Fluorination Chemistry:

A Tale of Two Reagents

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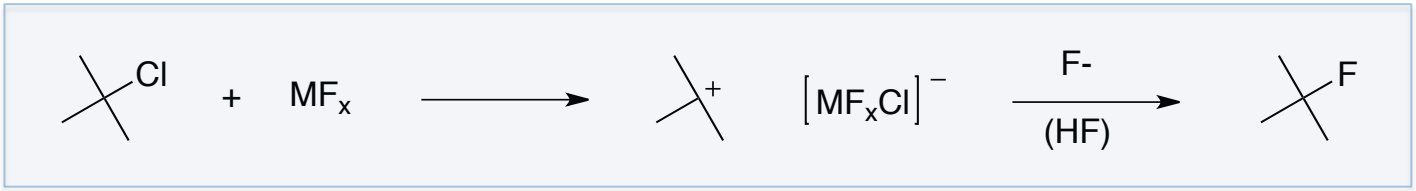
January 23rd, 2013

Outline

- Historical Development
- The C-F bond
- Fluorine, Who cares?
- Fluorine, Isn't it toxic?
- Fluorination Reactions

Historical Development

- In 1890 Moissan claimed to have isolated CF4, it was later found he was incorrect in his report.
- In 1892 Swarts also started working on preparation of fluorocarbons by exchange, usually from the chloro compounds. He was the sole author publishing in the field of organo-fluorine chemistry for 25 years!
- Midgley and Henne picked up after swarts in the 30's and developed fluoro-methanes and ethanes as refrigerants, bringing more funding to the field.



H. Moissan, Compt. Rend., **110,** 276 (1890) F. Swarts, Bull. Acad. Roy. Belg., [3], **24**, 474 (1892) T. Midgley and A. L. Henne, Ind. Eng. Chem., **22**, 542 (1930)

Historical Development

- In 1937 Simons and Block found mercury promoted the reaction between carbon and fluorine and isolated several purely fluorinated compounds.
- Simons proposed these highly fluorinated compounds may be chemically resistant to UF_6.
- Use of fluorcarbons in the machinery for enriching U caught a lot of chemists attention and the field really took off.
- Polytetrafluoroethylene (Teflon), was patented in 1941.
- Research in organofluorine chemistry has slowly caught on and has become very attractive recently due to the prevalence on F in pharmaceuticals.

J. H. Simons and L. P. Block, J. Amer. Chem. Soc., **59**, 1407 (1937) R.J. Plunkett, U.S. Pat. 2,230,654 (Feb. 4, 1941)

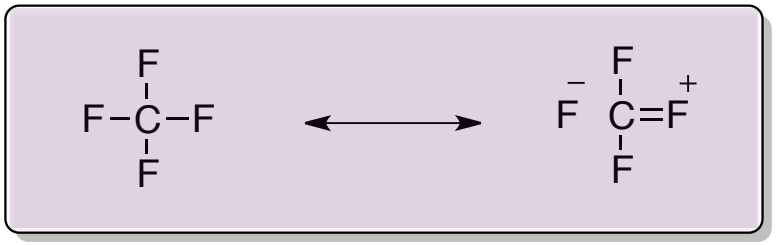
The C-F Bond, and more

- Fluorine forms strong bonds to carbon, ~115 Kcal/mol, making it relatively stable to metabolic degradation, and making elemental fluorine highly reactive.

- The van der Waals radii is 1.47 compared to 1.20 Angstrom for H. Also the bond length is closer to that of C – O bond, suggesting it is more like an alcohol sterically speaking; however, it is often considered an isostere of H.

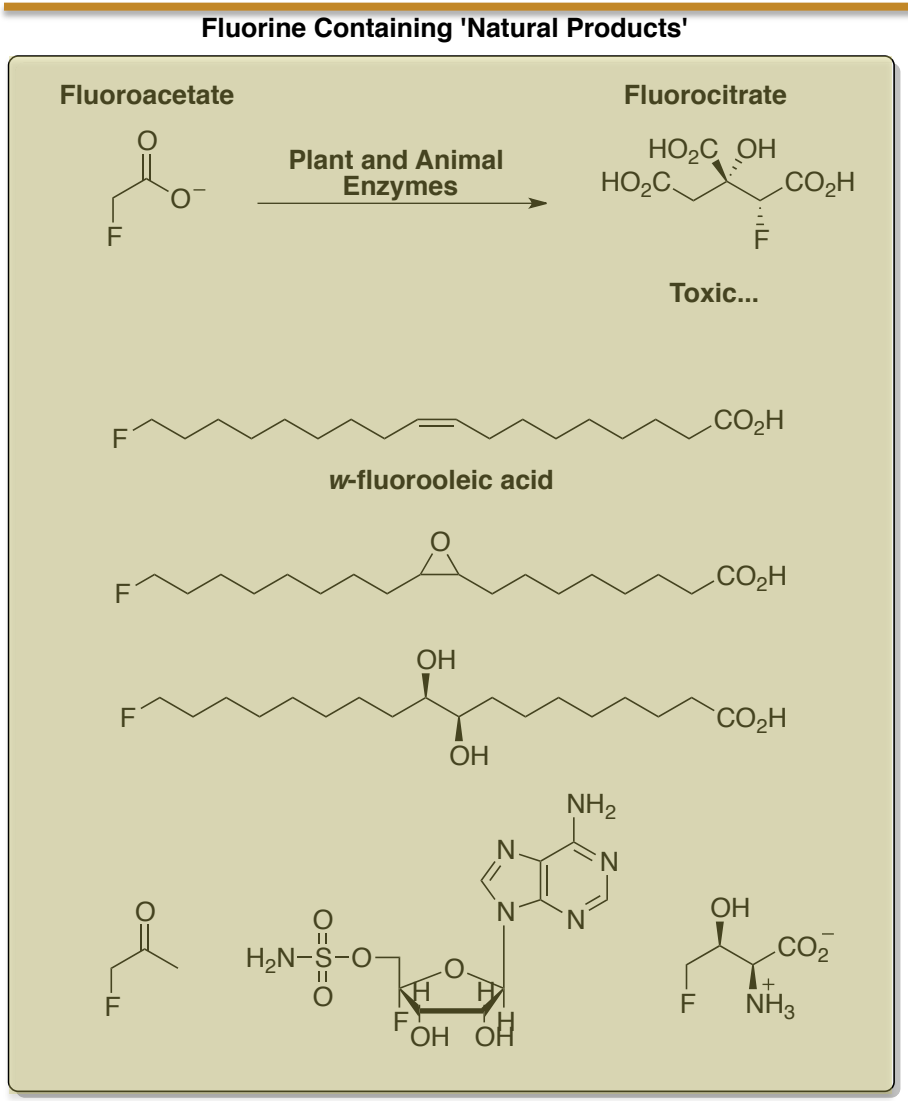
- The more F added to a carbon the stronger and shorter all of the fluorine bonds become.

