** was developed by Kalman and coworkers as an irreversible thymidylate synthase inhibitor that did not require folate cofactors.[83,84] The reverse transcriptase inhibitor **1** was developed as part of a lead optimization program aimed at developing drugs for the treatment of HIV and AIDS (Chart 7).[85,86]

Propargylic fluorides **144** and **145** can act as selective modulators of glucocorticoid receptors.[87] Quinolinecarboxamides **146**[88] and **147**[89] are antiviral agents, and **146** has also been used for the prevention or treatment of atherosclerosis or restenosis.[90] The fluorinated alkynylpyrazolotriazolopyrimidine **148** has been studied as an adenosine A2a receptor antagonist used for the treatment of central nervous system

Chart 7. Fluorinated Pharmaceuticals

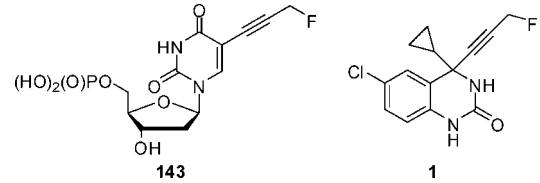
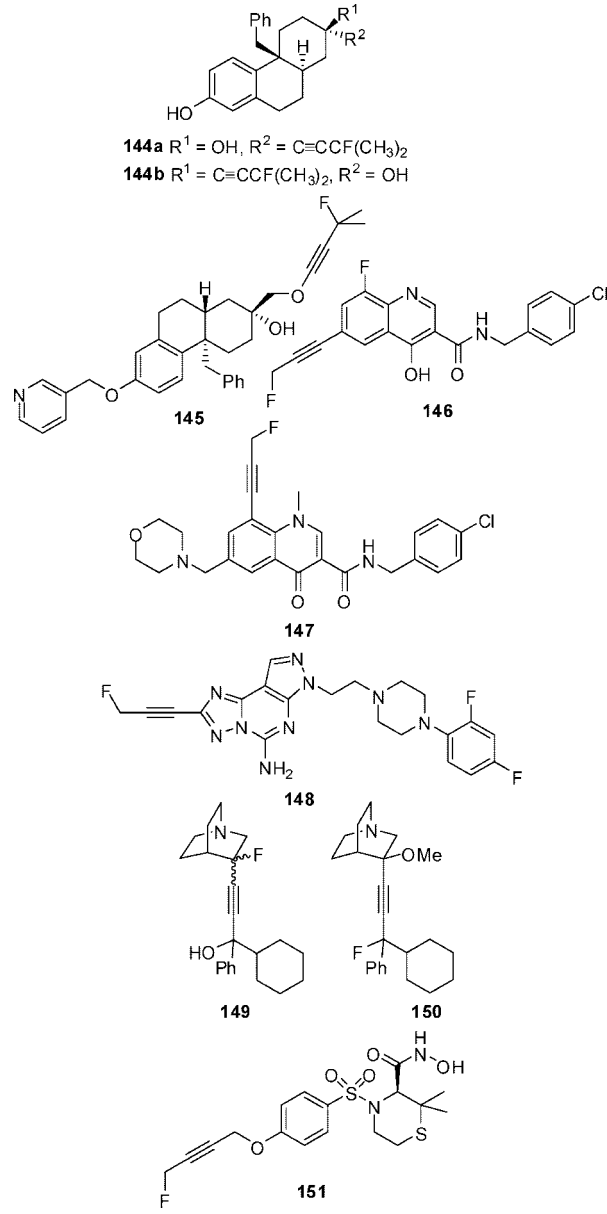


Chart 8. Fluorinated Pharmaceuticals



diseases.[91] Quinuclidine derivatives **149** and **150** have been synthesized as M_2 and/or M_3 muscarinic receptor inhibitors.[92] Finally, the hydroxamic acid **151** was prepared as an inhibitor of tumor necrosis factor alpha converting enzyme (TACE)[93,94] (Chart 8).

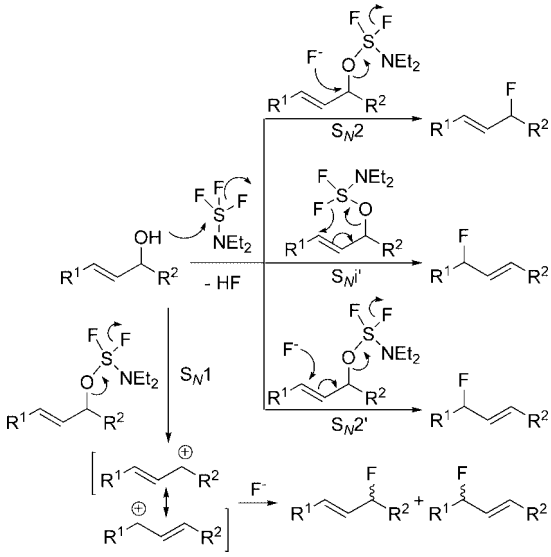
3. Allylic Fluorides

3.1. Synthesis

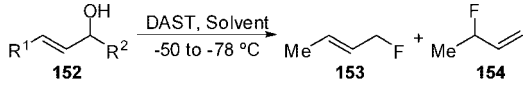
3.1.1. Nucleophilic Fluorination

3.1.1.1. Dehydroxyfluorination. *3.1.1.1.1. DAST.* Despite the fact that DAST is the most widely used reagent for the

Scheme 45. Mechanism of DAST-Mediated Dehydroxyfluorination of Allylic Alcohols

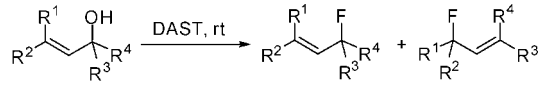


Scheme 46. DAST-Mediated Dehydroxyfluorination of Allylic Alcohols Reported by Middleton



Alcohol	R^1	R^2	Solvent	153	154
152a	Me	H	Diglyme	28	72
152a	Me	H	Isooctane	36	64
152b	H	Me	Diglyme	22	78
152b	H	Me	Isooctane	9	91

Scheme 47. DAST-Mediated Dehydroxyfluorination of Alkyl-Substituted Allylic Alcohols



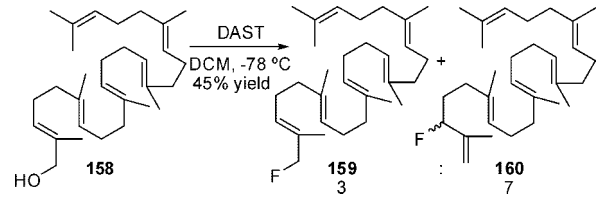
a $R^1 = R^3 = R^4 = H$, $R^2 = Me$	1	3	36 % yield
b $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = i$-Pr	2	3	43 % yield
c $R^1 = R^3 = H$, $R^4 = H$, $R^2 = Ph$	1	2	76 % yield

dehydroxyfluorination of allylic alcohols, control over regio- and stereoselectivity is not always favorable. The fluorination step can proceed through an S_N2, S_N2', S_Ni', or S_N1 mechanism, depending on the structure of the substrate. Thus, the reaction can occur with or without transposition of the double bond and with retention or inversion of configuration. Side products resulting from carbonium type rearrangements and dehydration are also occasionally observed (Scheme 45).[95]

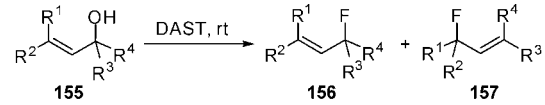
The first example of a dehydroxyfluorination using DAST was conducted by Middleton in 1975 using crotyl alcohol (**152a**) and 3-buten-2-ol (**152b**). The product outcome was a mixture of 1-fluorobut-2-ene **153** and 3-fluorobut-1-ene **154**, the secondary fluoride **154** being the major product. The amount of product resulting from a transposition of the double bond was significantly minimized by changing the solvent from diglyme to the less polar isooctane (Scheme 46).[7]

The influence of the structural features of the starting allylic alcohol on the regioselectivity of fluorination has been extensively studied. When the allylic alcohol is substituted with alkyl groups, regioselectivity is poor (Scheme 47).[96–100]

Scheme 48. Synthesis of Fluorinated Squalene Derivatives

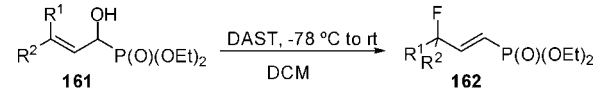


Scheme 49. Regioselective DAST-Mediated Dehydroxyfluorination



d $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = Ph$	0	1	71 % yield
e $R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = Me$	1	0	71 % yield
f $R^1 = R^3 = H$, $R^2 = CN$, $R^4 = Me$	1	0	50 % yield
g $R^1 = R^3 = H$, $R^2 = CO_2Me$, $R^4 = Me$	1	0	80 % yield
h $R^1 = R^3 = H$, $R^2 = COPh$, $R^4 = Me$	1	0	70 % yield
i $R^1 = R^3 = H$, $R^2 = COPh$, $R^4 = t$-Bu	1	0	41 % yield
j $R^1 = H$, $R^2 = Me$, $R^3 = R^4 = CO_2Et$	1	0	55 % yield

Scheme 50. Synthesis of (γ-Fluoroallyl)phosphonates Reported by Blackburn and Hammond



a $R^1 = H$, $R^2 = H$	25 % yield
b $R^1 = H$, $R^2 = Me$	76 % yield
c $R^1 = H$, $R^2 = Ph$	73 % yield
d $R^1 = H$, $R^2 = n$-Pr	78 % yield
e $R^1 = H$, $R^2 = CH(OMe)_2$	54 % yield
f $R^1 = R^2 = Me$	51 % yield

The poor level of regioselectivity is a drawback in the fluorination of the squalene derivative **158**, giving a 3:7 mixture of primary and secondary allylic fluorides (Scheme 48).[101,102]

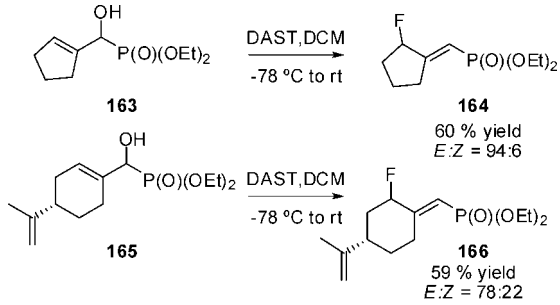
In contrast to alkyl groups, allylic alcohols substituted with phenyl groups or strongly electron withdrawing groups can undergo DAST-mediated dehydroxyfluorination with high levels of regioselectivity. Phenyl-substituted **155d** reacts with DAST to give the allylic fluoride **157** with clean transposition of the double bond. The structural isomer **155e** reacts with no double-bond transposition to give the same product with the phenyl group in conjugation with the double bond. When an electron-withdrawing group substituted the double bond, the reaction proceeded without transposition of the double bond to afford secondary fluorides **156f−j** in moderate to good yields (Scheme 49).[96,97]

In an attempt to synthesize a series of (α-fluoroallyl)phosphonates by reaction of the corresponding (α-hydroxyallyl)phosphonate esters **161a−c** with DAST, Blackburn et al. observed clean transposition of the double bond and isolated the (γ-fluoroallyl)phosphonate esters **162a−c** in poor to moderate yields. The electron-withdrawing phosphonate defined the site of fluorination (Scheme 50).[98,99]

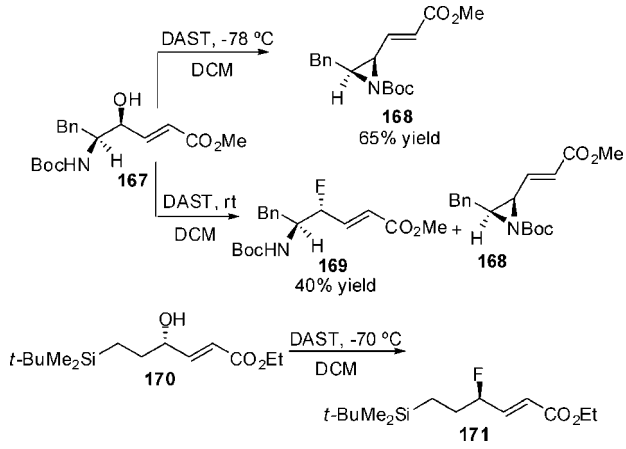
Hammond et al. expanded upon the scope and limitations of the conversion of (α-hydroxyallyl)phosphonate esters into (γ-fluoroallyl)phosphonate esters. The transformation tolerated alkyl-, aryl-, and heteroatom-containing substituents (Scheme 50), as well as cyclic substrates such as **163** and **165**. Upon fluorination, these substrates delivered the allylic fluorides **164** and **166**, respectively, both featuring an exocyclic double bond (Scheme 51).[100]

Hammond found that (α-fluoroallyl)phosphonate esters could be accessed by a two-step sequence featuring a

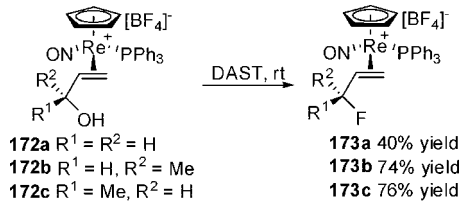
Scheme 51. Synthesis of (γ-Fluoroallyl)phosphonate Esters Reported by Hammond and Co-Workers



Scheme 52. Fluorination of γ-Hydroxy α,β-Unsaturated Esters



Scheme 53. Fluorination of Re Complexes of Allylic Alcohols Reported by Grée and Co-Workers



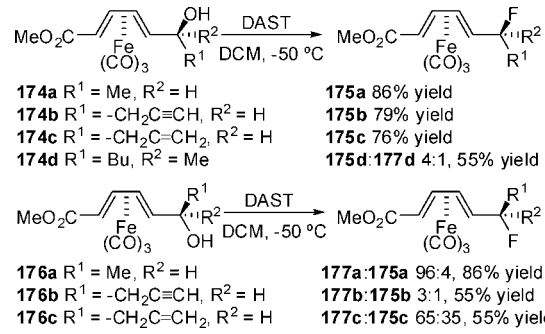
fluorination of the corresponding (α-hydroxypropargyl)phosphonate esters, followed by partial hydrogenation.[12,13]

The product outcome of the fluorination of alcohol **167** with DAST showed very strong temperature dependence. At low temperature, the nonfluorinated aziridine **168** was obtained, resulting from an intramolecular displacement of the activated alcohol. However, at room temperature, both the desired allylic fluoride **169** and aziridine **168** were formed.[103] Fluorination of the ester **170** at low temperature gave the corresponding allylic fluoride **171** with inversion of configuration, with no deprotection of the silyl group occurring under the reaction conditions[104] (Scheme 52).

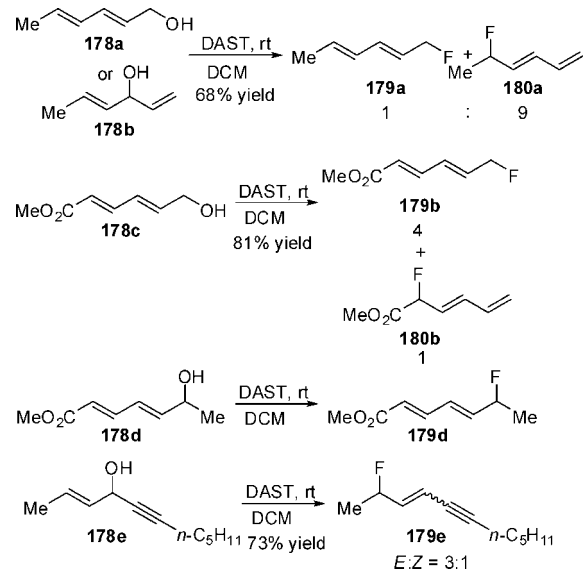
It is clear that the structure of the allylic alcohol and the reaction conditions can have a profound effect on the level of both regio- and diastereocontrol upon dehydroxyfluorination using DAST. Grée and co-workers were able to control selectivity by complexing the allylic alcohol with a transition metal prior to fluorination. The nucleophilic displacement of the hydroxy group in the rhenium complexes **172** occurred with complete regiocontrol to give allylic fluorides **173** as single diastereomers resulting from retention of configuration (Scheme 53).[105]

$Fe(CO)_3$ complexes of dienyl alcohols can also be used to control diastereoselectivity. When a secondary alcohol was

Scheme 54. Fluorination of Fe Complexes of Dienyl Alcohols Reported by Grée and Co-Workers



Scheme 55. Dehydroxyfluorination of Dienyl Alcohols Reported by Grée and Co-Workers



used, the fluorination of complexes **174** proceeded with retention of configuration. In the case of substrates **176**, erosion in the stereochemical integrity of the reaction led to a mixture of diastereomers (Scheme 54).[106]

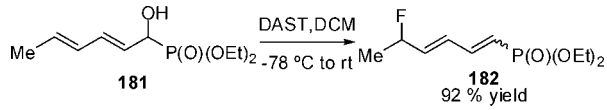
Grée and co-workers also studied the regioselectivity of the fluorination of uncomplexed dienyl alcohols. The linear and branched alcohols **178a**,**b** reacted with DAST to give the same product outcome, a mixture of conjugated fluorodienes **179a** and **180a** in a 1:9 ratio, with the secondary fluoride being formed preferentially. The dehydroxyfluorination of dienyl alcohols **178c**,**d**, bearing an electron-withdrawing group, occurred with little or no transposition of the double bond, an observation consistent with the reactivity of the corresponding allylic alcohols. Alcohol **178e**, featuring a hydroxyl group which is both allylic and propargylic, reacted with DAST to give the fully conjugated enyne **179e** in 73% yield as a 3:1 *E*:*Z* mixture (Scheme 55).[96]

Hammond et al. studied the fluorination of dienic (α-hydroxy)phosphonate ester **181**. Upon fluorination, full transposition of the double bond afforded the (γ-fluoroallyl)phosphonate ester **182** in high yield (Scheme 56).[100]

The direct fluorination of the γ-hydroxy ester **183** is a rare example of high levels of regiocontrol in a system not containing a regiodirecting group and proceeded apparently without double-bond transposition to give the fluorinated $PPAR_\gamma$ agonist **184** in moderate yield (Scheme 57).[107]

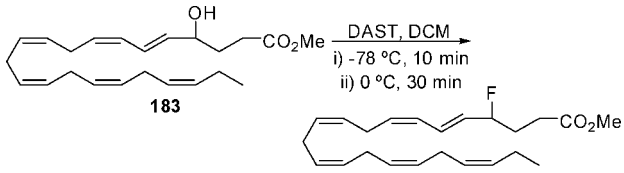
DAST-mediated dehydroxyfluorination has been utilized for the synthesis of various fluorinated analogues of natural

Scheme 56. Dehydroxyfluorination of Dienic (α-Hydroxy)phosphonate Esters Reported by Hammond and Co-Workers



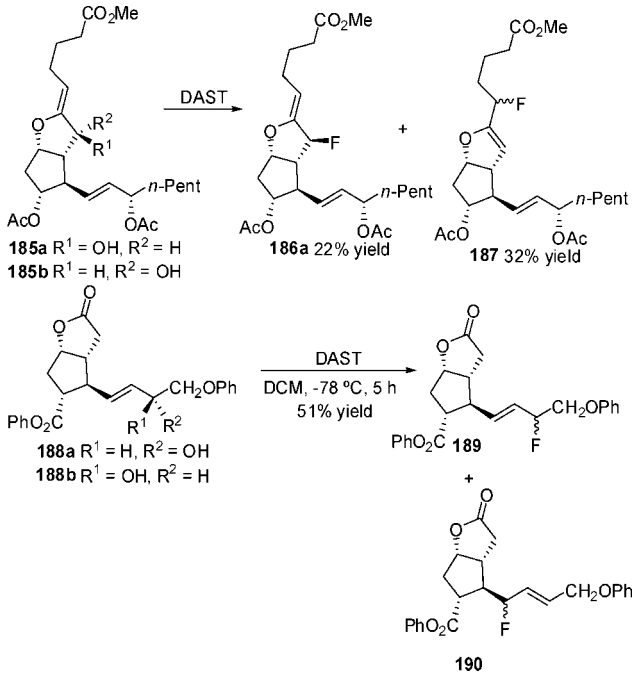
181 **182** 92 % yield

Scheme 57. Synthesis of a Fluorinated PPARγ Agonist Reported by Itoh and Co-Workers