no bond resonance



J. H. Simons and L. P. Block, J. Amer. Chem. Soc., **59**, 1407 (1937) R.J. Plunkett, U.S. Pat. 2,230,654 (Feb. 4, 1941) Chem. Rev. **2008**, 108, PR1-PR43

Fluorine, Who Cares?

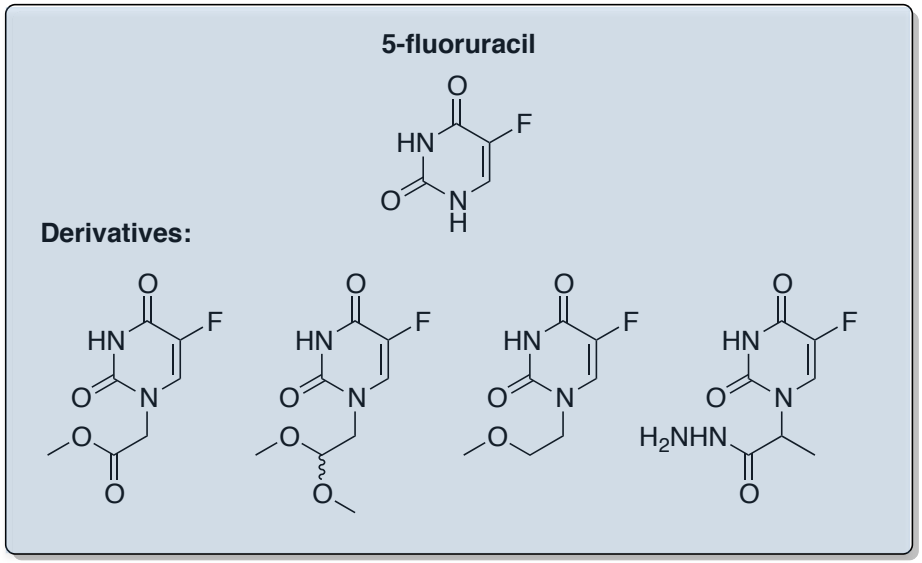


- ~ 3000 halogen containing natural products
- Fluorine is the most abundant halogen in the crust, yet there are only 13 secondary metabolites containing F
- Of the 13, only 6 discrete natural products.
- Fluoride is a poor nucleophile in water and can not be oxidized to X+ by haloperoxidases, resulting in it's extremely low bioavailability in surface water (1.3ppm vs 3000ppm for chloride)

Journal of Fluorine Chemistry 100 (1999) 127-133 Nat. Prod. Rep., 2004, 21, 773-784

Fluorine, Who Cares?

Possible Natural Products



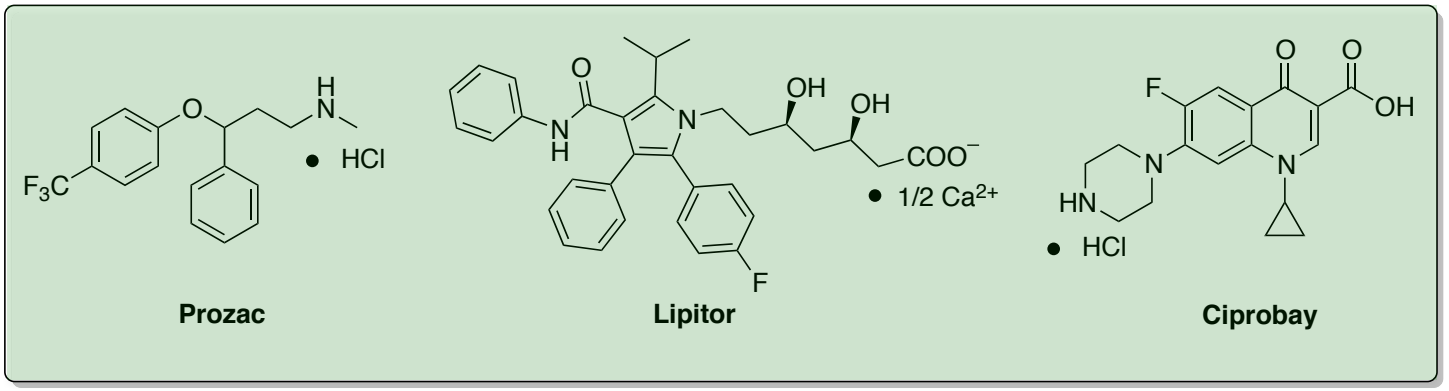
- 5-fluorouracil and four derivatives were isolated from a sponge in the South China Sea, but it is unclear whether the sponge was incorporating fluorine or simply derivatizing 5FU that was polluting the waters.

- Biologists and biochemists have been equally intrigued in fluorine over the last several decades and have shown certain plants that don't generally produce fluorinated metabolites will in the presence of elevated levels of fluoride

- A so-called 'fluorinase' enzyme has been isolated that is responsible for fluorinating metabolites in a certain bacteria species.

Journal of Fluorine Chemistry 100 (1999) 127-133 Nat. Prod. Rep., 2004, 21, 773-784

Fluorine, Who Cares?