183 **184** 42 % yield

Scheme 58. Synthesis of Fluorinated Prostacyclin Analogues

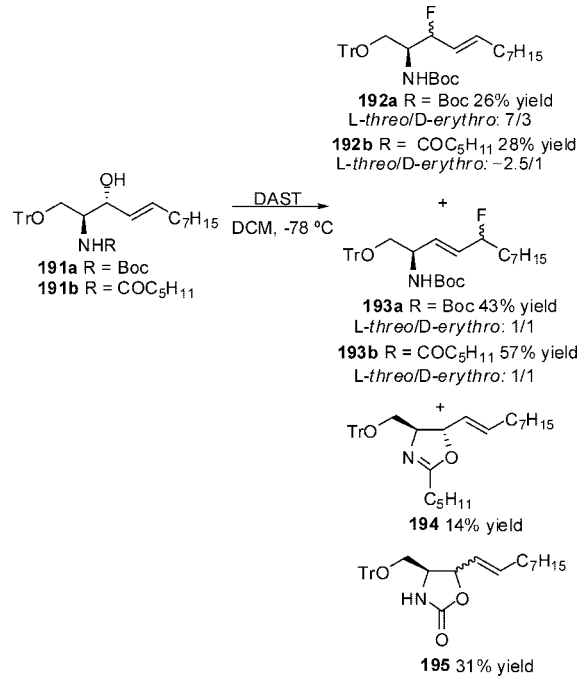


185a R^1 = OH, R^2 = H
185b R^1 = H, R^2 = OH
186a 22% yield
187 32% yield
188a R^1 = H, R^2 = OH
188b R^1 = OH, R^2 = H
189
190

products. Fluorinated prostaglandin analogues have been the object of several studies. When either of the epimers of the (7*R*)- and (7*S*)-7-hydroxy-PGI_2 derivatives **185a**,**b** was treated with DAST, a single diastereomer, the (7*S*)-7-fluoro-PGI_2 derivative **186a**, was obtained, along with the corresponding regioisomer **187**.[108,109] The authors suggest the involvement of an allylic carbonium ion intermediate, to which the fluoride ion preferentially approaches from the least hindered face at the C7 position. After rearrangement of the double bond, the fluoride can approach from either face at the C5 position, giving a mixture of diastereomers for the regioisomer **187**.[109] The dehydroxyfluorination of either the diastereomerically pure allylic alcohol **188a** or a 1:1 mixture of diastereomers **188a**,**b** delivered the same mixture of isomers **189** and **190** (Scheme 58).[110]

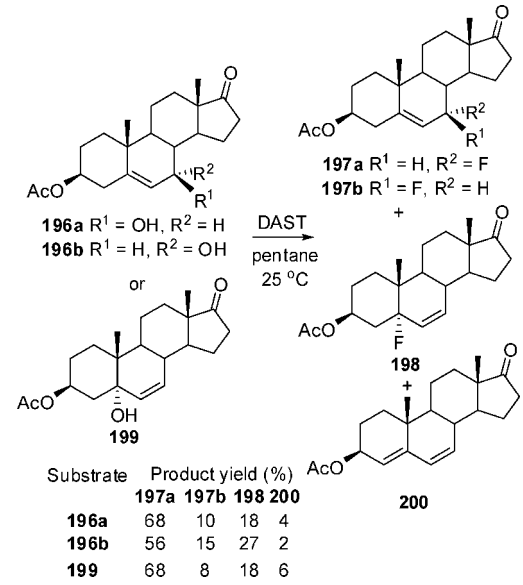
The synthesis of fluorinated analogues of *N*-Boc-protected sphingosine was reported to have poor regio- and stereoselectivity.[111,112] The reaction of allylic alcohol **191a** with DAST afforded both allylic fluorides **192a** and **193a** as well as the oxazolidinone **195**.[111] Under the same conditions, the corresponding N-acyl-protected allylic alcohol **191b** produced the product resulting from double-bond transposition

Scheme 59. Synthesis of Fluorinated Sphingosine Analogues Reported by Herdewijn and Co-Workers



192a R = Boc 26% yield
L-*threo*/D-*erythro*: 7/3
192b R = COC_5H_{11} 28% yield
L-*threo*/D-*erythro*: ~2.5/1
191a R = Boc
191b R = COC_5H_{11}
193a R = Boc 43% yield
L-*threo*/D-*erythro*: 1/1
193b R = COC_5H_{11} 57% yield
L-*threo*/D-*erythro*: 1/1
194 14% yield
195 31% yield

Scheme 60. Synthesis of Fluorinated Steroids Reported by Marwah and Co-Workers



196a R^1 = OH, R^2 = H
196b R^1 = H, R^2 = OH
197a R^1 = H, R^2 = F
197b R^1 = F, R^2 = H
198
199
200

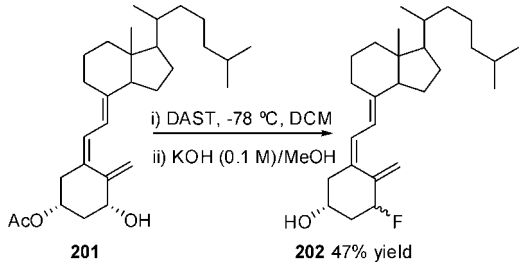
Substrate	Product yield (%)			
	197a	**197b**	**198**	**200**
196a	68	10	18	4
196b	56	15	27	2
199	68	8	18	6

as the major product as well as the nonfluorinated oxazoline **194**.[112] Both allylic fluorides **192a**,**b** were formed preferentially as the L-*threo* isomer, but compounds **193a**,**b** did not exhibit a preference for either the L-*threo* or the D-*erythro* stereoisomer (Scheme 59).

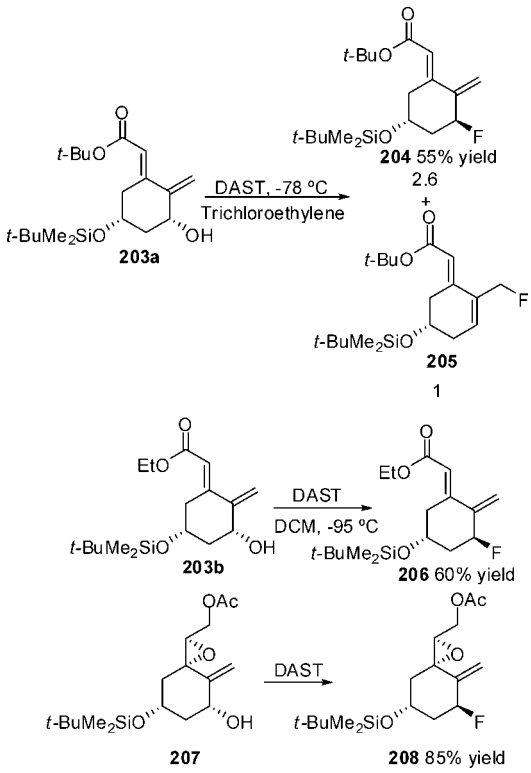
Dehydroepiandrosterone derivatives **196a**,**b** were treated with DAST to furnish the 7α-fluoro steroid **197a** as a major product, regardless of whether the substrate was a pure diastereomer (**196a** or **196b**) or a 1:1 mixture of diastereomers (**196a**,**b**). The isomeric tertiary alcohol **199** also gave allylic fluoride **197a** as the major product. Trace amounts of nonfluorinated 3β-acetoxyandrosta-4,6-dien-17-one **200** were detected in all cases (Scheme 60).[113]

DeLuca and co-workers reported the synthesis of the fluorinated analogue of cholecalciferol **202** through the

Scheme 61. Preparation of a Fluorinated Vitamin D Analogue Reported by DeLuca and Co-Workers



Scheme 62. Diastereoselective Dehydroxyfluorination



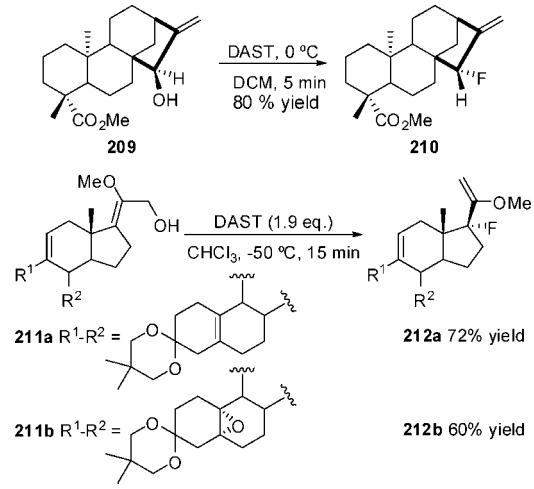
dehydroxyfluorination of vitamin D_3 analogue **201** with no transposition of the double bond (Scheme 61).[114,115]

The fluorination of allylic ester **203a** in trichloroethylene at −78 °C yielded a mixture of the desired S_N2 product **204** and the corresponding S_N2' product **205** in a 2.6:1 ratio, with an overall 55% yield.[116] The allylic ester **203b** required a large excess of DAST at low temperature and high dilution to afford the allylic fluoride **206** as a single regio- and stereoisomer in moderate yield,[117] whereas the all-syn epoxide **207** was effectively fluorinated to give the desired product **208** in an excellent 85% yield. The dehydroxyfluorination of esters **203** or epoxide **207** was the key fluorination step, allowing for the synthesis of fluorinated analogues of calcitrol, ergocalciferol, and Ro 26-9229 (Scheme 62).[118]

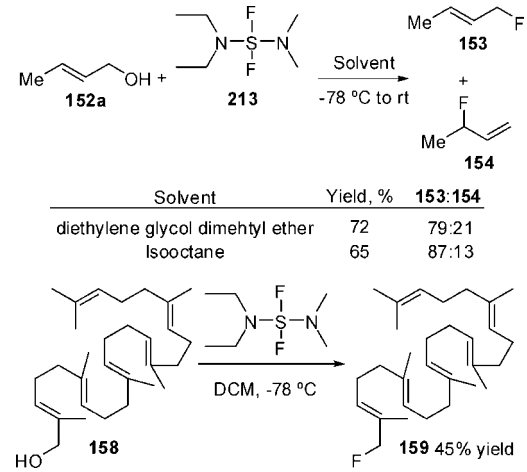
Allylic fluoride **210**, a precursor of fluorogibberellins, was synthesized by dehydroxyfluorination of ester **209** with DAST at 0 °C with no transposition of the double bond.[104,119] In contrast, reaction of the steroidal intermediate **211a** or epoxide **211b** with DAST produced exclusively the rearranged enol ethers **212a**,**b** in 72% and 60% yields, respectively (Scheme 63).[120]

3.1.1.1.2. Other Reagents. Only a few examples of dehydroxyfluorination of allylic alcohols performed with a fluorinating reagent other than DAST have been reported.

Scheme 63. Synthesis of Fluorogibberellins and Fluorosteroids Reported by Cross and by Neef



Scheme 64. Dehydroxyfluorination of Allylic Alcohols Using Bis(dialkylamino)sulfur Difluorides Reported by Middleton and Mann

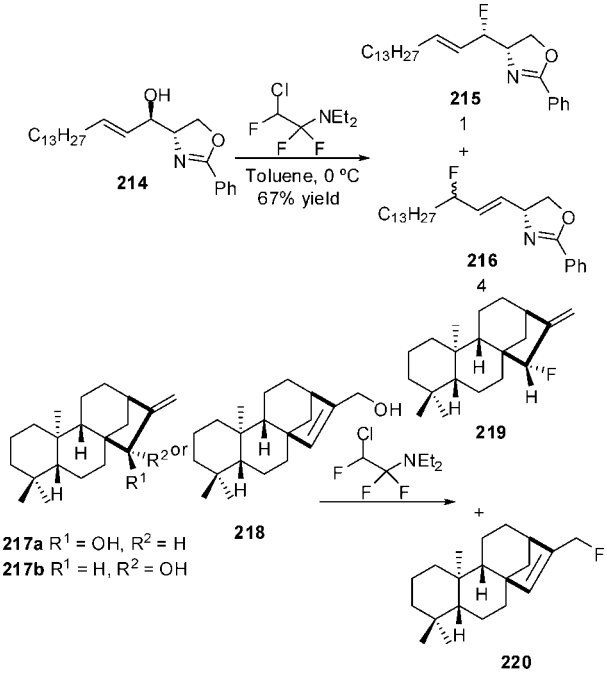


The alternative nucleophilic sources of fluorine used to date are bis(dialkylamino)sulfur difluorides, Yarovenko's and Ghosez's reagents, IF_5 in $Et_3N \cdot 3HF$ solution ($IF_5/Et_3N \cdot 3HF$), and SF_4.

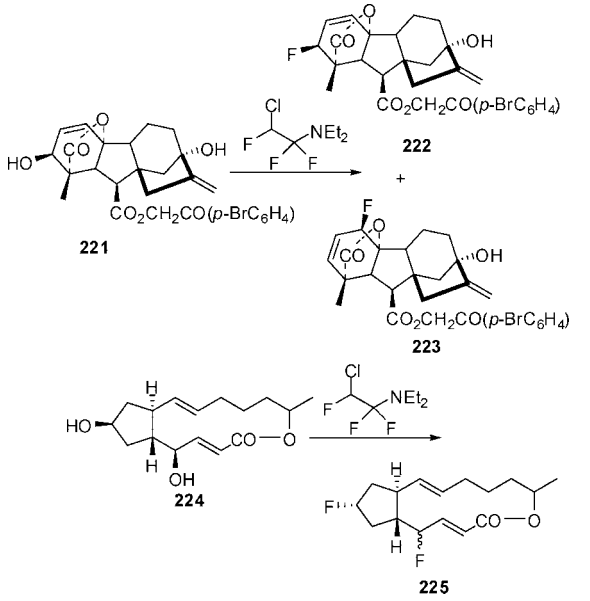
Bis(dialkylamino)sulfur difluorides, in particular (diethylamino)(dimethylamino)sulfur difluoride (**213**), are attractive alternatives to the corresponding trifluorides, as less double-bond transposition is observed with these reagents. For example, crotyl alcohol in the presence of **213** afforded the allylic fluoride **153** as the major product. This result is in contrast to the product distribution obtained with DAST (Scheme 46, section 3.1.1.1.1).[7] The replacement of diethylene glycol dimethyl ether for a less polar solvent, such as isooctane, further improved the regioselectivity of the reaction. The ability of **213** to afford exclusively the primary fluoride was confirmed with the synthesis of fluorosqualene **159**[101] (as compared to DAST Scheme 48, section 3.1.1.1.1) and the precursor of fluorinated geraniol[8] (Scheme 64).

Yarovenko's reagent, 2-chloro-*N*,*N*-diethyl-1,1,2-trifluoroethanamine, often leads to a mixture of regioisomers (Schemes 65 and 66). The rearranged compound **216** was the major product obtained upon fluorination of the sphingosine oxazoline derivative **214** with this trifluoroamine. Allylic fluoride **216** was obtained as an approximately 1:1 mixture of diastereomers (Scheme 65).[121] Upon treatment

Scheme 65. Dehydroxyfluorination of Allylic Alcohols Using Yarovenko's Reagent



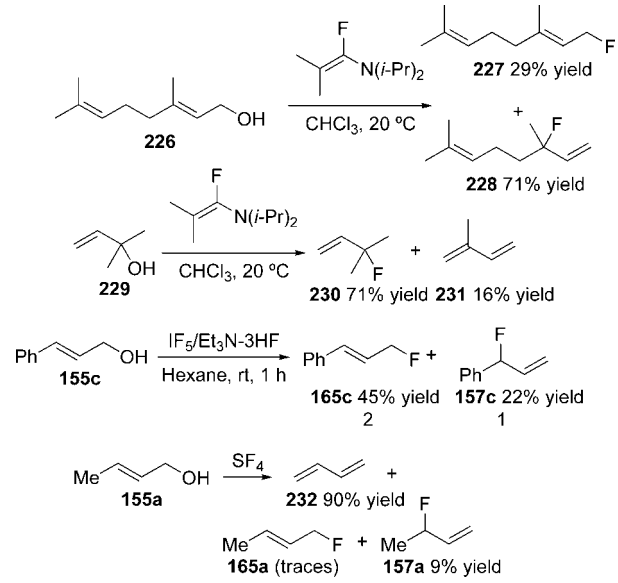
Scheme 66. Synthesis of Fluorinated Gibberellic Acid and Brefeldin A Derivatives Using Yarovenko's Reagent



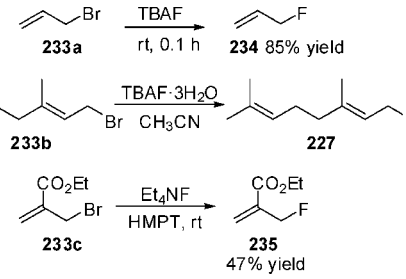
with Yarovenko's reagent, hydroxykaurenes **217a**,**b** and **218** gave a mixture of allylic fluorides **219** and **220**, the secondary fluoride being the major product.[122] The product distribution being similar regardless of which epimeric alcohol was used implies the existence of a common allylic carbocation. This intermediate is likely to be approached from the less hindered α face, favoring the formation of fluorokaurene **219** (Scheme 65).

For compound **221**, featuring more than one hydroxy group, Yarovenko's reagent reacted chemoselectively. Treatment of gibberellic acid ester **221** with an excess of the fluoroamine yielded regioisomers **222** and **223** as single stereoisomers (Scheme 66).[123] The fluorination occurred selectively on the A ring, leaving the 7-hydroxy group unaffected. When a large excess of Yarovenko's reagent was used, double fluorination was observed. The reaction of

Scheme 67. Dehydroxyfluorination Using Ghosez's Reagent, $IF_5/Et_3N\cdot 3HF$, and SF_4



Scheme 68. Fluorination of Allylic Bromides



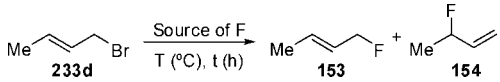
Brefeldin A (**224**) with an excess of 2-chloro-*N*,*N*-diethyl-1,1,2-trifluoroethanamine gave the difluoro derivative **225** as the major product (Scheme 66).[124]

Further examples of dehydroxyfluorination of allylic alcohols with Ghosez's reagent, *N*,*N*-diisopropyl-1-fluoro-2-methylpropenamine, $IF_5/Et_3N\cdot 3HF$, and SF_4 are shown in Scheme 67. While Ghosez's reagent favored the formation of the more substituted fluoride,[125] $IF_5/Et_3N\cdot 3HF$ led preferentially to the primary allylic fluoride.[126] SF_4 was not suitable for the fluorination of crotyl alcohol into allyl fluorides **156a** and **157a**, as butadiene, resulting from a competitive elimination, was obtained as the major product[7] (Scheme 67).

3.1.1.2. Fluorination of Halides, Activated Allylic Alcohols, and Sulfides. *3.1.1.2.1. Halides.* Tetraalkylammonium or metal fluorides are among the most common reagents used for the substitution of a halide for fluorine in the synthesis of allylic fluorides. 3-Bromo-1-propene (**233a**) was converted to allyl fluoride (**234**) using anhydrous TBAF at room temperature (Scheme 68).[127] Similar yields were obtained when TBAF was prepared in situ by heating a mixture of tetrabutylammonium bromide (TBAB) and an alkali-metal fluoride (CsF or KF).[128] $TBAF\cdot 3H_2O$ was successfully used in the synthesis of geranyl fluoride **227**.[129,130] Ethyl α-bromomethylacrylate (**233c**) could be successfully fluorinated with tetraethylammonium fluoride, affording ester **235** in a moderate 47% yield[131] (Scheme 68).

Due to the low solubility and nucleophilicity of metal fluorides in polar aprotic solvents, high temperatures and long reaction times are required. Various additives have been used

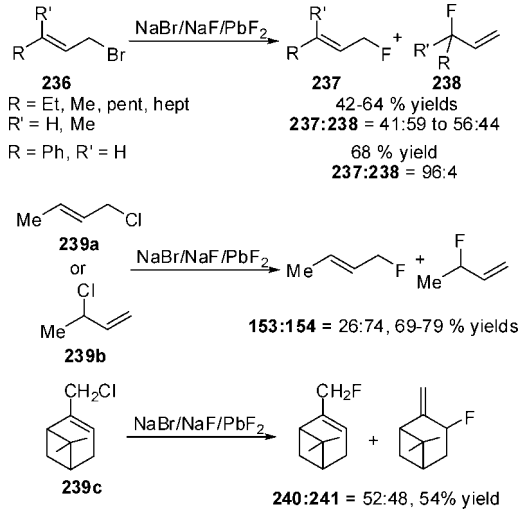
Table 1. Inorganic Fluorides as a Source of Fluorine



entry no.	source of F	T (°C)	t (h)	**153**:**154**	yield, %[a]
1	KF/CaF_2	90	38	98:2	83
2	KF/18-crown-6	90	48	97:3	86
3	PbF_2	90	24	32:68	37
4	$NaBr/PbF_2$	90	5	31:69	80

[a] Determined by GC.

Scheme 69. Fluorination of Allylic Halides Using PbF_2 Reported by Ichihara



to improve reactivity. The primary allylic fluoride **153** was obtained almost exclusively when KF was used as the fluoride source. PbF_2 led preferentially to the secondary allylic fluoride **154** (Table 1).[132,133]

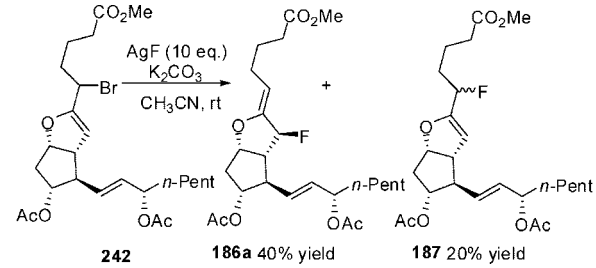
Ichihara et al. further investigated the scope and limitations of PbF_2 as a fluorinating reagent. They found that a NaBr/NaF/PbF_2 composite was an efficient reagent for the fluorination of allyl bromides and chlorides, the substitution occurring with significant allylic rearrangement. When a phenyl group was present in the starting material (R = Ph), the corresponding allyl fluoride was formed cleanly without transposition of the double bond (Scheme 69).[133]

The allylic rearrangement of allyl bromide **242** upon treatment with AgF, was exploited in the synthesis of the fluorinated prostacyclin analogue (7*S*)-7-fluoro-PGI_2 (**186a**). Upon treatment with AgF, the acetyl-protected 5-bromo-Δ^6-PGI_1 methyl ester **242** afforded a 2:1 mixture of the desired prostacyclin **186a** and 5-fluoro-Δ^6-PGI_1 derivative **187** in higher yields than observed for the corresponding dehydroxyfluorination reaction (Scheme 70).[108,109,134]

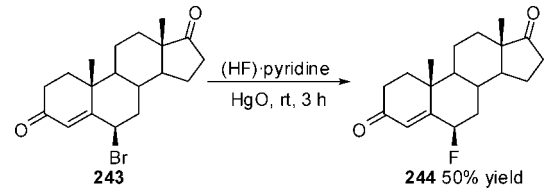
Mann and Pietrzak used Olah's reagent[135] in combination with mercury(II) oxide for the synthesis of the 6-fluoro analogue of 4-hydroxyandrost-4-ene-3,17-dione (**244**), a potential inhibitor of the biosynthesis of estrogens. When the same transformation was carried out in the presence of TBAF, the elimination product androsta-4,6-diene-3,17-dione was formed (Scheme 71).[136]

3.1.1.2.2. Activated Alcohols and Sulfides. Dollé and co-workers prepared ^{18}F and ^{19}F (*E*)-1-fluoro-4-tosyloxybut-2-ene (**246**), an intermediate in the synthesis of a highly selective dopamine transporter ligand.[137] Upon treatment

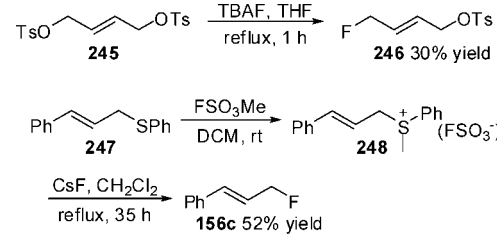
Scheme 70. Synthesis of Fluorinated Prostacyclin Analogues Using AgF Reported by Bannai



Scheme 71. Fluorination of Allylic Bromides using a Combination of Olah's Reagent and Hg(II) Oxide Reported by Mann and Pietrzak



Scheme 72. Fluorination of Allylic Tosylates and Sulfides



with TBAF, (*E*)-1,4-ditosyloxybut-2-ene (**245**) gave **246**, resulting from monosubstitution, in 30% yield (Scheme 72). In the presence of an activated K[^{18}F]F-Kryptofix222 complex, ^{18}F-labeled **246** was formed with radiochemical yields ranging from 30 to 50%. The fluorodesulfurization of sulfides has also been reported as an efficient methodology for the formation of allylic fluorides. Methylation of sulfide **247**, followed by substitution of the resulting sulfonium salt with CsF, gave **156c** in moderate yield (Scheme 72).[138]

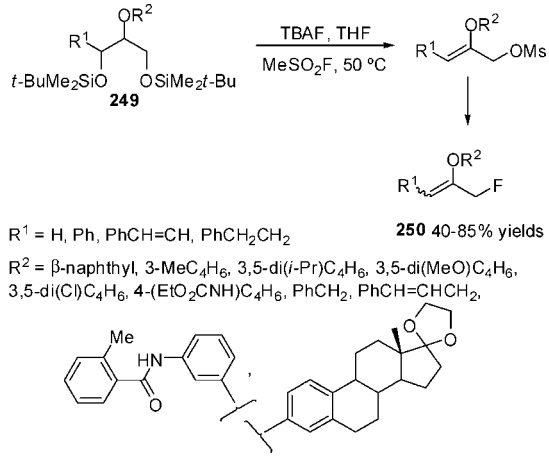
3.1.1.3. Cascade Elimination−Fluorination. The fluoroalkenylation of 1,2,3-triol derivatives was performed by reacting bis(siloxy)isopropyl ethers **249** with TBAF−$MeSO_2F$ in THF. The resulting allylic fluorides are masked α-fluorinated ketones.[139,140] The reaction proceeded through an intermediate allylic methanesulfonate, TBAF acting as a base and as a nucleophile (Scheme 73).[139] The 1,2,3-triol derivative *syn*-**251** led exclusively to fluoroolefin *Z*-**252**, whereas the anti diastereomer gave a mixture of (*Z*)- and (*E*)-fluoroolefins in a 1:1 ratio (Scheme 74).[140]

The scope and limitations of the cascade elimination−fluorination reaction was extended to carbamates **253** and ethers **255** (Scheme 75).[141] Magnusson and co-workers used this methodology for the preparation of the fluorinated disaccharide glycoside **258** (Scheme 76).[142]

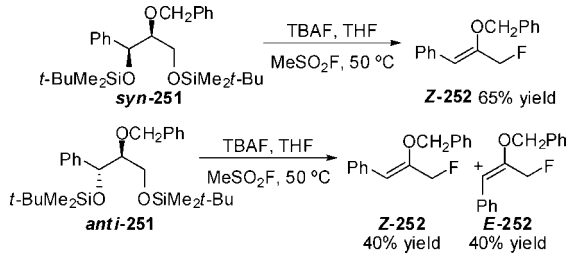
3.1.1.4. Ring Opening of Tertiary Cyclopropyl Silyl Ethers. The reaction of tertiary cyclopropyl silyl ethers with DAST is strongly substrate dependent, delivering a mixture of regiomeric allylic fluorides and/or the fluorinated cyclopropane[143–145] (Scheme 77).[143,144]

It was postulated that the mechanism for this transformation involves a cyclopropyl carbocation. The degree of stabilization of this cationic intermediate determines the product outcome of the reaction (Scheme 78).[143–145]

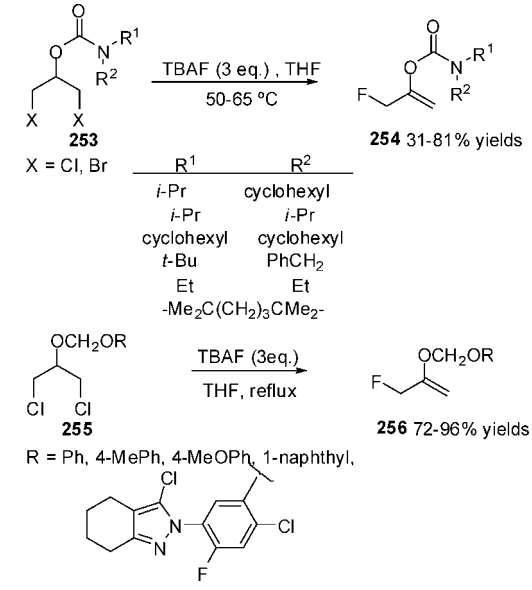
Scheme 73. Cascade Elimination−Fluorination Reported by Shimizu and Co-Workers



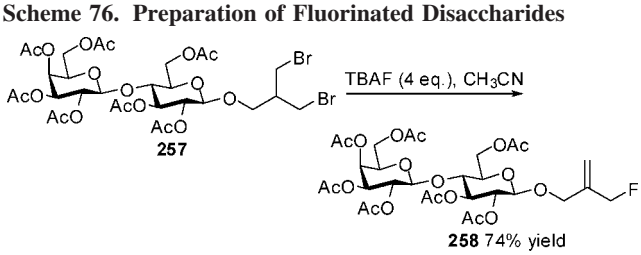
Scheme 74. Cascade Elimination−Fluorination of Syn and Anti Triol Derivatives



Scheme 75. Cascade Elimination−Fluorination of Carbamates and Acetals

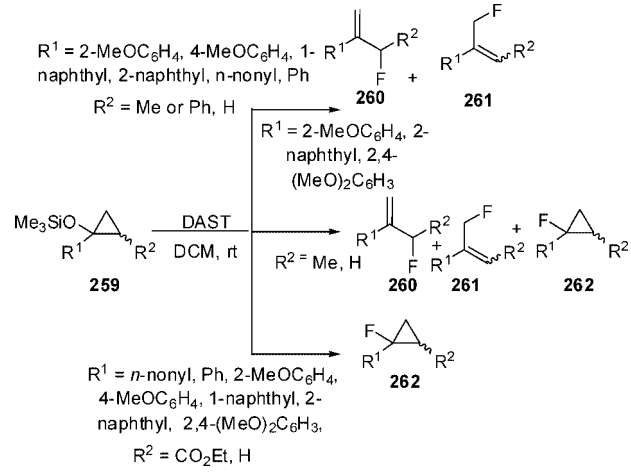


Scheme 76. Preparation of Fluorinated Disaccharides

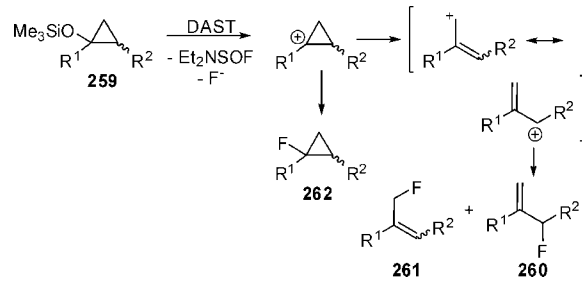


3.1.1.5. Miscellaneous. Other methodologies, such as the opening of an epoxide[146,147] or the reaction of an electron-rich diene with hypervalent iodoarene difluoride, have also been developed for the preparation of allylic fluorides. Davies and co-workers reported the opening of epoxide **263** in the presence of Olah's reagent to afford a mixture of epimeric fluorohydrins **264** and the regioisomer **265** in a moderate yield.[146] The reaction of activated dienes **266** with hypervalent iodoarene difluorides **267** gave the fluorinated β-isomer **268a** as the major product, although in very poor yields (Scheme 79).[148]

Scheme 77. Reaction of Cyclopropyl Silyl Ethers with DAST Reported by Kirihara and Co-Workers



Scheme 78. Postulated Mechanism of Fluorination of Cyclopropyl Silyl Ethers Reported by Kirihara and Co-Workers



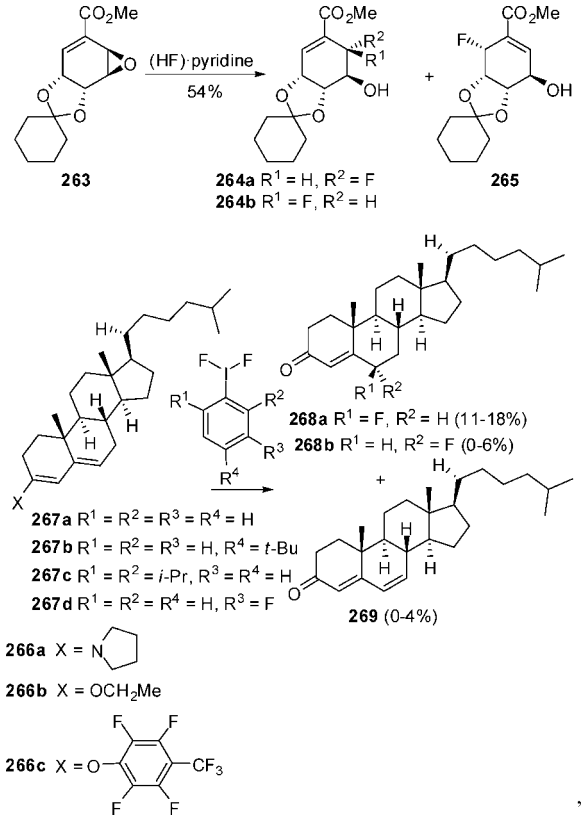
3.1.2. Electrophilic Fluorination

3.1.2.1. Fluorination of Alkenes. Fluorination of carvone **270** with acetyl hypofluorite occurred exclusively at the exocyclic double bond, the deactivated enone group remaining unaffected.[149] The mechanism of the reaction is likely to proceed via addition of AcOF on the double bond, followed by elimination of HOAc. In contrast to AcOF, *N*-F reagents are electrophilic sources of fluorine which do not require any specialist equipment and are easy to handle, air-stable solids. Treatment of the electron-rich enol ether **273** with *N*-fluoropyridinium triflate (**274a**) at room temperature furnished 1-methoxy-6-fluorocyclohexene (**275**) along with the major product of addition, **276**.[150,151] When the reaction was carried out at 60 °C, the desired allylic fluoride **275** was obtained exclusively (Scheme 80).[151]

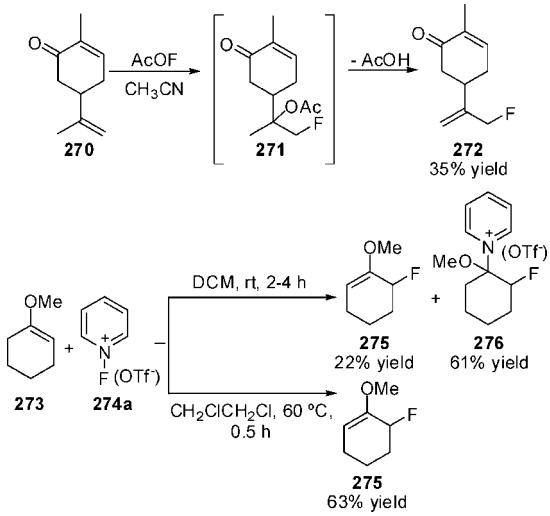
Fluorination of less activated olefins was possible using more reactive *N*-fluoropyridinium salts such as **274b**.[151,152] The use of a base[192] or a catalytic amount of ytterbium[152] was necessary to obtain the allyl fluorides (Scheme 81).

The electrophilic fluorination of electron-rich dienes **279** has been widely utilized in the synthesis of fluorinated steroids. More specifically, dienes featuring enamines, enol ethers, silyl enol ethers, and boron enolates were treated with

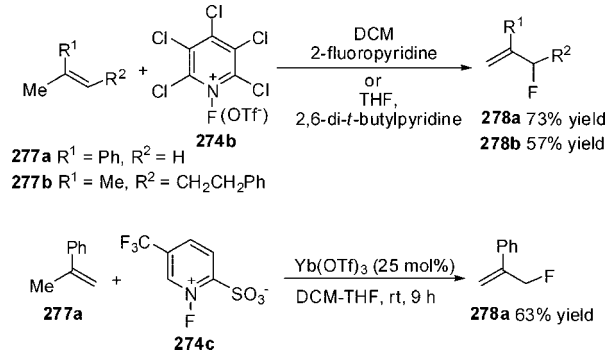
Scheme 79. Synthesis of Allylic Fluorides by Ring Opening of Epoxides



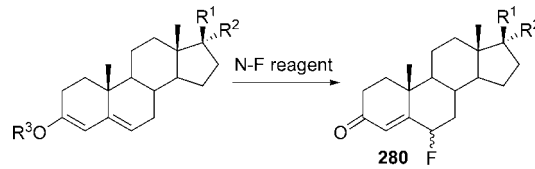
Scheme 80. Electrophilic Fluorination of Alkenes



Scheme 81. Electrophilic Fluorination of Alkenes Using *N*-Fluoropyridinium Salts

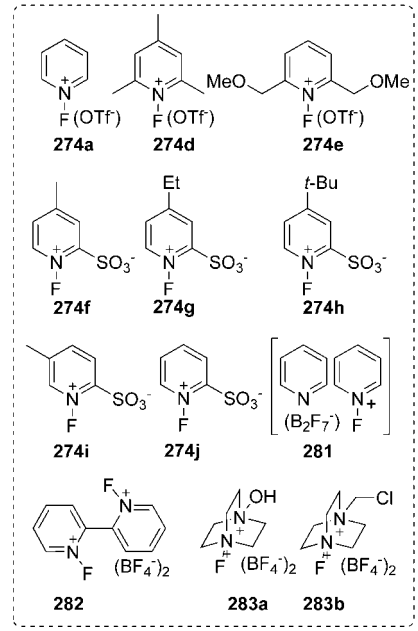


Scheme 82. Synthesis of Fluorinated Steroids by Electrophilic Fluorination



279a R^1 = OAc, COMe, $COCH_2OAc$, O; R^2 = H, O, OAc; R^3 = OAc; 28-96% yields; α:β 1:0 to 1:8.5

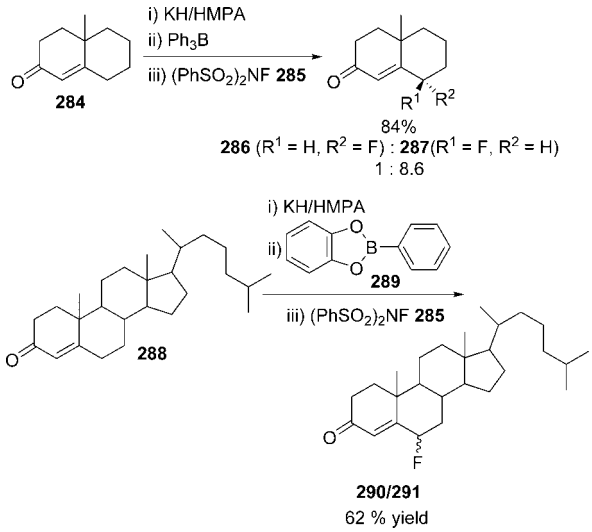
279b R^1 = OAc, OTMS, 1,5-dimethylhexyl; R^2 = H; R^3 = $SiMe_3$, $SiMe_2t$-Bu, $SiEt_3$, $Si(i\text{-}Pr)_3$; 24-93% yields, 6-F/4-F 1.3:1 to >99:1; α:β 2.4:1 to 1:5



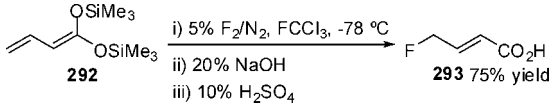
N-F fluorinating reagents in order to obtain the desired allylic fluorides. Electrophilic fluorination of dienol acetates were highly regioselective and tolerated a wide range of functionalities.[150,151,153–156] Several *N*-F fluorinating reagents, namely *N*-fluoropyridinium triflates **274a**,**d**,**e**,[150,151] *N*-fluoropyridinium pyridine heptafluorodiborate (**281**),[153] *N*,*N*′-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (**282**),[154] and *N*-fluoro DABCO derivatives **283a**[155] and **283b**,[156] were able to carry out the fluorination at the 6-position exclusively. In most cases treatment of dienol acetates with an electrophilic *N*-F fluorinating reagent afforded the corresponding allyl monofluorides as a mixture of the α and β diastereomers, with the β isomer being the major product. The use of **283a** (Accufluor) or **283b** (Selectfluor) as the source of fluorine gave the best yields.