- Around a 1/3 of agrochemicals contain fluorine and around 1/5 of pharmaceuticals contain fluorine. (over 150 have come to market since the first in 1957)

- These companies are interested in fluorine because it can change the binding interactions, metabolic stability, physical properties, and reactivity.

- Fluorine can change the way a compound is metabolized (phase I P450), it can change the solubility of a compound (better oral availability), and fluorine forms many unique bioisosteres.

Journal of Fluorine Chemistry 100 (1999) 127-133 Nat. Prod. Rep., 2004, 21, 773-784 Science **317**, 1881 (2007) J. Med. Chem., 2008, 51, 4359

Fluorine, Isn't it toxic?

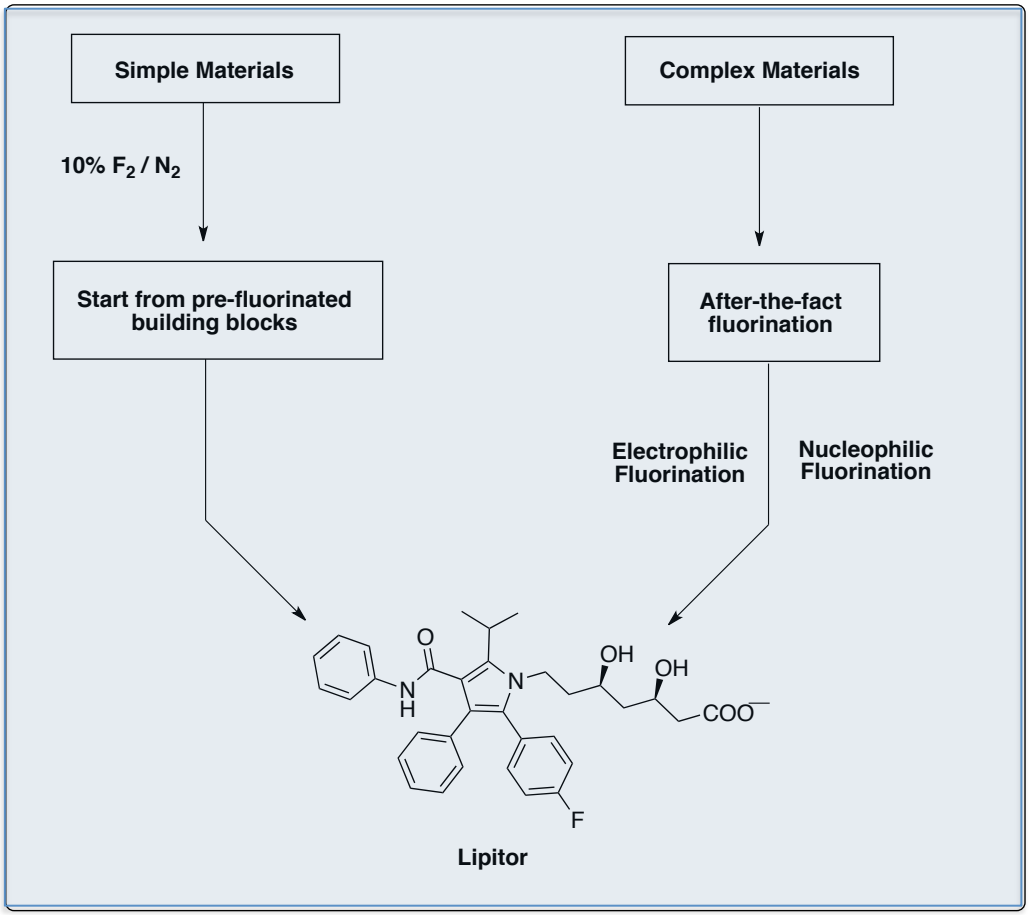
- Although fluoroacetate is toxic, most organo-fluorides are not toxic. Fluoroacetate is an exception, because it inhibits an important enzyme of the TCA cycle.

- Fluoride ion is toxic however, but organic compounds rarely release fluoride ion, lethal dose of NaF is 5-10g. (not very lethal)

- Upon heating of Teflon (polytetrafluoroethylene), small molecules containing fluorine can be given off through decomposition, and it has been shown that these molecules are lethal to birds and may cause flu-like symptoms for humans, but you have to heat the pans to temperatures that are unreasonable for cooking.

Baselt, RC (2008). Disposition of toxic drugs and chemicals in man. Dupont, Key Questions about Teflon, accessed Jan, 2013,

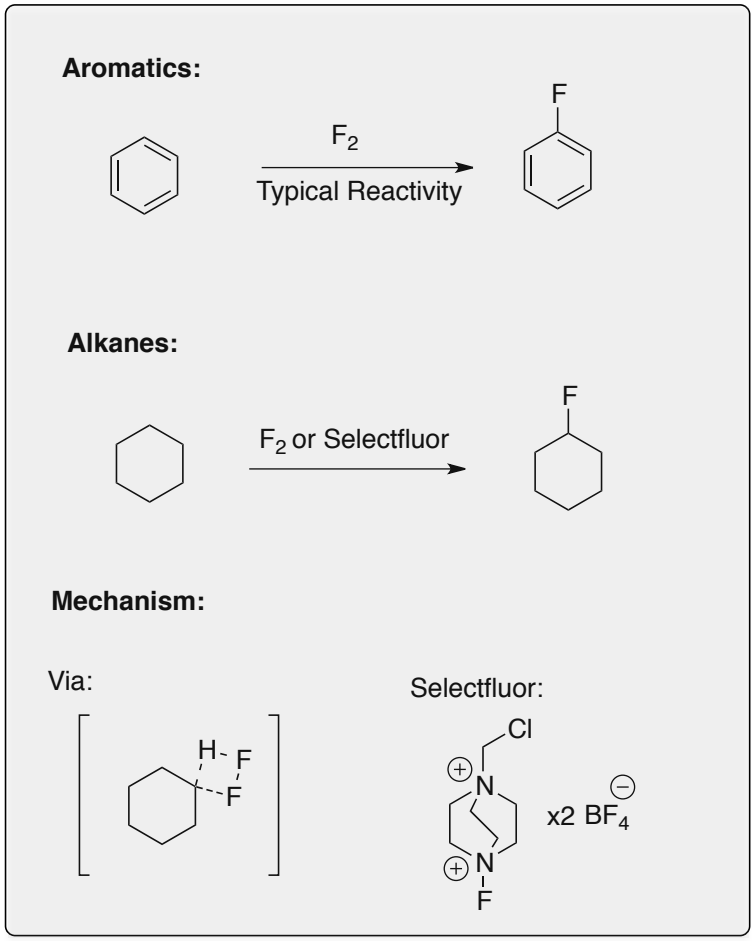
Fluorination Reactions



- Elemental fluorine is extremely reactive, but can be used on an industrial scale with simple compounds, the different products can be isolated and sold.
- The compounds used in laboratories to add fluorine are generally not atom economical.
- However, if you want to install the fluorine yourself you have lots of reactions available to you

Fluorination Reactions

Fluorination with F_2



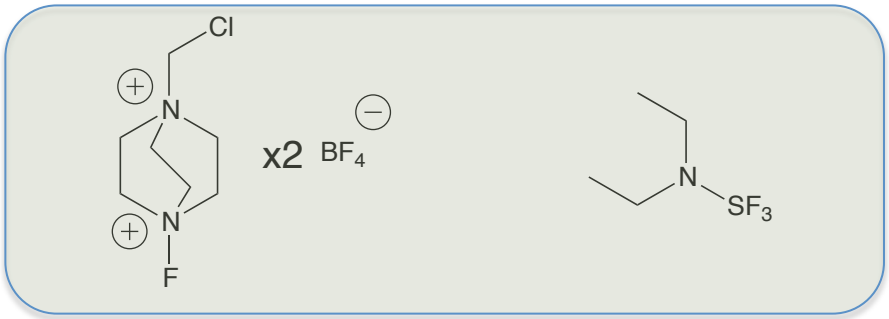
Chambers, Chem. Commun., 2000, 959-960

- Fluorination of aromatics with fluorine gas will give you your typical product distributions you see with electrophilic aromatic substitution
- Fluorination of alkanes is believed to go through an electrophilic mechanism rather than a radical mechanism, this was rationalized by the fact that Selectfluor generally gave the same products as elemental fluorine.
- Vicinal fluorides are not practically prepared via fluorination of alkenes

J. Chem. Soc., Perkin Trans. I, 2002, 2190-2197 Beilstein Journal of Organic Chemistry 2006, 2, No. 19

Fluorination Reactions

Problem:
Elemental fluorine easily reacts with aromatics, alkanes, and reacts with alkenes
Solution:
Develop more selective fluorinating reagents



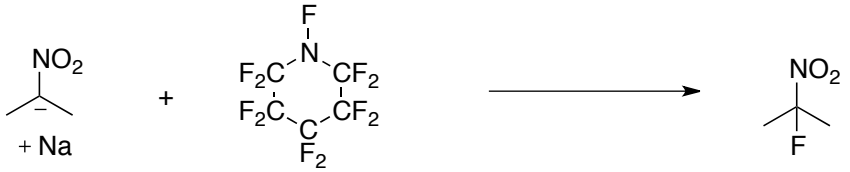
Selectfluor

DAST

Electrophilic Fluorination

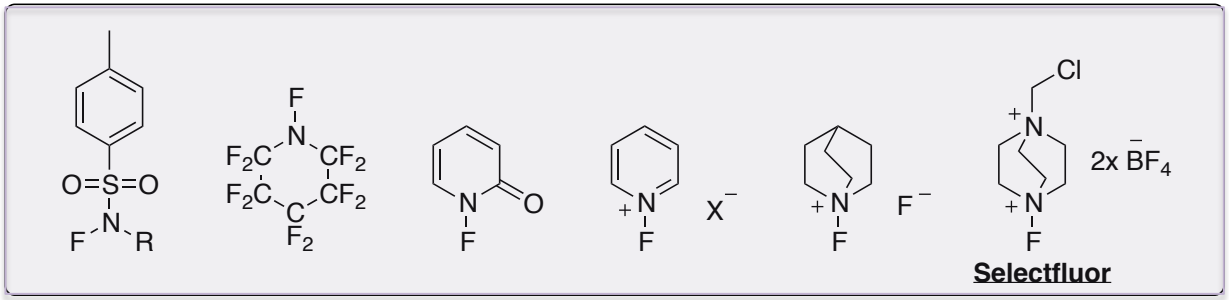
- As mentioned previously, due to the difficulty in handling fluorine, selective and user friendly fluorination reagents were sought out

- The 1950's development of Perchloryl fluoride FClO3, a very dangerous gas, inspired the development of perfluoro-N-fluoropiperidine. Which was successful at fluorinating a handful of stabilized sodium salts.



Banks, Chem. Ind. (london), (1964) 1864.

- N-F reagents quickly caught on and many different compounds and their reactivity's were published

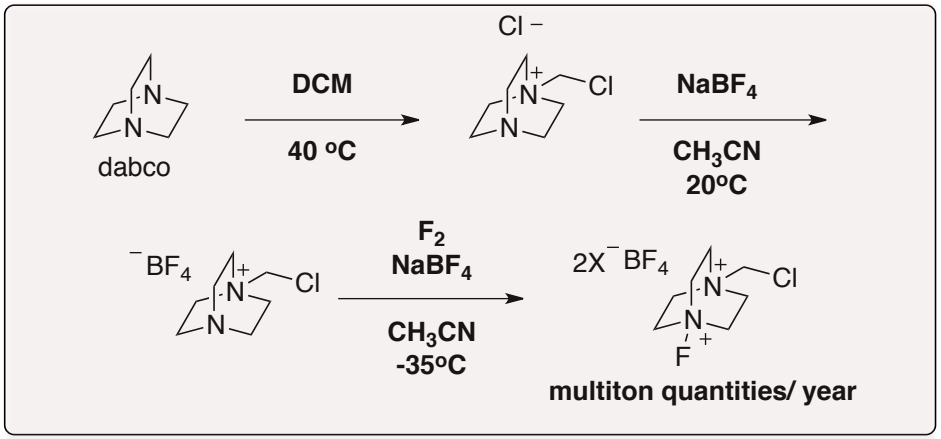


Journal of Fluorine Chemistry 87 (1998) 1-17 Angew. Chem. Int. Ed. 2005, 44, 192-212