The fluorination of conjugated silyl enol ethers were successfully performed with a range of different electrophilic fluorinating reagents, such as *N*-fluoropyridinium salts **274a**−**j** and compounds **281** and **282** (Scheme 82).[151,153,154,157,158] The regioselectivity of the fluorination increased with the steric bulk of the silyl group when *N*-fluoropyridinium salts were used as the fluorinated reagent.[157] The 6β-isomer was the main product when the reaction was carried out at room temperature and formation of the 6α-isomer was favored at higher temperatures.[158] Steroids featuring vinyl acetate moieties,[151,156] enol ethers,[151,155] have also been successfully fluorinated using various N−F reagents. A series of vinyl enamines furnished the corresponding vinylic fluoride rather than the desired allylic fluoride when treated with *N*-fluoropyridinium salts (Scheme 82).[154]

Scheme 83. Electrophilic Fluorination of Dienoxy Borates Reported By Poss and Shia



Scheme 84. Synthesis of 4-Fluorocrotonic Acid using Molecular Fluorine Reported by Purrington and Co-Workers



Poss and Shia performed direct fluorinations of potassium dienoxy borates generated in situ from the corresponding enones.[159] In an initial study, the enolate of enone **284** was prepared by deprotonation with KH and HMPA and treated with triphenylborane. The resulting enoxyborate was fluorinated with *N*-fluorobenzenesulfonimide (**285**; NFSI), yielding a 1:8.6 mixture of diastereomers α and *β*.[159] When the same conditions were applied to 4-cholesten-3-one (**288**), a lower α:*β* ratio of 1:1.5 was obtained. An increase in diastereoselectivity was observed when triphenylborane was replaced with borole **289** (Scheme 83).

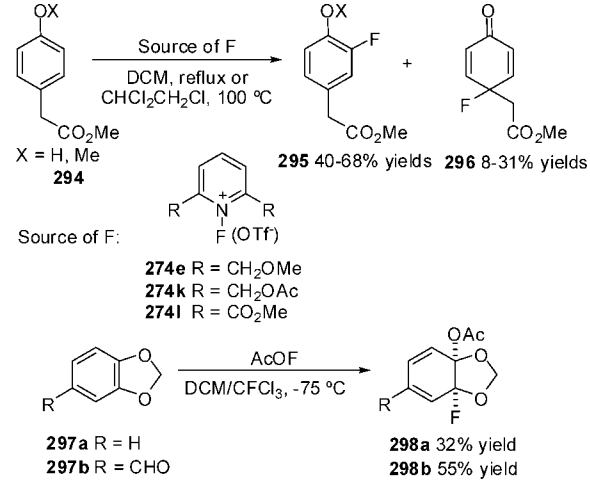
Purrington et al. reported the preparation of 4-fluorocrotonic acid (**293**) from silylated acetal **292** using molecular fluorine (Scheme 84).[160] The fluorination occurred selectively at the *γ*-position, as expected for the reaction of *O*-silylated dienolates with electrophiles.[161] This synthetic route leading to 4-fluorocrotonic acid in 75% yield was more efficient than the fluorination of methyl or ethyl 4-bromocrotonate.[162]

3.1.2.2. Fluorination of Aromatic Rings. Umemoto and co-workers described the formation of allylic monofluoride **296** as a minor product in the fluorination of electron-rich aromatic compounds **294** using *N*-fluoropyridinium triflate bearing two α substituents.[151] The major product was the fluoroaromatic **295**, resulting from fluorination at the ortho position followed by elimination to restore aromaticity. Allylic fluorides are formed upon fluorination at the para position, where elimination is disfavored. Rozen and co-workers explored the ability of AcOF to add in a syn fashion to an aromatic ring.[163] The allylic fluorides **298** were isolated in moderate yields, as elimination could not occur (Scheme 85).

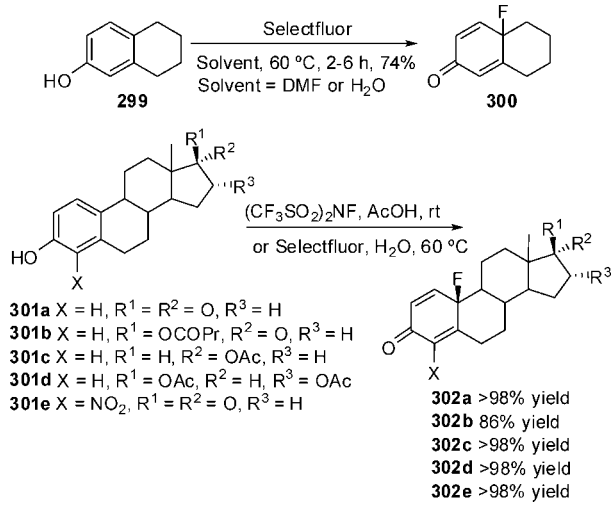
The electrophilic fluorination of phenol derivatives has proved to be a useful method for the preparation of fluorinated dienones **300** and **302** in excellent yields (Scheme 86).[164–166]

3.1.2.3. Fluorination of Carbonyl Compounds. Enantioenriched α-2-fluoroalk-3-enoic acid derivatives can be

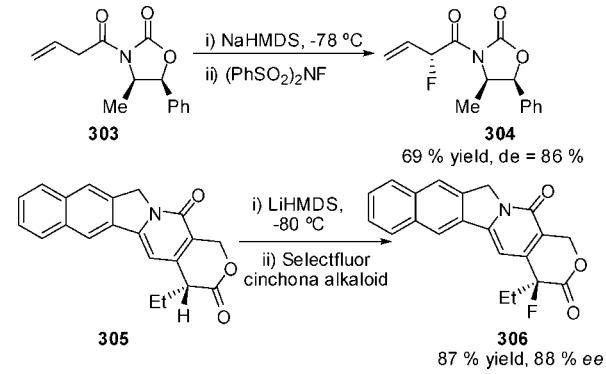
Scheme 85. Fluorination of Aromatics



Scheme 86. Electrophilic Fluorination of Phenol Derivatives



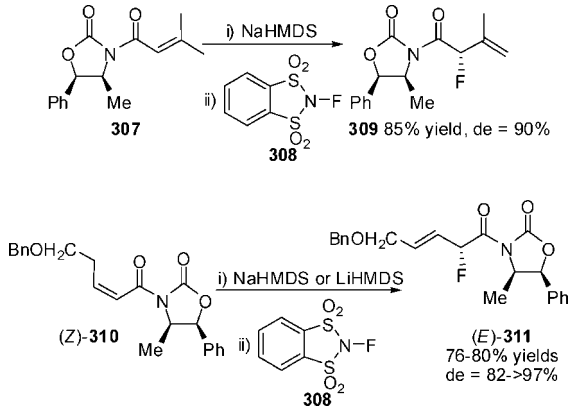
Scheme 87. Diastereoselective and Enantioselective Electrophilic Fluorination α to Carbonyl Groups



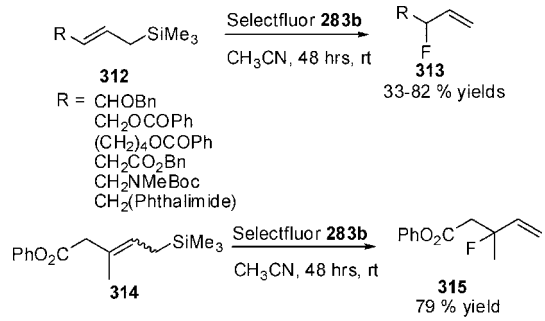
synthesized either by deprotonation α to a carbonyl group, followed by treatment with an electrophilic source of fluorine, or through deconjugative fluorination of chiral dienolates.[167] Shibata et al. successfully prepared such enantiopure allylic fluorides by fluorination of chiral enolates or by treatment of prochiral enolates with enantioenriched fluorinating agents derived from cinchona alkaloids[168] (Scheme 87).

Davis and Han reported that the chiral imide enolate derived from compound **307** in the presence of the fluorinating reagent **308** led to the formation of the allylic fluoride **309** by a diastereoselective deconjugative electrophilic fluorination.[169] A similar procedure was applied to access **311**,

Scheme 88. Diastereoselective Deconjugative Electrophilic Fluorination Reported by Davis and Han



Scheme 89. Sequential Cross-Metathesis Electrophilic Fluorodesilylation Reported by Gouverneur and Co-Workers



an intermediate in the synthesis of fluorinated carbohydrates.[170,171] Chiral lithium or sodium dienolate derived from the *Z*-α,β-unsaturated imide **310** yielded the allylic fluoride (*E*)-**311** in good yield and with a high level of stereocontrol (Scheme 88).[171]

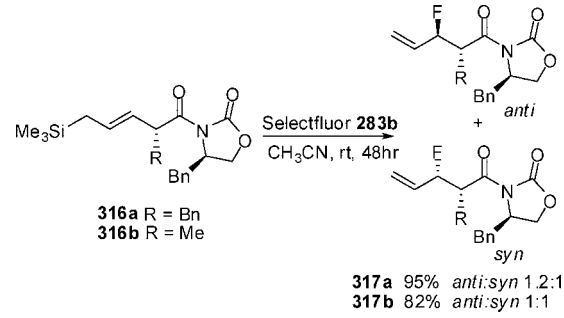
3.1.2.4. Electrophilic Fluorodesilylation. Organosilanes featuring the silyl group adjacent to a π system have emerged as valuable precursors for the preparation of a range of organofluorine compounds. Gouverneur and co-workers developed the concept of electrophilic fluorodesilylation for the synthesis of allylic fluorides. The reaction relies on the ability of the carbon−silicon bond to stabilize a carbocation in the β position, with a $\sigma \rightarrow \pi$ stabilization of the developing carbocation of approximately 30 kcal mol^{-1}. The mechanism of the reaction is believed to be S_E2', with the fluorine electrophile adding in the γ position and concomitant full transposition of the double bond.[172]

Racemic allylsilanes, prepared by cross-metathesis of various olefins with allyltrimethylsilane, were treated with the commercially available *N*-F fluorinating reagent Selectfluor in acetonitrile, to furnish the corresponding allylic fluoride (Scheme 89).[173]

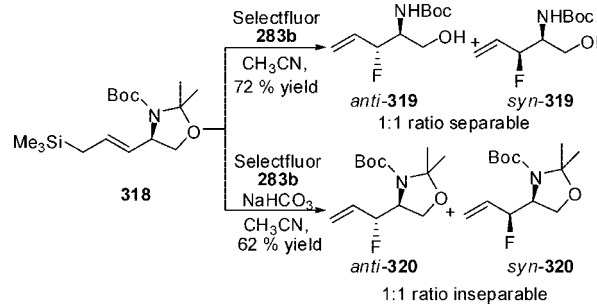
The electrophilic fluorodesilylation of the enantiopure allylsilane **316** was found to proceed smoothly to furnish the corresponding allylic fluorides *anti*-**317** and *syn*-**317** in a roughly 1:1 mixture. The diastereomers could be separated by careful silica gel chromatography (Scheme 90).[174]

The methodology was applied to the synthesis of an enantiopure fluorinated analogue of the signaling lipid sphingosine. The allylsilane **318** was treated with Selectfluor to afford the product of electrophilic fluorodesilylation. Notably, if the additive $NaHCO_3$ was not used, then concomitant partial deprotection occurred. In both cases, the fluorination occurred to give a 1:1 mixture of diastereomers;

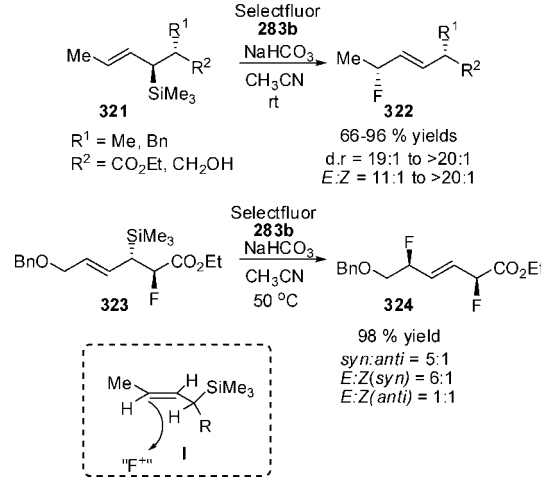
Scheme 90. Electrophilic Fluorodesilylation of Enantiopure Allylsilanes Reported by Gouverneur and Co-Workers



Scheme 91. Preparation of a Fluorinated Sphingosine Analogue by Electrophilic Fluorodesilylation Reported by Gouverneur and Co-Workers



Scheme 92. Diastereoselective Electrophilic Fluorodesilylation Reported by Gouverneur and Co-Workers

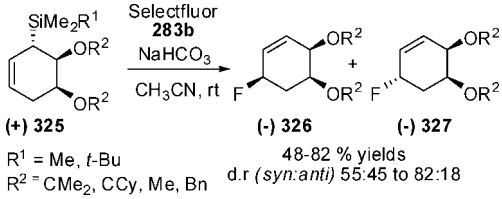


however, only *syn*- and *anti*-**319** could be separated by silica gel chromatography (Scheme 91).[175]

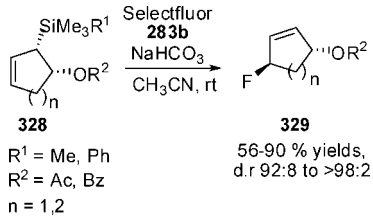
The authors discovered that allylsilanes featuring the silyl group on a stereogenic center underwent electrophilic fluorodesilylation with high levels of diastereocontrol. Crotylsilanes **321** furnished (*E*)-allylic fluorides **322** mostly as single diastereomers, with the fluorine preferentially approaching anti with respect to the silyl group. The stereochemical outcome can be rationalized by considering an anti approach of Selectfluor upon reactive conformer **I**, in which allylic 1,3-strain in minimized. This methodology was applied for the synthesis of the unusual bis allylic fluoride **324**, albeit with a lower level of selectivity (Scheme 92).[176]

The level of diastereocontrol upon electrophilic fluorodesilylation of enantioenriched cyclic allylsilanes was found to be dependent upon the relative stereochemistry of the allylsilane. This study was carried out in the context of the

Scheme 93. Electrophilic Fluorodesilylation of Anti, Syn Enantioenriched Cyclic Allylsilanes Reported by Gouverneur and Co-Workers



Scheme 94. Diastereoselective Electrophilic Fluorodesilylation of Syn Enantioenriched Cyclic Allylsilanes Reported by Gouverneur and Co-Workers

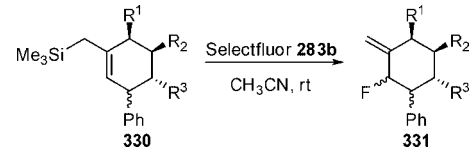


synthesis of enantioenriched fluorinated cyclitols. The anti, syn cyclic allylsilanes, prepared by enantioselective desymmetrization of the corresponding silylated cyclohexadienes, were subjected to electrophilic fluorodesilylation. The enantioenriched cyclic allylic fluorides were formed with the highest levels of diastereocontrol when the diol protecting group was either methoxy or benzyloxy, with the diastereomeric ratio reaching up to 82:18. In all cases Selectfluor preferentially approached anti with respect to the silyl group (Scheme 93).[177]

The electrophilic fluorodesilylation of enantioenriched five- and six-membered syn cyclic allylsilanes **328** proceeded with an excellent level of diastereocontrol. The syn allylsilanes, prepared by a tandem silylallylboration−ring-closing metathesis approach, were treated with Selectfluor, in the presence of $NaHCO_3$, to form the corresponding enantioenriched cyclic allylic fluorides **329**, in most cases, as single diastereomers. It was observed that fluorination preferentially occurred anti with respect to the silyl stereodirecting group (Scheme 94).[178]

Asymmetric Diels−Alder reactions of silylated dienes, followed by highly diastereoselective electrophilic fluorodesilylation, represents a fundamentally different and general approach to the preparation of enantioenriched, highly functionalized fluorinated carbocycles, featuring an exocyclic double bond. Electrophilic fluorodesilylation of the cycloadducts proceeded in good yield (60−91%) and, in most cases, a good level of diastereocontrol with fluorination occurring preferentially anti with respect to the phenyl group. However, when the cycloadducts featured a methyl group in the 5-position (**330e**), a reversal of selectivity was observed, with the fluorination occurring preferentially syn with respect to the phenyl group (Table 2). This result was rationalized by considering two possible conformations reacting via an S_E2' mechanism. In conformation **A**, with the phenyl group in a pseudoaxial position, Selectfluor undergoes a preferential axial approach anti to the phenyl group, followed by a ring flip to give the observed product. Conformation **B** is likely to prevail when there is an addition of a methyl group in the 5-position, in order to minimize $\mathbf{A}^{1,2}$ strain. An axial approach of Selectfluor in this case occurs syn to the now pseudoequatorial phenyl group (Chart 9).[179]

Table 2. Diastereoselective Electrophilic Fluorodesilylation of Silylated Cycloadducts Reported by Gouverneur and Co-Workers



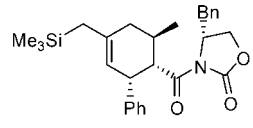
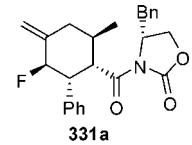
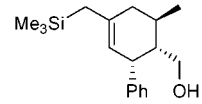
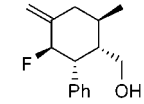
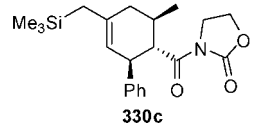
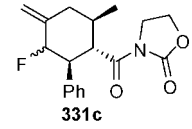
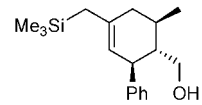
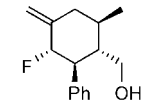
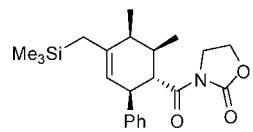
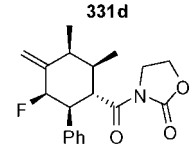
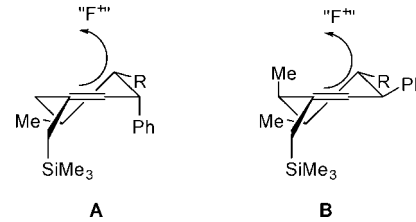
Substrate	Product	d.r	Yield (%)
 **330a**	 **331a**	>20:1	75
 **330b**	 **331b**	9:1	69
 **330c**	 **331c**	1:1	83
 **330d**	 **331d**	5:1	60
 **330e**	 **331e**	6:1	91

Chart 9. Axial Approach of Selectfluor Postulated by Gouverneur and Co-Workers

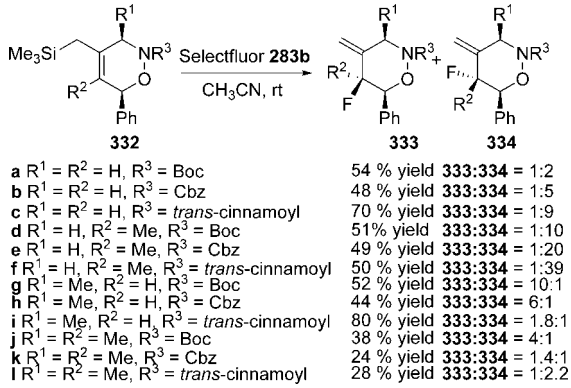


For the endo adducts (**330a**,**b**), the fluorination is more selective for the substrate featuring the chiral auxiliary than for the corresponding substrate featuring the primary alcohol. However, the reverse is true for the exo adducts (**330c**,**d**), for which the fluorination is substantially more diastereoselective for the substrate featuring the primary hydroxyl group.[179]