Selectfluor

- Selectfluor is an easily handled solid, is resistant to elevated temperatures, and is relatively nontoxic: LD50 = 640mg/kg in adult rats

Preparation of Selectfluor



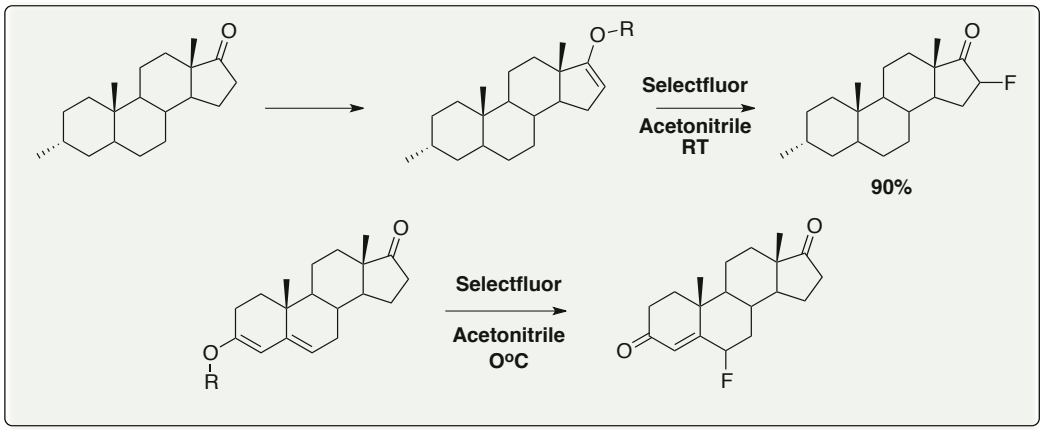
J. Fluorine. Chem. 1999, 100, 157

- Tuning the reactivity of Selectfluor can be achieved by changing the alkylating reagent and the counter-ion, it has been shown that these can enhance the solubility, changing the fluorinating agent's reactivity.

J. Org. Chem. 1999, 64, 5264

Selectfluor

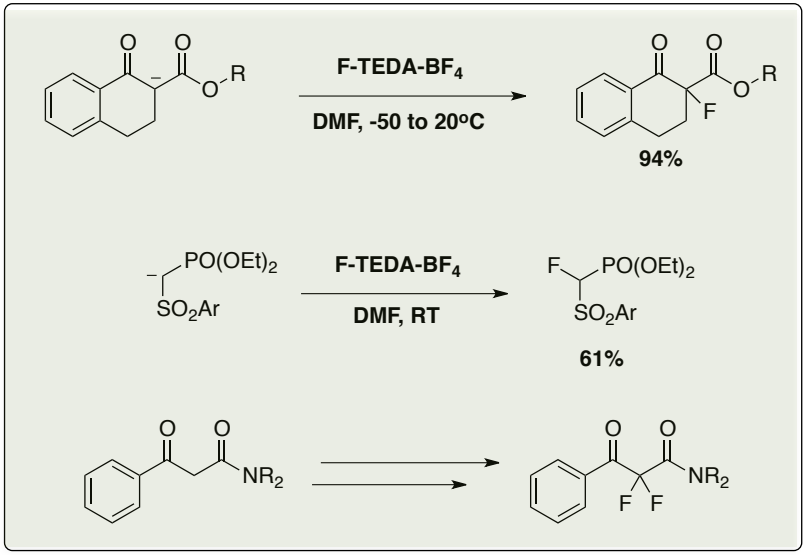
alpha-Fluorination of steroids



Lal, J. Org. Chem. 1993, 58,2791
Herrinton, Org. Process Res. Dev. 1997, 1, 217

- Ketones must first be converted to the enol-acetates
- Both alpha and gamma fluorination can be achieved

fluorination of beta-ketoesters



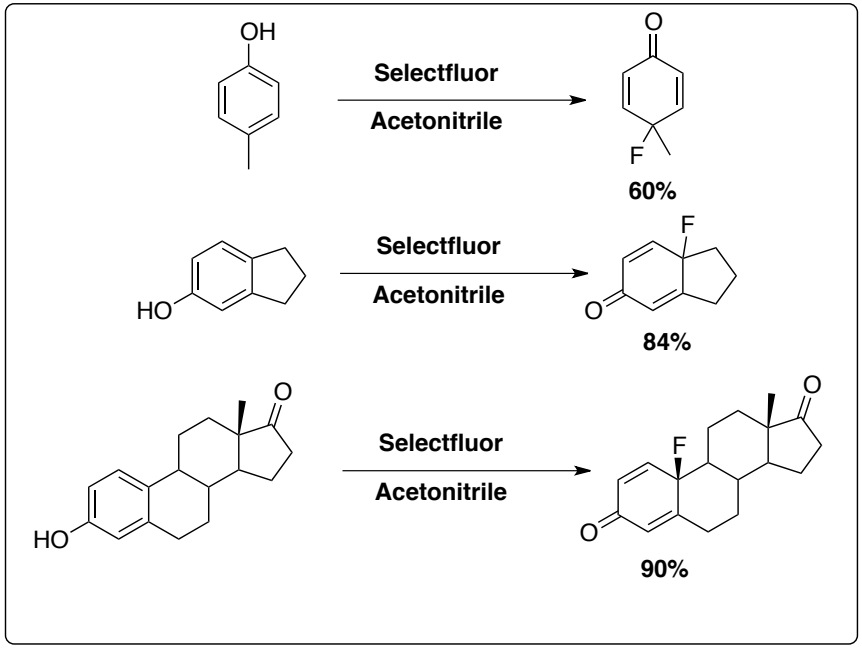
- Beta-ketoesters are good substrates and can be fluorinated twice