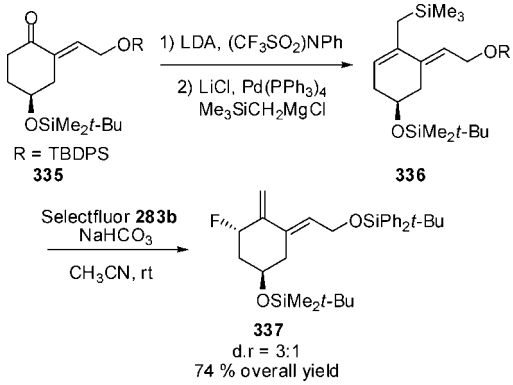
Fluorinated N,O-heterocycles **333** and **334** were synthesized by electrophilic fluorodesilylation of the corresponding allylsilanes, formed by a nitroso Diels−Alder reaction. It was found that fluorination of the cycloadducts **332a**−**f** favored the anti isomer **334**. When an additional methyl substituent was present at the 3-position, **332g**−**k**, the syn isomer **333** was favored (Scheme 95).[180]

The six-membered fluorinated carbocyclic motif, featuring an exocyclic double bond, is found in the A-ring fragment of a fluorinated analogue of vitamin D_3. The electrophilic

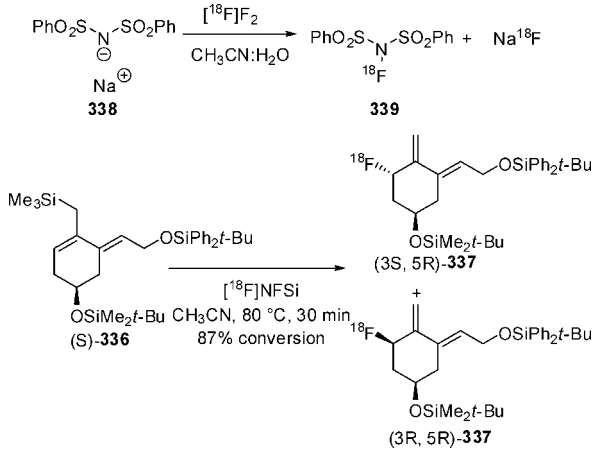
Scheme 95. Electrophilic Fluorodesilylation of N,O-Heterocycles Reported by Gouverneur and Co-Workers



Scheme 96. Synthesis of the A-Ring Fragment of a Fluorinated Analogue of Vitamin D Reported by Gouverneur and Co-Workers



Scheme 97. Synthesis of an ^{18}F-Labeled Vitamin D Analogue Reported by Gouverneur and Co-Workers

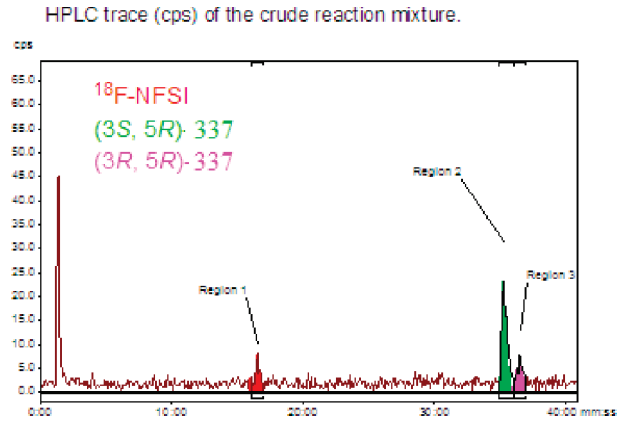


fluorodesilylation reaction was used as the key step in the synthesis of the key A-ring intermediate **337**, used in the synthesis of 1α-fluoro vitamin D_3 (Scheme 96).[181]

The key fluorinated intermediate, **337**, was also labeled with ^{18}F using [^{18}F]-*N*-fluorobenzenesulfonimide (**339**; [^{18}F]NFSi). Treatment of the enantioenriched allylsilane **336** with [^{18}F]NFSI in acetonitrile at 80 °C for 30 min gave the radiolabeled diastereomers (3*S*,5*R*)-**337** and (3*R*,5*R*)-**337** (Scheme 97 and Chart 10).[182]

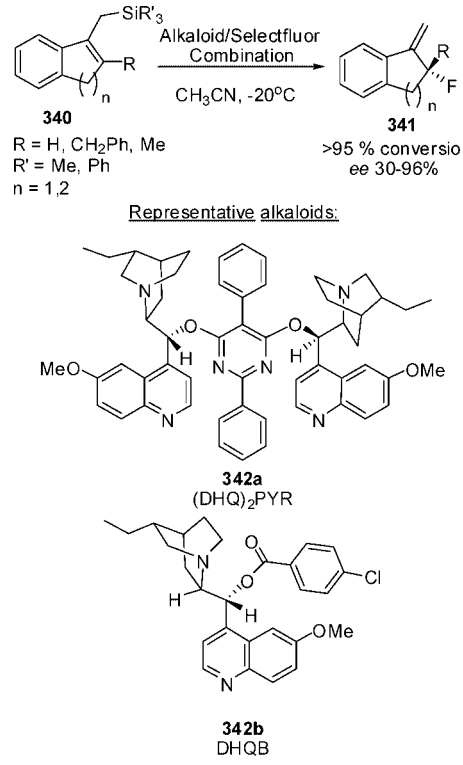
For the preparation of enantiopure allylic fluorides an alternative strategy to diastereoselective electrophilic fluorodesilylation of nonracemic allylsilanes is the use of a reagent-based asymmetric fluorination. The enantioselective

Chart 10. Radio-HPLC Trace of an ^{18}F-Labeled Vitamin D Analogue Reported by Gouverneur and Co-Workers[a]



[a] Reprinted with permission from ref 182. Copyright Royal Society of Chemistry 2007.

Scheme 98. Enantioselective Electrophilic Fluorodesilylation using Selectfluor−Cinchona Alkaloid Reported by Gouverneur and Co-Workers

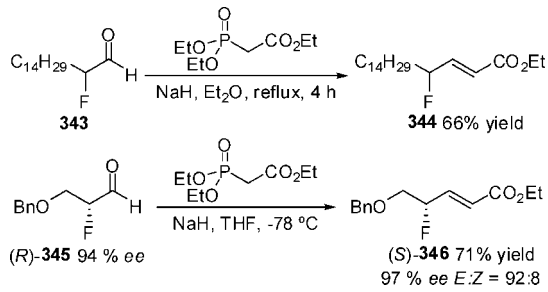


electrophilic fluorodesilylation of prochiral allylsilanes **340** was performed using a Selectfluor−cinchona alkaloid combination. Of the commercially available cinchona alkaloids screened, the F-reagent derived from $(DHQ)_2PYR$ (**342a**) was found to be superior, giving enantiomeric excesses of up to 96%. The enantiomeric excesses were found to be higher for substrates derived from indanones ($n = 1$) than from tetralones ($n = 2$), and for the more heavily substituted substrates (e.g., R = Bn) (Scheme 98).[183]

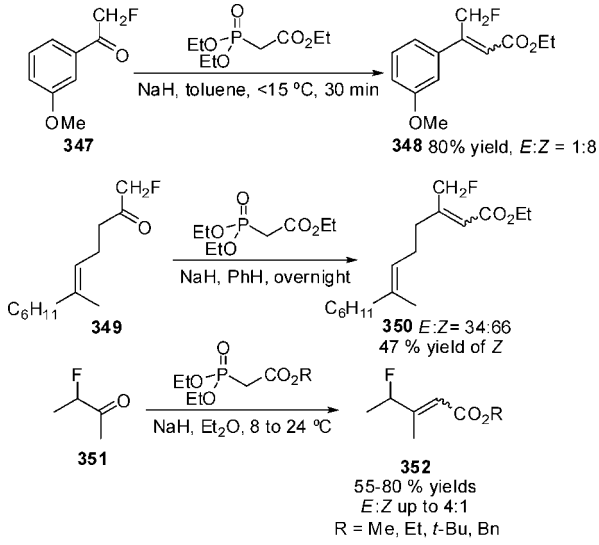
3.1.3. Fluorinated Building Blocks

3.1.3.1. Wittig-Type Reaction. The Wittig olefination of α-fluoroaldehydes or ketones has been successfully applied for the preparation of allylic fluorides. Under Horner−Wadsworth−Emmons conditions, α-fluoroaldehydes af-

Scheme 99. Horner-Wadsworth-Emmons Reactions of α-Fluorinated Aldehydes



Scheme 100. Horner−Wadsworth−Emmons Reactions of α-Fluorinated Ketones



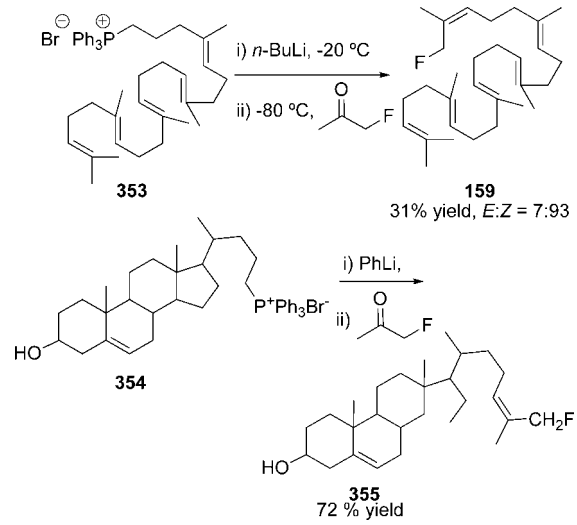
forded the corresponding (*E*)-α,β-unsaturated esters. Oldendorf and Haufe reported the synthesis of fluorinated ester **344** with moderate yield and good selectivity when aldehyde **343** was treated with triethylphosphonium acetate and sodium hydride.[184] Davis and co-workers described the preparation of nonracemic allylic fluoride (*S*)-**346** as a 92:8 *E*:*Z* mixture, in good yield, relying on a Horner−Wadsworth−Emmons condensation of enantiopure α-fluoroaldehyde (*R*)-**345** (Scheme 99).[185]

The olefination of several α-fluoroketones with different substitution patterns and the influence of their structure over the *E*:*Z* selectivity is illustrated in Scheme 100. Reaction of α-fluoro-3-methoxyacetophenone (**347**) with NaH/triethyl phosphonoacetate gave the allylic fluoride **348** in a 1:8 *E*:*Z* ratio.[186] Fluoroketone **349** afforded ester **350**, an intermediate in the synthesis of 13-fluorofarnesyl diphosphate, in a 1:2 *E*:*Z* mixture.[187] However, when 3-fluorobutan-2-one (**351**) was used as the substrate, the *E*-allylic fluoride **352** was the major product, independent of the R group (Scheme 100).[188]

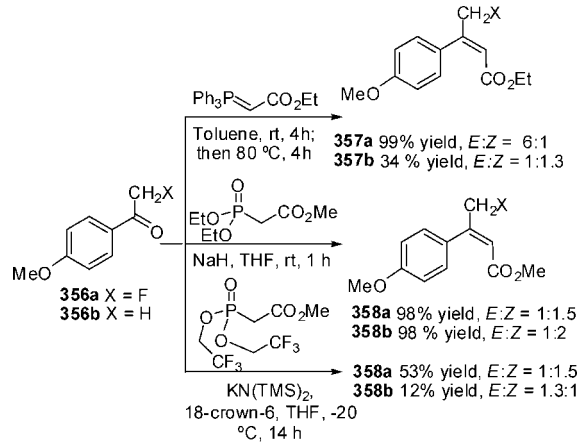
The treatment of triphenylphosphonium bromide **353** with base and the reaction of the resulting ylide with fluoroacetone gave allylic fluoride **159** as a 7:93 *E*:*Z* mixture. Phosphonium salt **354** served as a precursor for 26-fluorodesmosterol **355** (Scheme 101).[189−191]

Kakinuma and collaborators compared the olefination of fluorinated and nonfluorinated alkyl aryl ketones. The reaction of α-fluoroketone **356a** with an α-carbonyl-stabilized phosphorus ylide afforded allylic fluoride **357a** as a 6:1 *E*:*Z* mixture. Ester (*Z*)-**358a** was formed as the major product when either triethylphosphonium acetate or Still's fluorinated phosphonate anion were used. The nonfluorinated

Scheme 101. Wittig Reactions of Fluoroacetone



Scheme 102. Horner−Wadsworth−Emmons Reactions of Fluorinated and Nonfluorinated Alkyl Aryl Ketones Reported by Kakinuma and Co-Workers



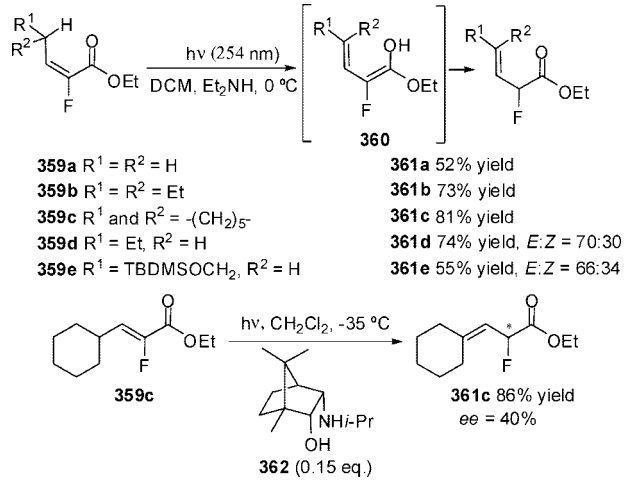
ketone **356b** preferentially gave the *Z* isomers under the same reaction conditions, albeit with longer reaction times (Scheme 102).[192]

3.1.3.2. Rearrangements and Isomerizations. *3.1.3.2.1. Vinyl Fluorides.* Certain vinyl fluorides can rearrange into allylic fluorides via photodeconjugation or Claisen rearrangements. Upon irradiation at 254 nm and in the presence of a base, α-fluoro-α,β-unsaturated esters **359** underwent photodeconjugation to give α-fluoro-β,γ-unsaturated esters **361** (Scheme 103).[193] This methodology was successfully applied for the preparation of enantioenriched ester **361c** when chiral aminobornanol **362** was used as a chiral base. In the presence of excess triethyl orthoacetate and catalytic amounts of propionic acid, allylic alcohol **363** underwent a [3,3]-sigmatropic Claisen rearrangement to afford the γ,δ-unsaturated tertiary fluoro ethyl ester **365** with excellent transfer of chirality (Scheme 104).[194]

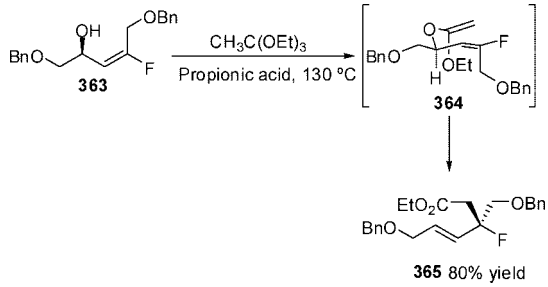
3.1.3.2.2. Cyclic Dienes. The irradiation of cyclic dienes **366** was used as an alternative approach to the direct fluorination with DAST[114] in the synthesis of 1α-fluorovitamin D_3 analogues **367**. Irradiation of the dienes **366** allowed for the regio- and stereoselective introduction of fluorine at the 1α-position, but only in poor yields (Scheme 105).[195,196]

3.1.3.3. Elimination. *3.1.3.3.1. Opening of Epoxides.* Treatment of epoxide **368** with a Grignard reagent, prepared in situ from ethylmagnesium chloride and lithium TMP,

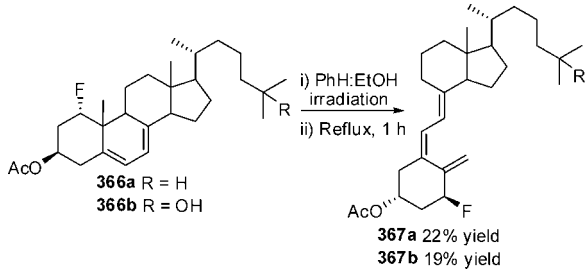
Scheme 103. Rearrangement of Vinylic to Allylic Fluorides by Photodeconjugation



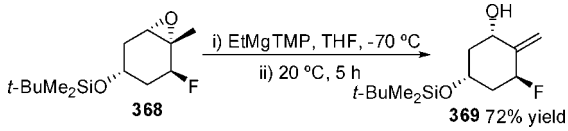
Scheme 104. Vinylic to Allylic Fluorides by Johnson−Claisen Rearrangement



Scheme 105. Synthesis of Allylic Fluorides by Irradiation of Cyclic Dienes Reported by Ohshima and Co-Workers



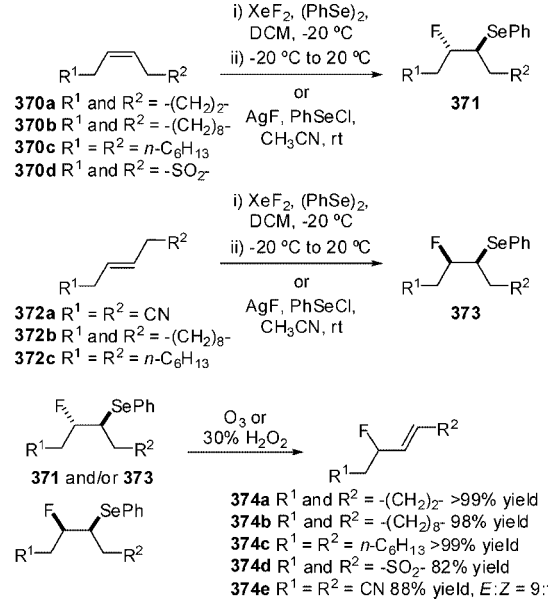
Scheme 106. Synthesis of a Precursor to a Fluorinated Analogue of Vitamin D Opening an Epoxide Reported by Barbier and Co-Workers



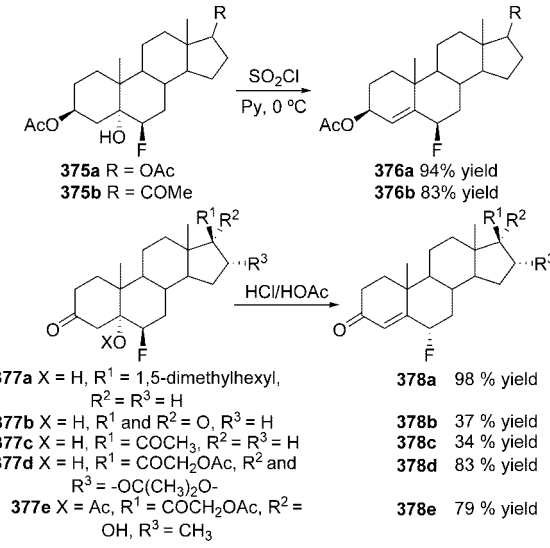
furnished allylic fluoride **369**, a precursor of fluorinated vitamin D, in 72% yield.[197] This is in contrast to the thermal isomerization of monofluorocyclopropanes, which furnish *trans*- and *cis*-1-fluoropropenes rather than the corresponding allylic fluorides (Scheme 106).[198]

3.1.3.3.2. Oxidative Deselenylation. McCarthy and Uneyama's groups developed a sequential fluoroselenylation−oxidative deselenylation procedure for the preparation of allylic fluorides.[199,200] Trans addition of phenylselenyl fluoride[201] (formed in situ) to cyclic or internal olefins (*Z*)-**370** and (*E*)-**372** provided β-fluorophenylselenides **371** and **373**, respectively. Upon treatment with ozone[202,203] or 30% H_2O_2,[204] syn elimination of the corresponding selenoxides furnished

Scheme 107. Oxidative Deselenylation



Scheme 108. Dehydration of 6β-Fluorohydrins under Acidic Conditions

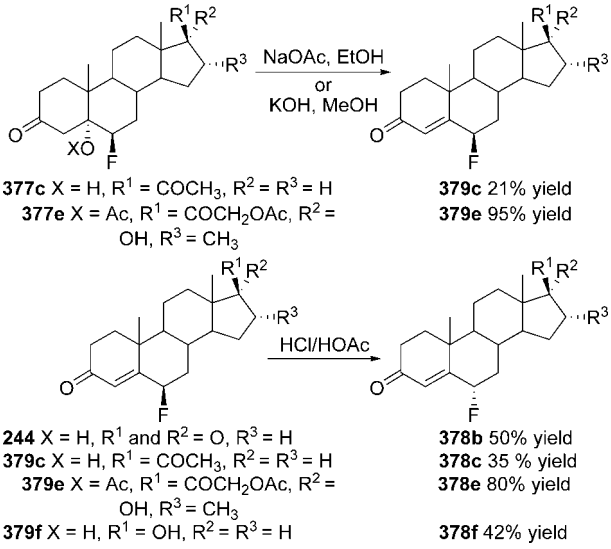


the desired allylic fluorides **374** in good to excellent yields[199,200] (Scheme 107). Regioselective elimination was also observed in the deselenylation of β-hydroxyselenides,[202,204] but β-chloroselenides gave mixtures of both allylic and vinylic products.[205,206]

3.1.3.3.3. Dehydration. The dehydration of 6β-fluorohydrins **375** in the presence of thionyl chloride afforded 6β-fluoro esters **376** in good yields (Scheme 108).[207] The 6β-fluorohydrins **377** also underwent dehydration with anhydrous hydrogen chloride in acetic acid to yield the corresponding 6α-fluoroepimers **378**.[207–209] The fact that β-hydroxyketone **377c** and keto ester **377e** gave the 6β-fluoroepimers **379c**,**e**, when treated under basic conditions, led the authors to postulate that epimerization of the fluorinated carbon occurred during the acid-catalyzed dehydration (Scheme 109). This theory was corroborated when 6β-fluoro allylic compounds **244** and **379c**,**e**,**f** were treated with hydrogen chloride in acetic acid to give the corresponding 6α-fluoroepimers.

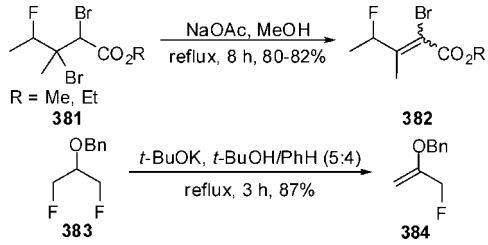
3.1.3.3.4. Dehydrohalogenation. The dehydrohalogenation of dihalo compounds has also been used for the preparation of allylic monofluorides. Refluxing the dibromo compound

Scheme 109. Dehydration of 6β-Fluorohydrins

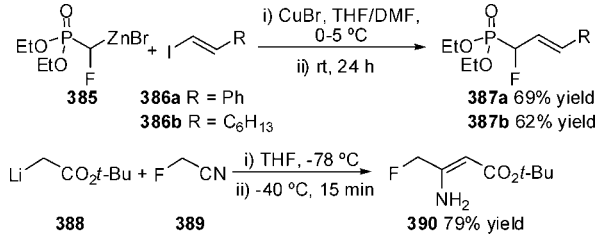


377c X = H, R^1 = $COCH_3$, R^2 = R^3 = H — **379c** 21% yield
377e X = Ac, R^1 = $COCH_2OAc$, R^2 = OH, R^3 = CH_3 — **379e** 95% yield
244 X = H, R^1 and R^2 = O, R^3 = H — **378b** 50% yield
379c X = H, R^1 = $COCH_3$, R^2 = R^3 = H — **378c** 35 % yield
379e X = Ac, R^1 = $COCH_2OAc$, R^2 = OH, R^3 = CH_3 — **378e** 80% yield
379f X = H, R^1 = OH, R^2 = R^3 = H — **378f** 42% yield

Scheme 110. Dehydrohalogenation



Scheme 111. Reactivity of Fluorinated Organocuprates and Fluorinated Cyanides



381 and difluoro compound **383**, in the presence of a base, afforded allyl monofluorides **382**[188] and **384**,[210] respectively, in good yields (Scheme 110).

3.1.3.4. Miscellaneous. α-Fluorophosphonate organocuprate, freshly prepared via transmetalation of the zinc reagent **385** with CuBr, reacted with vinyl iodides **386** to give (α-fluoroallyl)phosphonate esters **387a**,**b** in moderate yields.[52] 1,2-Addition of organolithium **388** to the nitrile group of **389** yielded *tert*-butyl 3-amino-4-fluoro-2-butenoate (**390**), a direct precursor of 3-amino-4-fluorobutanoic acid (a known inhibitor of GABA transaminase)[211] (Scheme 111).

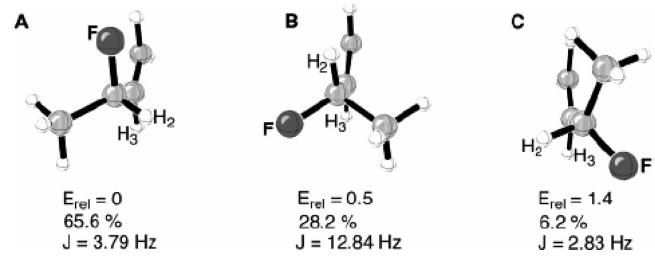
Allylic fluorides can be prepared by reduction of propargylic fluorides, and this chemistry is discussed in section 2.

3.2. Reactivity

3.2.1. Cycloadditions

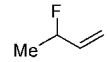
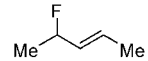
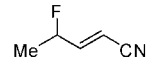
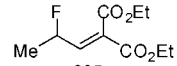
Allylic fluorides are viable dienophiles for cycloaddition reactions. Grée and Houk investigated, experimentally and theoretically, the selectivity of Diels−Alder reactions of allylic fluorides with 2,3-dimethyl-1,3-butadiene. The authors performed theoretical predictions of selectivity on the basis of transition-state modeling, which was in good agreement with experimental observations.

Chart 11. B3LYP/6-31G* Optimized Geometries of 3-Fluoro-1-butene[a]



[a] Energies are in kcal/mol; populations were calculated using the Boltzmann distribution at 298 K; coupling constants for H2−H3 were calculated using the Karplus relationship. Reprinted with permission from ref 94. Copyright American Chemical Society 2001.

Table 3. Calculated and Experimentally Measured Coupling Constants of Allylic Fluorides Reported by Grée and Houk

Structure	Measured J_{HH} (Hz)	E_{rel} (kcal/mol) F eclipsed H eclipsed Me eclipsed	Calculated J_{HH}
 **392**	6.4	0.0 0.5 1.4	6.3
 **393**	6.7	0.4 0.0 1.5	6.1
 **394**	3.5	0 1.8 2.5	4.1
 **395**	6.6	1.2; 1.2 0.0 ---	9.3

Ground-state conformation studies on a series of representative acyclic allylic fluorides showed that there was a preference for the fluorine to adopt a position in which it is eclipsed with the double bond. Compounds featuring an electron-withdrawing group at the β position showed an even greater preference for the fluorine to be eclipsed (Chart 11).[97]

Coupling constants, *J*, which were calculated using the Karplus relationship, were in good agreement with measured values (Table 3).

The allylic fluorides were heated at 60 °C with 2,3-dimethyl-1,3-butadiene to give the corresponding cycloadducts with varying degrees of selectivity (Table 4).

The Diels−Alder reaction of 3-fluoro-1-butene and butadiene was used as a model for theoretical calculations. It was found that the transition state of lowest energy positioned the fluorine in the inside position and the methyl anti, in accordance with the experimental results (Chart 12).

Bernardi et al. performed 1,3-dipolar cycloadditions with allylic fluorides to access fluorinated isoxazolidine and amino polyols.[212] Grée and Houk investigated the selectivity of nitrile oxide cycloadditions with chiral allylic fluorides.[213] 1,3-Dipolar cycloadditions of three representative allylic fluorides and in situ generated propionitrile oxide, formed a mixture of regio- and diastereomers. For the dipolarophile **403**, a trace amount of the product **404d** resulting from a Michael addition was also observed (Scheme 112).

3-Fluoro-1-butene was used to model the transition state of these reactions. Twelve possible transition-state structures

Table 4. Diels−Alder Reactions of Allylic Fluorides with 2,3-Dimethyl-1,3-butadiene Reported by Grée and Houk

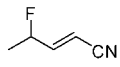
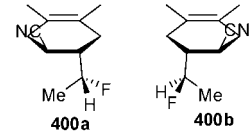
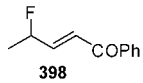
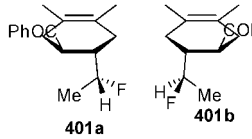
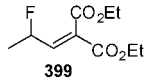
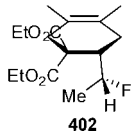
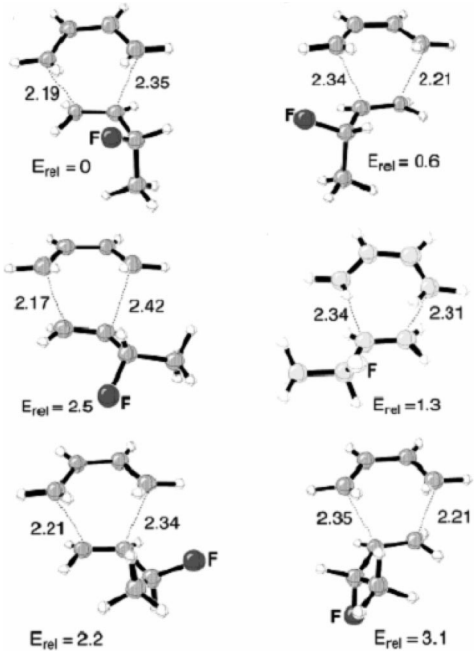
Diene	Dienophile	Products	Ratio
	 **397**	 **400a** **400b**	50:50
 **396**	 **398**	 **401a** **401b**	76:24
	 **399**	 **402**	100:0

Chart 12. B3LYP/6-31G* TS for the Reaction of Butadiene with 3-Fluorobutene. [a]



[a] Reprinted with permission from ref 97. Copyright American Chemical Society 2001.

were identified: two possible regioisomers, *Re* or *Si* face attack on the alkene, and three staggered structures. It was found that the selectivity of the 5-substituted regioisomer is governed by the fluorine adopting the favorable inside position, with the alkyl group anti with respect to the newly forming bond (Chart 13).[213]

For the transition states of the reactions detailed in this section, the allylic fluorine substituent sits preferentially in the inside position, rather than the outside, or the anti, position. This observation is consistent with the well-established inside *alkoxy effect*. In the case of the 1,3-dipolar cycloadditions, the fluorine prefers to sit in the inside position over the outside in order to minimize lone-pair−lone-pair electron repulsions with the nitrile oxide oxygen. The anti position is least favorable, due to electron withdrawal

Scheme 112. 1,3-Dipolar Cycloadditions of Allylic Fluorides Reported by Grée and Houk

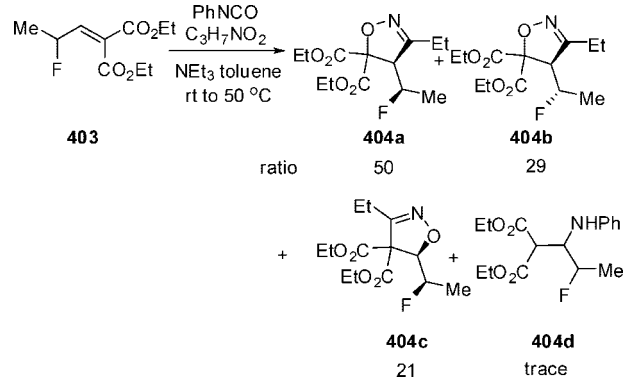
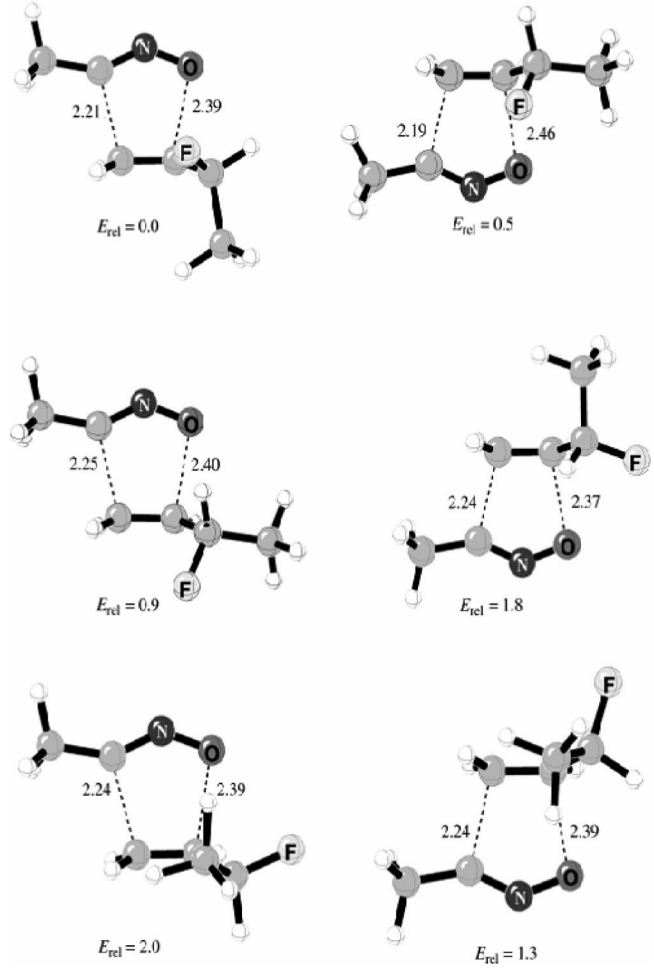


Chart 13. B3LYP/6-31G(d) Transition States for the Cycloaddition of Acetonitrile Oxide with (*S*)-3-Fluorobutene Leading to the 5-Substituted 2-Isoxazoline[a]



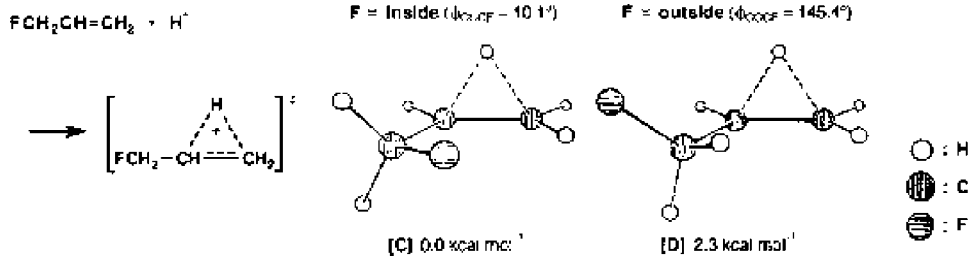
[a] Relative energies are given in kcal mol^{-1}. Distances are in angstroms. Reprinted with permission from ref 213. Copyright Wiley 2003.

resulting from an unfavorable $\sigma^*_{C-F}-\pi$ overlap in an already electron-deficient transition state.[213]

3.2.2. Epoxidation

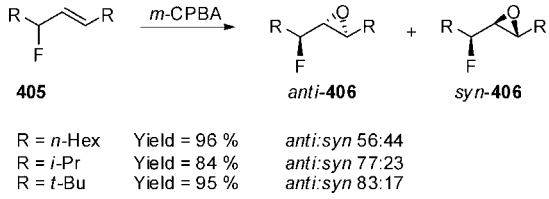
Fujita et al. used allylic fluorides to elucidate the electronic effects associated with epoxidation of allylic systems.[214] Fluorine was used, as it was deemed to have minimal steric effects, allowing for any π-facial stereoselectivity to be arising predominantly from electronic effects. Epoxidation

Chart 14. Transition States Optimized by Calculation at STO-3G[a]

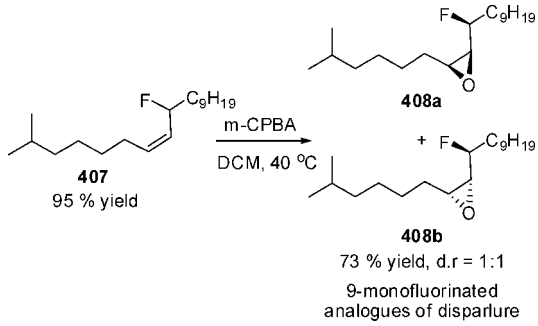


[a] Reprinted with permission from ref 214. Copyright Elsevier 1991.

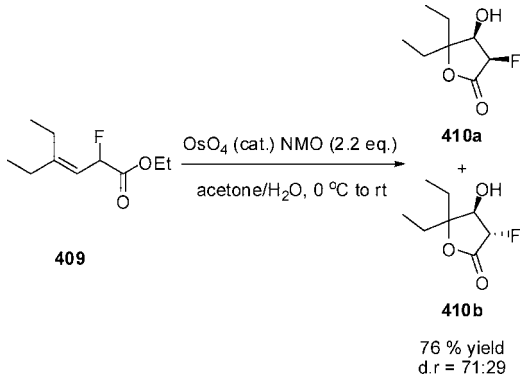
Scheme 113. Epoxidation of Allylic Fluorides with m-CPBA Reported by Fujita and Co-Workers



Scheme 114. Synthesis of a Fluorinated Analogue of Disparlure Reported by Grée



Scheme 115. Dihydroxylation of Allylic Fluorides with Concomitant Lactonization Reported by Piva

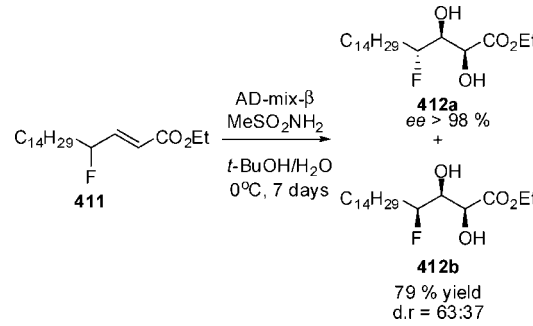


of three representative allylic fluorides was carried out using *m*-CPBA (Scheme 113).

The observation that the larger the R group (*n*-Hex < *i*-Pr < *t*-Bu), the greater the amount of the anti product, is consistent with an increase in preference of the R group to occupy an anti position. The authors chose 3-fluoroprop-1-ene to perform theoretical calculations, which highlighted the preference of the allylic fluorine to adopt the inside position and the bulky alkyl group to adopt the favored anti position (Chart 14).

The epoxidation of allylic fluorides has been exploited in the synthesis of 9-fluoro analogues of disparlure, the pheromone of the Gipsy moth.[57] The authors observed that the key epoxidation step showed no selectivity, giving an equal mixture of both diastereomers. This is in contrast to the epoxidation of the corresponding alcohol, which is a highly stereoselective process, confirming that the role of hydrogen bonding is crucial for high levels of selectivity (Scheme 114).

Scheme 116. Sharpless Asymmetric Dihydroxylation of Allylic Fluorides Reported by Haufe and Co-Workers



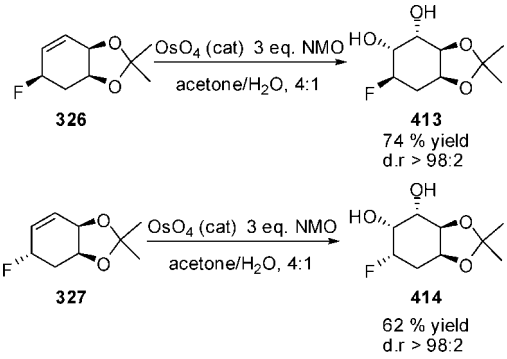
3.2.3. Dihydroxylation

Dihydroxylation of allylic fluorides was first exemplified by Piva.[193] Upon treatment of the allylic fluoride **409** with a catalytic amount of osmium tetroxide in the presence of a co-oxidant, dihydroxylation with concomitant lactonization afforded the diastereomeric α-fluoro-β-hydroxy lactones **410a**,**b** in a syn:anti ratio of approximately 7:3 (Scheme 115).