Lal, J. Org. Chem. 1993, 58,2791

Selectfluor

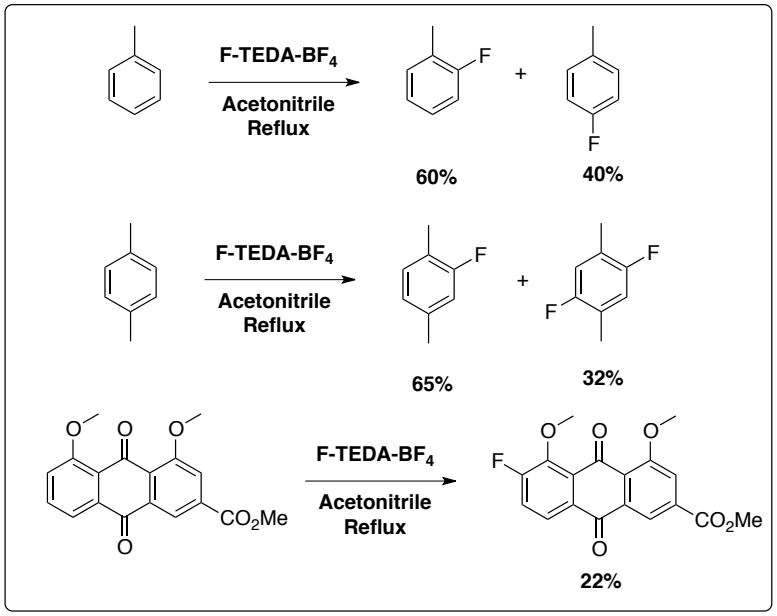
- Fluorination of phenols gives 4-fluorocyclohexadienones as products

4-fluorocyclohexadienones



Zupan, Synlett 1999, 9, 1375

Electrophilic Aromatic Substitution

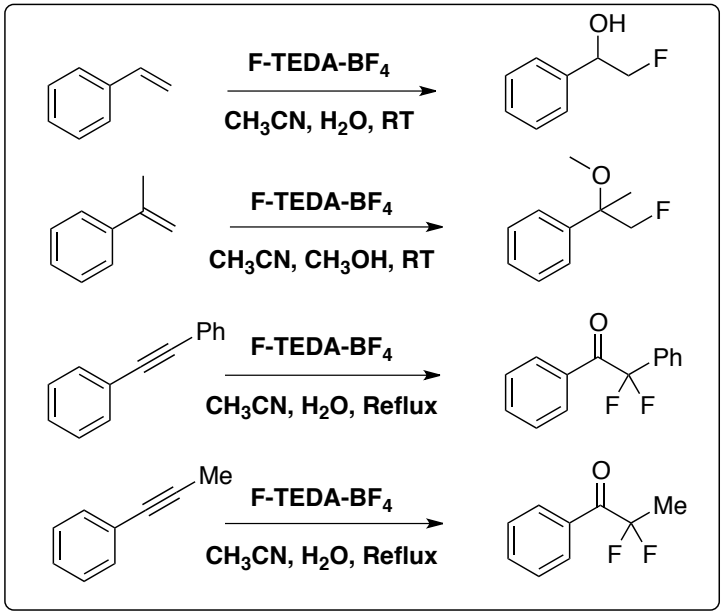


J. Fluorine Chem. 68 (1994) 201
Sharif, Chem. Soc., Perkin Trans. 1 (1996) 2069

- Fluorination of most aromatics gives substitution products

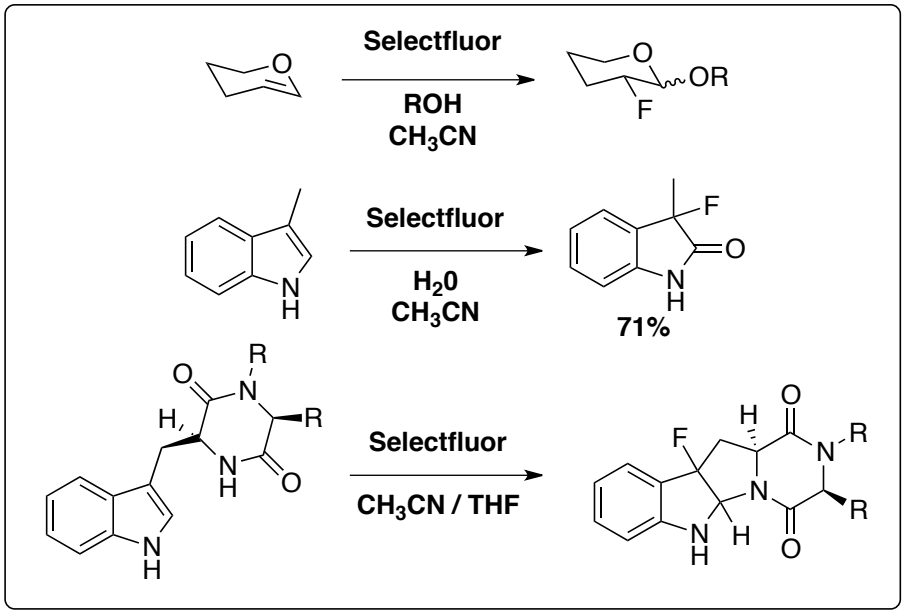
Selectfluor

Fluorination of Syrene and Phenylacetylene



Zupan, Bull. Chem. Soc. Jpn. 69, (1996) 169.