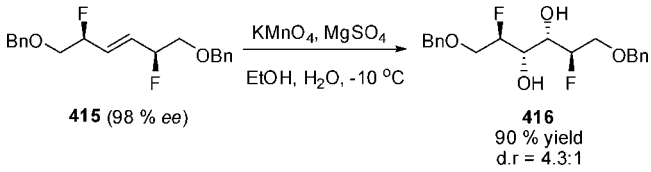
Haufe et al. used the dihydroxylation of an allylic fluoride as a key step in the total synthesis of two enantioenriched diastereomeric 4-fluoro-4,5-dihydroceramides.[184] An asymmetric dihydroxylation was performed using the Sharpless protocol with the commercially available AD-mix β. After 7 days, a reaction time significantly longer than for the corresponding allylic alcohol, 80% of the starting material had been converted to the diol. The enantiomeric excess of the major diastereomer was excellent (>98% measured using ^{19}F NMR and Eu(hfc)$_3$). Diastereoselectivity was modest (63:37), but the diastereomers could be separated by column chromatography. The major diastereomer resulted from an anti dihydroxylation with respect to the fluorine substituent, in line with the findings of Kishi, who studied the dihydroxylation of allylic alcohols[215–217] (Scheme 116).

Dihydroxylation of enantioenriched cyclic allylic fluorides for the preparation of fluorinated cyclitols has been documented by Gouverneur and co-workers.[177] The cyclic allylic fluorides, prepared by an electrophilic fluorodesilylation reaction of the corresponding cyclic allylsilanes, were subjected to conditions of the "Upjohn process". The reaction was highly diastereoselective, with dihydroxylation occurring solely anti with respect to the acetonide protecting group,

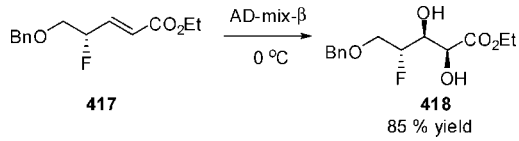
Scheme 117. Dihydroxylation of Enantioenriched Fluorinated Carbocycles Reported by Gouverneur and Co-Workers



Scheme 118. Dihydroxylation of a Difluorinated Alkene Reported by O'Hagan and Co-Workers



Scheme 119. Sharpless Asymmetric Dihydroxylation of an Allylic Fluoride Reported by Davis and Co-Workers



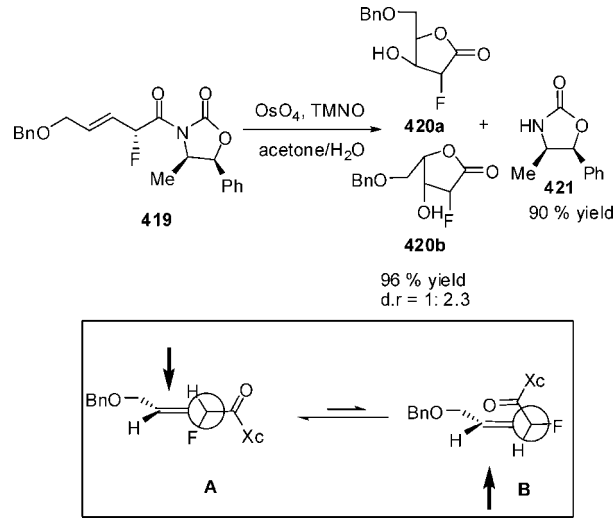
regardless of the stereochemistry at the fluorinated center (Scheme 117).

O'Hagan and researchers utilized a dihydroxylation reaction of a symmetrical difluorinated alkene, to access a key intermediate in the synthesis of an all-syn vicinal fluorine motif.[147] The sense of diastereocontrol is likely to be controlled by the two fluorine atoms flanking the double bond (Scheme 118).

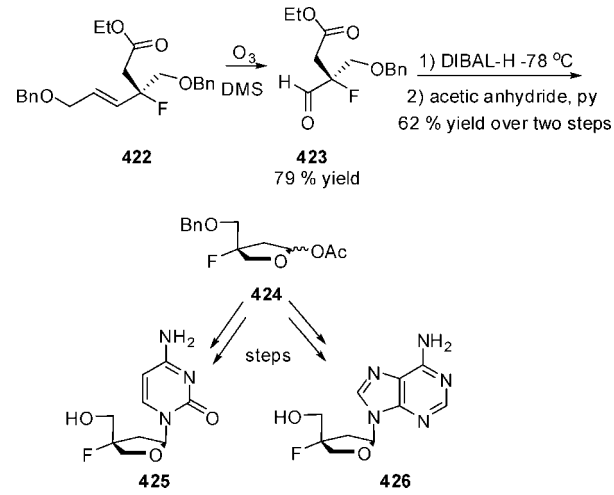
Davis et al. utilized the allylic fluoride **417** in the synthesis of 4-deoxy-4-fluoro-D-arabinopyranose. The dihydroxylation step proceeded with complete diastereoselectivity if the reagents constituting AD-mix were added separately, furnishing the diol **418** as a single diastereomer in high yield. The fluorinated diol was then subjected to conditions for cyclization to give a 1:1 mixture of the two arabinopyranose anomers (Scheme 119).[185]

Sequential dihydroxylation cyclization has also been applied to the synthesis of deoxyfluorosugar derivatives.[170,171] The allylic fluoride **419** was treated with osmium tetroxide in the presence of the co-oxidant TMNO (triethylamine *N*-oxide) to furnish the lactones **420a**,**b** in a 1:2 ratio, the Evans chiral auxiliary **421** being recovered in 90% yield. The chiral auxiliary was not expected to influence greatly the selectivity, as is it fairly remote from the site of reaction. For this study, it was suggested that the conformer **A**, where the fluorine adopts the inside position, is in fact less stable than conformer **B**, featuring the fluorine in the outside position. This was accounted for by the authors referring to allylic 1,3-strain minimization (Scheme 120).[171]

Scheme 120. Sequential Dihydroxylation−Cyclization Reported by Davis and Co-Workers



Scheme 121. Ozonolysis of an Allylic Fluoride Reported by Chu and Co-Workers



3.2.4. Oxidative Cleavage

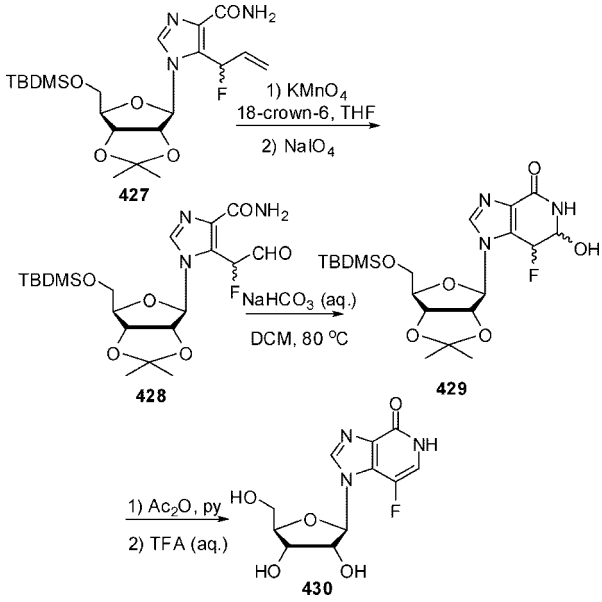
Ozonolysis of the allylic fluoride **422** was utilized by Chu et al. in the synthesis of enantioenriched 3′-fluoro-apionucleosides.[194] The enantioenriched allylic fluoride was subjected to ozonolysis, thereby delivering the aldehyde. Reduction and cyclization formed the key intermediate **424**, which after several synthetic manipulations was transformed into the fluorinated apionucleosides **425** and **426** (Scheme 121).

In a study of 3-deaza-3-halopurine ribonucleosides, Matsuda et al. utilized the acyclic allylic fluoride **427** as a key intermediate toward the synthesis of a fluoropurine analogue.[26] Dihydroxylation followed by oxidative cleavage with sodium metaperiodate furnished the corresponding aldehyde. The aldehyde **428** was not isolated but cyclized in situ upon intramolecular addition of the carbamoyl group at the 4-position. Elimination and global deprotection gave the desired fluoropurine **430** (Scheme 122).

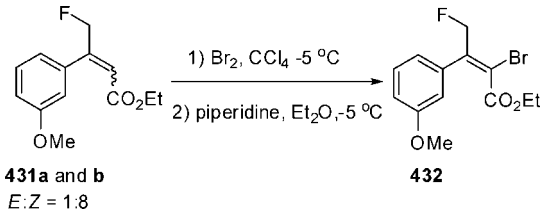
3.2.5. Bromination

In the synthesis of (*E*)-*β*-(fluoromethylene)-*m*-tyrosine, McDonald et al. performed a bromination on the mixture of *E* and *Z* allylic fluorides **431a**,**b** followed by dehydrobromination to give the *Z* isomer. The resulting bromide **432**

Scheme 122. Oxidative Cleavage of an Allylic Fluoride in the Synthesis of a Fluoropurine Analogue Reported by Matsuda and Co-Workers



Scheme 123. Bromination of an Allylic Fluoride Reported by McDonald and Co-Workers



was converted to the corresponding amine and deprotection furnished the desired fluorotyrosine analogue (Scheme 123).[186]

In an attempt to synthesize the fluorinated amino acid γ-fluoroisoleucine, a compound believed to have antineoplastic activity, Butina and Hudlicky synthesized structurally related allylic fluorides which were brominated to give the corresponding α-bromo acids.[188]

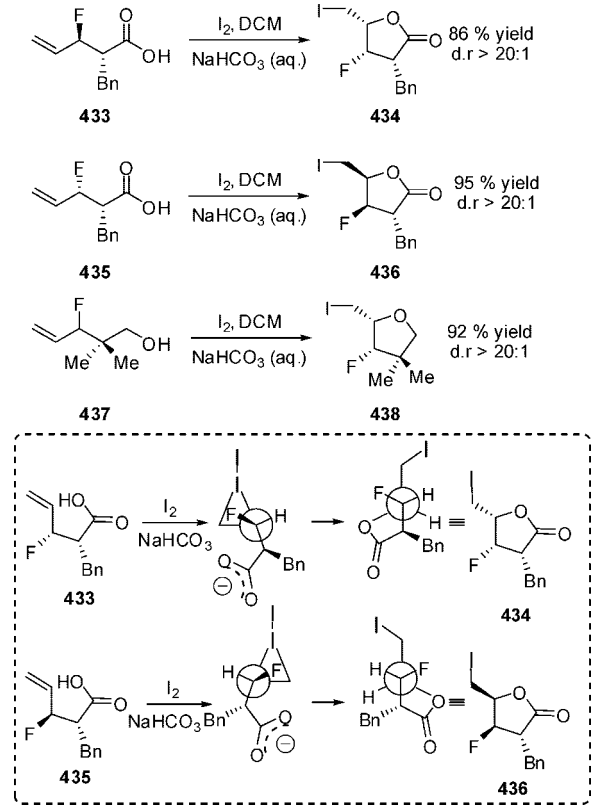
3.2.6. Iodocyclization

Gouverneur and Houk performed a series of highly diastereoselective iodocyclization reactions of allylic fluorides to furnish fluorinated γ-lactones and tetrahydrofurans. In all cyclic products, the fluorine and iodomethyl substituents were syn. The authors believed that the cyclization reactions were under kinetic control. The relative energies between the two possible diastereomeric products were within 1 kcal mol^{-1} of each other, which is not significant enough to explain the high level of diastereoselectivity. Calculations showed that the syn preference could be rationalized by considering a transition state positioning the fluorine in the inside position (Scheme 124).[218,219]

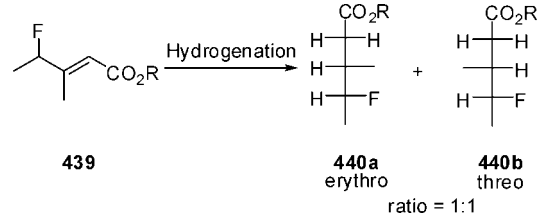
3.2.7. Hydrogenation

In addition to the bromination of allylic fluorides described in section 3.2.5, Butina et al. performed a hydrogenation of the geometrically pure allylic fluoride *E*-(**439**). The hydrogenation gave a mixture of the two diastereomers **440a**,**b** (Scheme 125).[188]

Scheme 124. Iodocyclization of Allylic Fluorides Reported by Gouverneur, Houk, and Co-Workers



Scheme 125. Hydrogenation of an Allylic Fluoride Reported by Butina and Co-Workers



3.2.8. Isomerization

Abell and Adolf investigated the relative equilibria of gas-phase isomerizations of allyl fluoride, allyl chloride, and allyl bromide to the corresponding 1-halopropenes.[220] Hydrogen bromide and UV light were used to catalyze the isomerizations in the temperature range 150−250 °C and pressures of 5−50 Torr. Calculated equilibrium constants for the allyl−vinyl isomerizations showed that the fluoro compound has a decided preference for the vinyl isomer. This is consistent with the differing abilities of the filled p orbital of the halogen to overlap with the π system of the double bond. Considering the bond lengths of the vinylic−halogen bonds (C−F = 0.1325 nm, C−Cl = 0.172 nm, C−Br = 0.189 nm) it would be expected that fluorine would have a greater interaction with the double bond (Table 5).

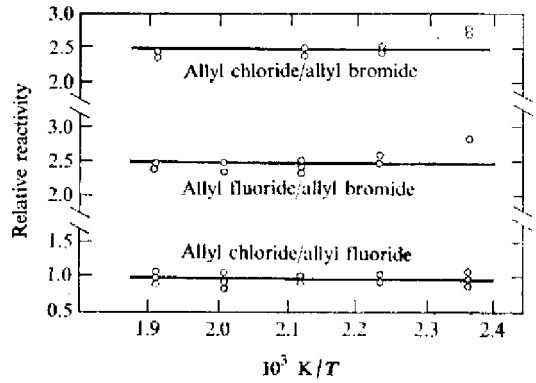
The activation energies for the conversion of the allyl halides to vinyl halides were not found to vary much across the halogens. The low magnitudes of the values are thought to indicate that bond breaking and bond making are energetically similar, suggesting that the resonance interaction of the halogen with the double bond in the transition state is small (Chart 15).

The finding that vinylic fluorine substitution is thermodynamically favored over allylic fluorine substitution is

Table 5. Equilibrium Constants as a Function of Temperature *T* for the Isomerizations

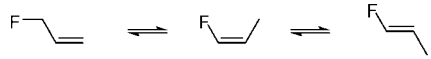
T (°C)	110	130	150	175	200	225	250
 **441**	-	-	-	25.1	18.8	13.1	11.1
 **442**	-	-	16.9	14.5	12.7	11.1	9.1
 **443**	4.26	3.96	3.89	3.65	3.51	3.25	3.35

Chart 15[a]



[a] Reprinted with permission from ref 219. Copyright Elsevier 1969.

Scheme 126. Isomerization between Allyl and Vinyl Fluorides Reported by Dolbier, Medinger, and Co-Workers



444 **445** **446**

444→445 ΔH = -3.34 kcal.mol^{-1}, ΔS = -1.4 kcal.K^{-1}
444→446 ΔH = -2.86 kcal.mol^{-1}, ΔS = -1.7 kcal.K^{-1}
445→446 ΔH = +0.64 kcal.mol^{-1}, ΔS = -0.3 kcal.K^{-1}

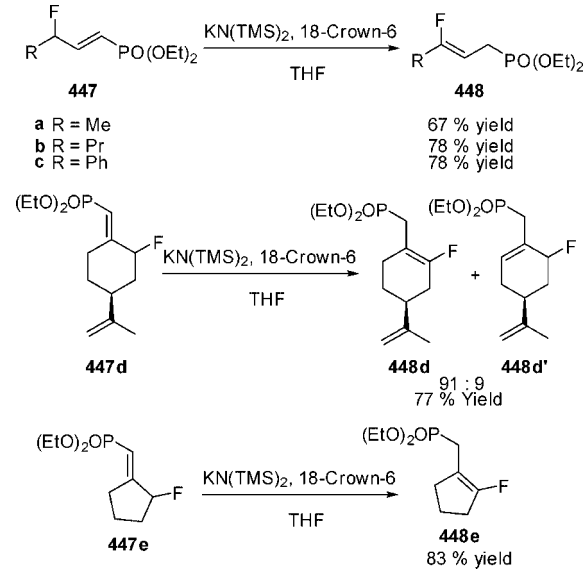
corroborated by the findings of Dolbier and Medinger (Scheme 126).[221]

The preference for fluorine to sit on the sp^2 center of a vinylic fluoride rather than the sp^3 center of an allylic fluoride was exploited in base-promoted deconjugation reactions, giving rise to (*Z*)-γ-fluoroallylphosphates. Hammond postulated that the mechanism for the transformation involves deprotonation of the γ-carbon of **447**, leading to a resonance-stabilized system.[100] The major resonance contributor then leads to the predominant isomer after workup. Semiempirical calculations (AM1) showed that for acyclic systems the vinyl fluorides were predicted to be more stable than the allylic fluorides; however, in the cyclic systems there was negligible difference (Scheme 127).

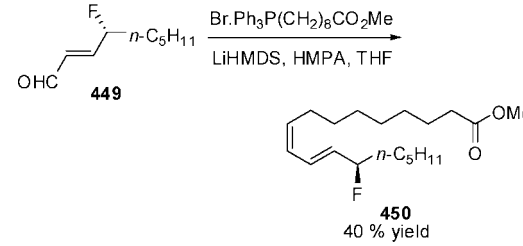
3.2.9. Wittig-Type Reactions

Allylic fluorides are compatible with Wittig reactions, as exemplified by Grée and co-workers in the synthesis of fluorinated analogues of fatty acid metabolites. 13-(*R*)-Hydroxyoctadeca-9-(*Z*),11-(*E*)-dieneoic acid is a natural product believed to be involved in cell tumor adhesion, among other biological activities. The single diastereomer (+)-(13*R*)-13-fluorooctadeca-9-(*Z*),11-(*E*)-dienoic acid methyl ester (**450**) was obtained in 40% yield via a Wittig reaction of the corresponding enal **449** and 8-(methoxycarbonyl-octyl)-triphenyl-phosphorane (Scheme 128).[17]

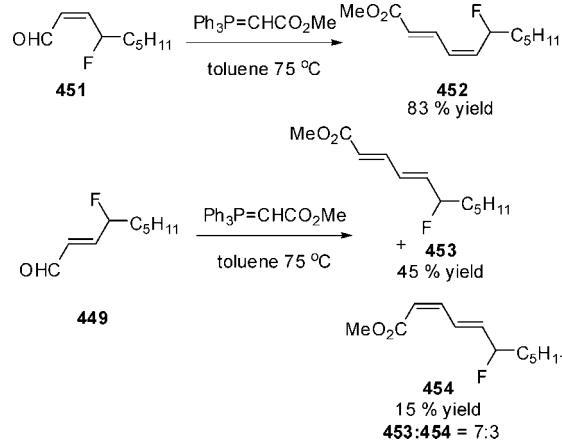
Scheme 127. Synthesis of (Z)-γ-Fluoroallylphosphates by Base-Promoted Deconjugation Reported by Hammond and Co-Workers



Scheme 128. Synthesis of Fluorinated Analogues of Fatty Acid Metabolites by a Wittig Reaction Reported by Grée and Co-Workers

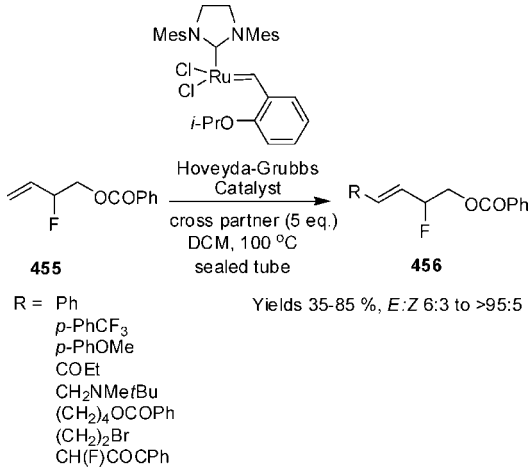


Scheme 129. Synthesis of Fluorinated Dienes by Wittig Reactions Reported by Grée and Co-Workers

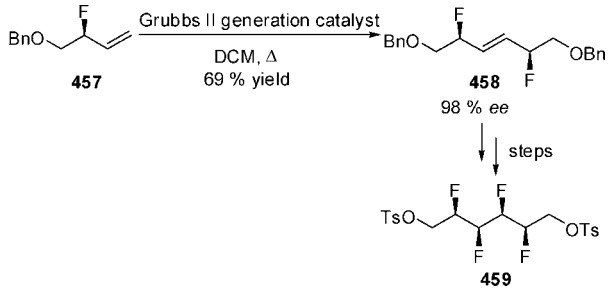


The same authors investigated Wittig reactions of racemic allylic fluorides and a stabilized phosphorus ylide and observed, in some cases, high levels of control of the double-bond geometry.[222] It was found that the allylic fluorides were sufficiently thermally stable for the *Z* enal **451** not to undergo double-bond isomerization even after heating to 60 °C in benzene or DMSO for 24 h. The *Z* enal **451** afforded exclusively the *E,Z* diene **452**, whereas the *E* enal **449** gave a mixture of the *E,E* diene **453** and the *E,Z* diene **454** (Scheme 129).