Fluorination of Activated Alkenes



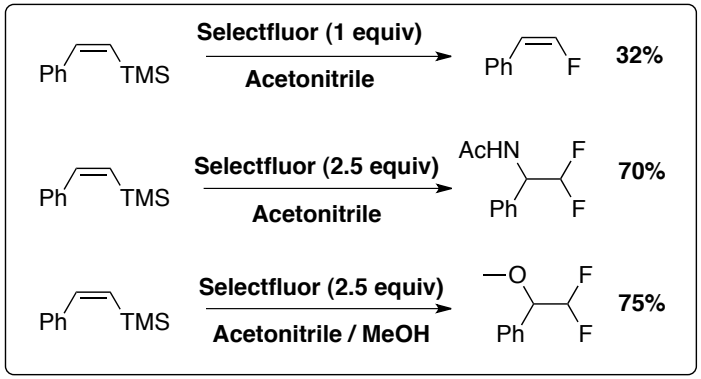
Wong, J. Org. Chem. 1999, 64, 5264
Shibata, Org. Lett. 2000, 2, 693
Kirk, Angew. Chem. 2001, 40, 4461

- Electron rich alkenes or alkenes that react to give stabilized carbocations will react with selectfluor

Selectfluor

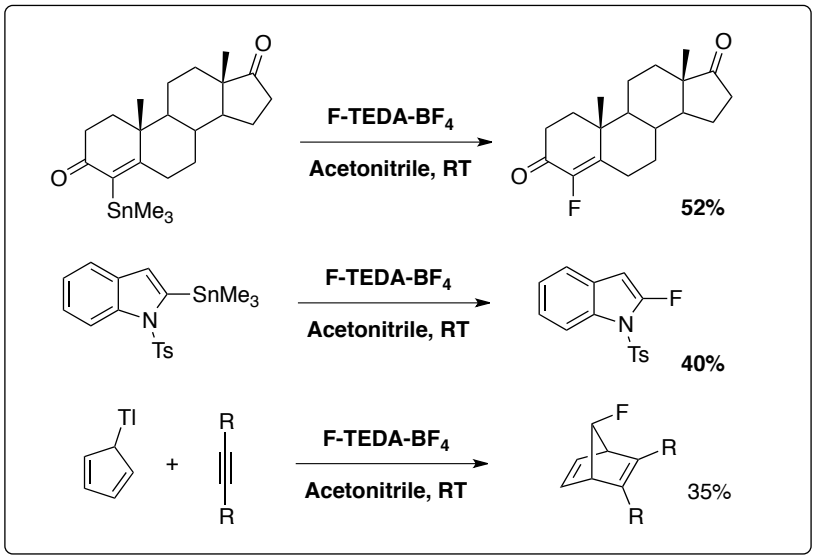
- Vinyl stannanes and silanes will react via electrophilic fluorination to give an array of products.

TMS Conversion to F



Gouverneur, Chem. Commun. 2001, 233

Sn and Tl Conversion to F

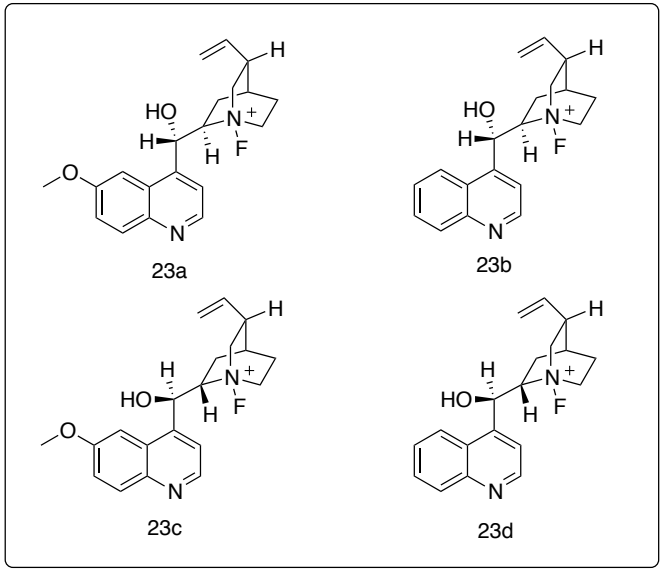


Widdowson, J. Chem. Soc., Perkin Trans. 1 (1995) 2965
Widdowson, Tetrahedron 50 (1994) 1899
Sik, J. Chem. Soc., Perkin Trans. (1992) 1891

- Quick method for producing F18 labeled compounds

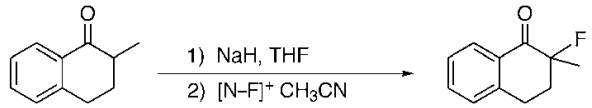
Selectfluor

Chiral N-F Reagents Synthesized From Selectfluor

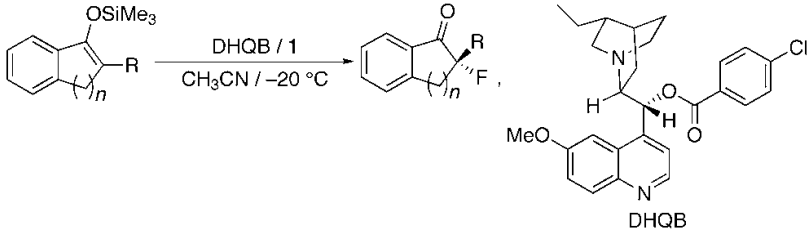


Roques, Org. Lett. 2000, 2, 3699
Roques, Tet. Lett. 2001, 42, 1867
Takeuchi, JACS, 2000, 122, 10728

- Chinchona alkaloids were fluorinated with selectfluor and used in enantioselective transformations



$[N-F]^+$	*ee* [%]	Configuration	Yield [%]
23 a	50	*S*	98
23 b	40	*R*	70
23 c	27	*R*	87
23 d	20	*S*	98