Scheme 130. Cross-Metathesis of Allylic Fluorides Reported by Gouverneur and Co-Workers



Scheme 131. Self-Metathesis of an Enantioenriched Allylic Fluoride Reported by O'Hagan and Co-Workers



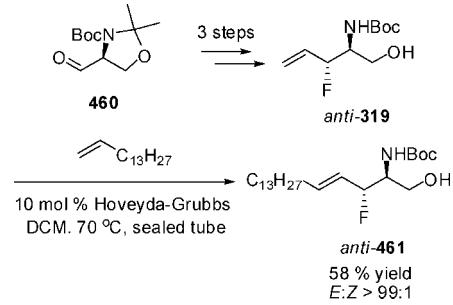
3.2.10. Metathesis

Gouverneur et al. were able to functionalize a series of terminal allylic fluorides via cross-metathesis.[173] It was found that the best results were obtained when the reactions were performed in DCM in a sealed tube at 100 °C. The model allylic fluoride **455** was treated with a variety of different cross partners, in the presence of the Hoveyda−Grubbs catalyst, to give the corresponding internal allylic fluorides. This methodology was not suitable when trisubstituted alkenes and allyltrimethylsilane were used as cross partners (Scheme 130).

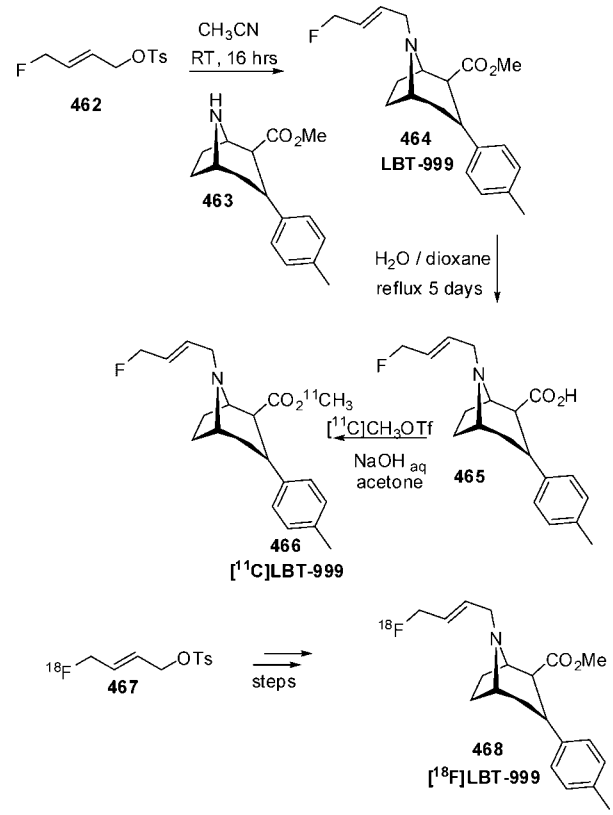
O'Hagan and co-workers utilized this methodology to access an enantioenriched all-syn four vicinal fluorine motif, **459**.[147] The self-metathesis reaction of the enantioenriched allylic fluoride **457** (a 9:1 mixture of *S* and *R* enantiomers) gave a statistical 8:4:1 mixture of *S,S*, *R,S*, and *R,R* isomers. The major isomer could be isolated by column chromatography to give the desired compound in 98% ee, which conveniently overcame the loss of enantiopurity suffered in the nucleophilic epoxide opening, when accessing the enantioenriched **457** (Scheme 131).

Gouverneur et al. also utilized a cross-metathesis functionalization of the allylic fluoride *anti*-**319** as a key step in the synthesis of an enantiopure fluorinated analogue of the signaling lipid sphingosine **461**. The terminal allylic fluoride *anti*-**319**, synthesized in three steps from Garner's aldehyde **460**, was treated with 10 mol % of the Hoveyda−Grubbs catalyst and 1-pentadecene in a sealed tube to furnish *anti*-**461** as the pure *E* isomer in 58% yield (Scheme 132).[175]

Scheme 132. Cross-Metathesis in the Synthesis of a Fluorinated Analogue of Sphingosine Reported by Gouverneur and Co-Workers



Scheme 133. Nucleophilic Substitution of an Allylic Fluoride Containing a Tosyl Group for the Preparation of both ^{18}F- and ^{11}C-Labeled Radiotracers Reported by Dollé



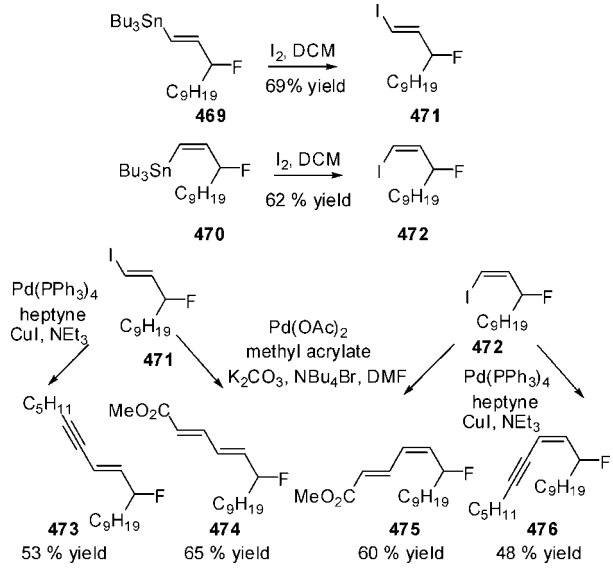
3.2.11. Substitution

A nucleophilic substitution of a tosyl group on allylic fluoride **462** was one of the key steps in the synthesis of both ^{11}C- and ^{18}F-labeled radiotracers of **466** and **468**. In the case of [^{11}C]-**466**, the radiolabeled carbon atom was introduced in the last step by methylation of the carboxylic acid group.[223] In the case of [^{18}F]-**468**, the radiolabeled allylic fluoride [^{18}F]-**467** was synthesized first, followed by coupling to the cocaine fragment.[137] Both radiotracers are possible candidates for the imaging of the neuronal dopamine transporter (DAT), which is implicated in, among other diseases, Parkinson's disease (Scheme 133).

3.2.12. Coupling Reactions

To functionalize allylic fluorides, Grée et al. used a strategically placed alkyl tin group, which could be converted to the corresponding iodide for use in Heck or Sonogashira couplings. In all cases the coupling reactions were stereospe-

Scheme 134. Sonogashira and Heck Couplings Reported by Grée and Co-Workers



cific, leading to the corresponding polyunsaturated allylic fluorides **473**−**476** in good yield with complete stereocontrol (Scheme 134).[22]

3.3. Applications

Allylic fluorides have wide-ranging applications in the biological, medicinal, and agrochemical fields, with numerous patents filed in these areas. Applications include antifungals,[224] nitric oxide synthase inhibitors,[225–229] treatment of cancer,[230,231] platelet aggregation inhibitors,[232] histamine H3 receptor agents,[233] serum glucose reducing agents,[234] treatment of chromic inflammatory or autoimmune disease,[235] and herbicides[236] and insecticides.[237,238]

3.3.1. Fluorinated Analogues of Vitamin D

Vitamin D_3 (**477**) is transported to the liver, where it becomes hydroxylated at the C25 position to become 1α,25-dihydroxyvitamin D (**478**), also known as calcitriol. The active metabolite is then transported to the kidneys, where further hydroxylation occurs. Calcitriol is the most active metabolite of vitamin D_3 and is implicated in the regulation of calcium and phosphorus metabolism and cell proliferation and is also used in the treatment of bone disease. Several fluorinated analogues of vitamin D_3 have been synthesized in order to be used as molecular probes for the study of structure−function relationships of the metabolites and their target molecules (Chart 16).

Hoffmann-La Roche have been particularly interested in analogues involving the replacement of the 1-hydroxy group with a fluorine, including the compound known as Ro 26-9228 (**3**). The principal limitation of 1α,25-dihydroxyvitamin D in the treatment of osteoporosis is that the concentration needed to restore bone density leads to hypercalcemia. It was found that Ro 26-9228 has a significantly improved pharmacological profile. In rats, up to 27 μg/kg did not increase serum calcium levels and only moderately increased urine calcium, whereas a dose of only 3 μg/kg induced significant increase in bone mineral density.[239,240]

Elocalcitol has also been found to arrest prostate growth in males with benign prostatic hyperplasia, without direct androgenic effects. The drug, still in clinical development, is also being investigated for treatment of chronic cystitis.[241–243]

Chart 16. Fluorinated Vitamin D Analogues

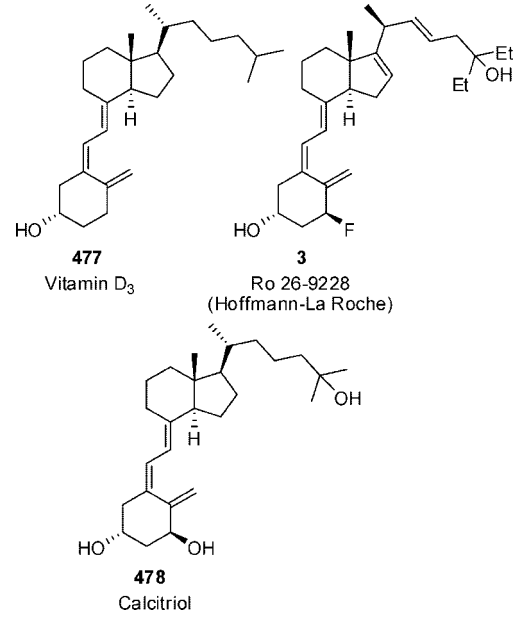
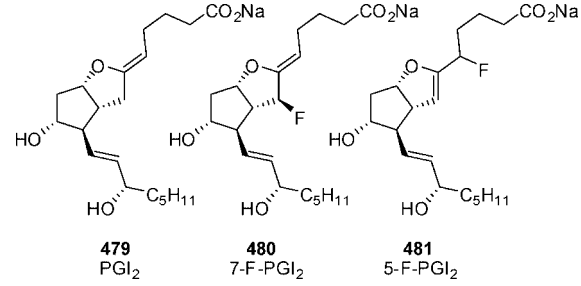


Chart 17. Fluorinated Prostanoids



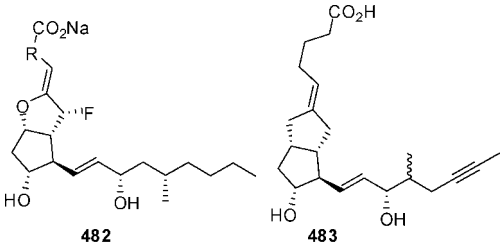
3.3.2. Fluorinated Prostanoids

Prostacyclin (PGI_2) (**479**) maintains homeostasis in circulation, acting to prevent or reverse platelet clumping and acting as a vasodilator to increase blood flow. However, it has limited therapeutic application, due to an inherent chemical and metabolic instability. Fluorinated prostacyclin analogues have been developed as chemically stable alternatives to prostacyclin, with fluorination in the 5- and 7-positions adjacent to the acid labile enol ether moiety, increasing the chemical half-life relative to the parent compound.[244] Bannai and co-workers measured the chemical half-life of the 7-F-PGI_2 analogue **480**, which was found to be greater than 1 month, compared to 10 min for PGI_2 at pH 7.4 (Chart 17).[245]

Matsumura and co-workers synthesized various 7-fluoro analogues of PGI_2 and measured their antiplatelet activity relative to iloprost (Ventavis, Schering AG), a drug used to treat pulmonary arterial hypertension. They observed that the derivatives **482a**−**c** showed strong inhibition of ADP-induced platelet aggregation in vitro, in comparison with iloprost (**483**) (Table 6).[244] The antianginal potency of these three lead compounds was examined, and compound **482a** was found to be 10−100 fold more potent than iloprost **483**.

Fluorinated prostaglandin analogues featuring an allylic fluoride have also found use in the medicinal and agrochemical industries: for example as a promoter of hair growth

Table 6. Inhibitory Effects of 7F-Prostacyclin Analogues and Iloprost on ADP-Induced Guinea Pig Platelet Aggregation in Vitro (ADP = 1 μM)[a]

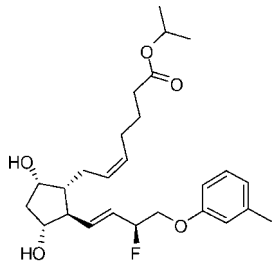


482 7-F prostacyclin analoges **483** iloprost

-R-	Inhibition of Platelet Aggregation[a]	-R-	Inhibition of Platelet Aggregation[a]
a	3.4	g	1.27
b	13.3	h	0.05
c	7.0	i	0.80
d	0.85	j	0.13
e	0.34	l	0.25
f	0.6	**483**	iloprost 10.8

[a] Relative potency to PGE_1.

Chart 18. Fluorinated Prostaglandin Analogue



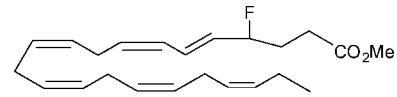
484 $PGF_{2\alpha}$ analogue

in mammalian skin (**484**; Chart 18)[246] or as an antimetabolite of methyl jasmonate, a synthesis and plant growth inhibitor.[247]

3.3.3. Fluorinated Docosahexaenoic Acid Analogues

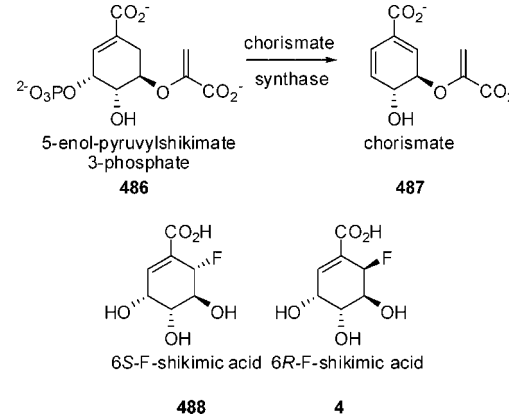
Yamamoto, Yamada, and co-workers used a fluoride analogue of the fatty acid docosahexaenoic acid (DHA), **485**, as an agonist of the peroxisome proliferator-activated receptors (PPARα,γ,δ) implicated in diabetes. The receptors act as biosensors of fatty acids and play a key role in fatty acid metabolism and homeostasis, disorders of which can lead to health problems, including type 2 diabetes. The fluorine was introduced in order to assess the structure−activity relationship, in particular the importance of hydrogen bonding at that position. All compounds tested in the series were found to have a greater potency as antidiabetics than the parent fatty acid (Chart 19).[248]

Chart 19. Fluorinated Analogue of Docosahexaenoic Acid



485

Scheme 135. Fluorinated Analogues of Shikimic Acid



3.3.4. Fluorinated Analogues of Shikimic Acid

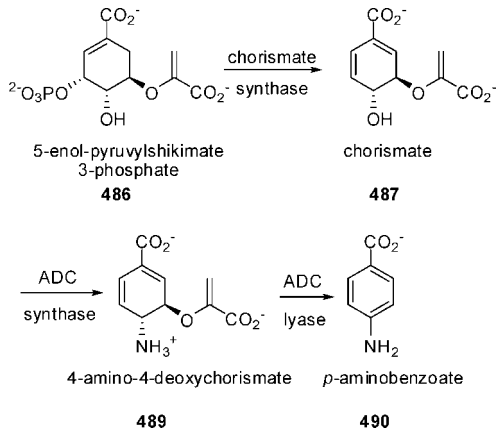
The shikimic acid pathway, also referred to as the aromatic biosynthetic pathway, involves a series of seven enzymes which is conserved in plants, algae, bacteria, and fungi. The overall pathway generates chorismate **487**, which is a common intermediate in the biosynthesis of the aromatic amino acids phenylalanine, tyrosine, and tryptophan, of *p*-aminobenzoic acid (which is converted into folates), and of ubiquinone. The pathway is absent in mammals, making inhibition an attractive prospect for selective antibacterial and antifungal agents. Fluorinated analogues of shikimic acid display potency against a variety of bacteria.

Abell et al. utilized the 6-fluoroshikimic acid derivatives **488** and **4** in order to investigate the mechanism of the seventh step in the pathway, the conversion of 5-enol-pyruvylshikimate-3-phosphate to chorismate. The fluorinated analogues (6*S*)-F-shikimic acid (**488**) and 6*R*-F-shikimic acid (**4**) were both found to competitively inhibit chorismate synthase, with **4** having an affinity of an order of magnitude greater than that of **488**. This was not surprising, as it is known that the pro-*R* hydrogen of shikimic acid is selectively abstracted during the [3,3]-sigmatropic rearrangement. The lack of irreversible inhibition indicates that a mechanism involving a covalent enzyme−intermediate adduct is unlikely, although the data did not preclude any other mechanisms (Scheme 135).[249]

Nichols et al. showed that, while the (6*R*)-fluoroshikimic acid **4** inhibits the chorismate synthase enzyme more effectively than the 6*S* analogue, (6*R*)-fluoroshikimic acid can be further processed down the pathway, leading to lethal synthesis. The 6*S* analogue **488** was found to be more potent against *E. coli* K-12 (wild type; NCTC 10538).[250] The pathway was also targeted in the malaria parasite *Plasmodium falciparum* by McConkey. (6*R*)-Fluoroshikimic acid was found in this case to be more potent than (6*S*)-fluoroshikimic acid against parasite growth, with both analogues inhibiting growth in a dose-dependent manner.[251]

Abell et al. were later able to establish that the antimicrobial effect of (6*R*)-fluoroshikimic acid is the result of irreversible inhibition of 4-amino-4-deoxychorismate synthase (ADCS) by 2-fluorochorismate. ADCS catalyzes the amination of chorismate **487**, generating 4-amino-4-deoxy-

Scheme 136. Generation of 4-Amino-4-deoxychorismate



486 **487** **489** **490**

chorismate (**489**), which is then converted to *p*-aminobenzoate, the precursor for folate (Scheme 136).[252]

4. Conclusions

Over the past few years, new methodologies to access allyl and propargyl fluorides have been developed, providing solutions to challenging transformations of importance to fluorine chemistry. This progress can be attributed to the increasing importance of fluorine chemistry in the pharmaceutical and agrochemical industry, combined with the emergence of milder fluorinating reagents. Propargylic fluorides, especially enantioenriched derivatives, remain underexplored building blocks. This is due to the fact that very few methods are available for the synthesis of enantiopure propargylic fluorides and the difficulties associated with the determination of optical purity and the assignment of absolute configuration. More methods are available for the synthesis of allylic fluorides, although relatively few lead to a clean product outcome and only a fraction of these methods deliver these compounds in high optical purity. While over the past decade some progress has been made in the development of catalytic enantioselective fluorinations, none to date allow access to enantioenriched propargylic or allylic fluorides, and this chemistry is still open for innovation.[253] The reactivity of propargylic fluorides has been explored with some interesting transformations. Of particular significance is their use as precursors of allylic fluorides or as dienophiles for the construction of aromatics and heteroaromatics. The discovery of new reactivity of allylic fluorides has enhanced our understanding of how the fluorine substituent affects reactivity as well as the sense and level of stereocontrol observed upon manipulation of the adjacent alkene. Undoubtedly, these developments and future work in this area will help synthetic, medicinal, and material chemists a great deal, broadening further the value of these building blocks for diverse academic and industrial applications.

5. Acknowledgments

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