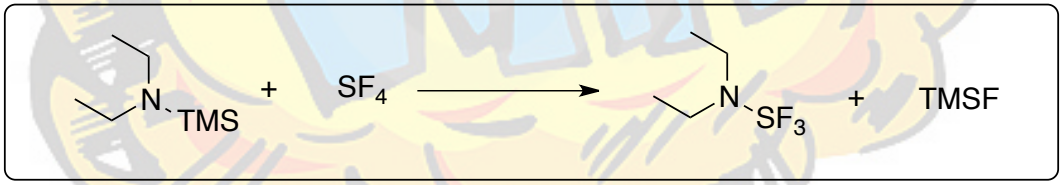


R	*n*	*ee* [%]	Configuration	Yield [%]
Me	1	53	*R*	93
Et	1	73	*R*	100
Bn	1	91	*R*	86
Me	2	40	*R*	94
Et	2	67	*R*	71
Bn	2	71	*S*	95

Shiro, JACS, 2001, 123, 7001

DAST

- DAST and Deoxofluor are by far the most useful nucleophilic fluorination reagents, DAST has been around since 1975.
- DAST will detonate if heated to about 90 C, so you have to be more careful when using it than you do with Selectfluor, but it is still relatively safe and easy to handle.
- Deoxyfluor has the same reactivity of DAST, but is more thermally stable.



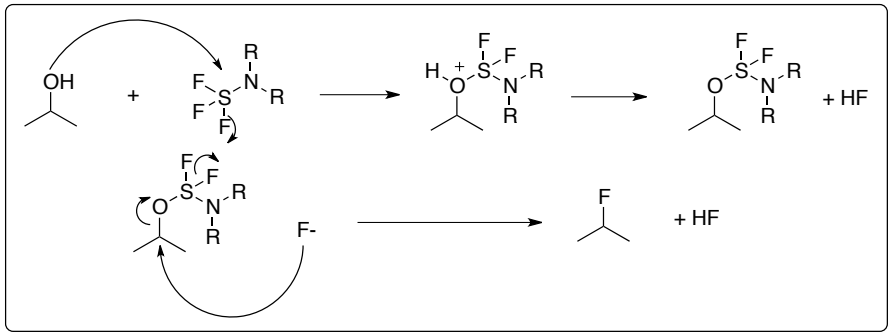
Diethylaminosulfurtrifluoride

Shreeve, synthesis, 2000, 2561

DAST

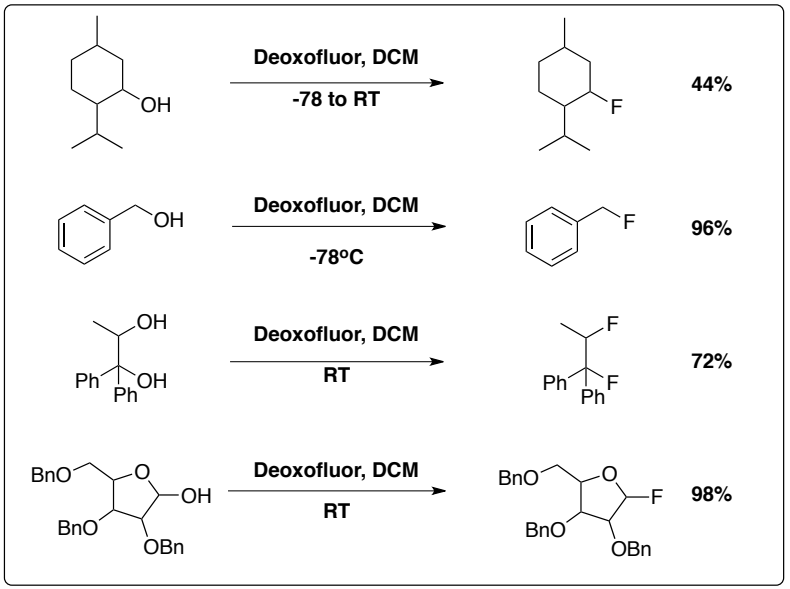
- Rate of the reaction is dependent on the steric accessibility of the alcohol

Proposed



- Similar mechanism to PBr3 and SOCl2

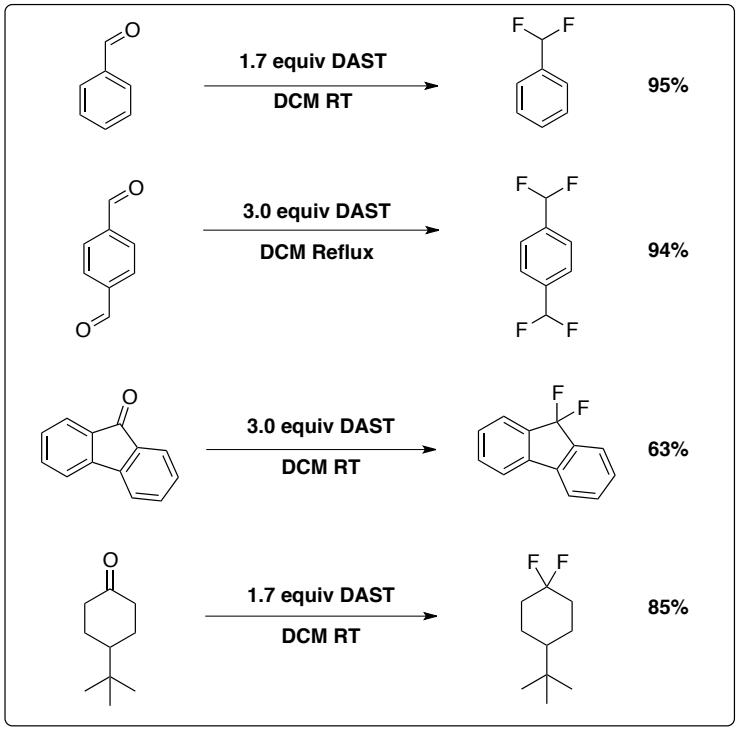
Fluorination of Alcohols



Prozonic, Chem. Commun. 1999, 215
Cheng, J. Org. Chem. 1999, 64, 7048
Shreeve, j. Fluorine Chem. 2002, 116, 23
Ball, J. Org. Chem, 2000, 65, 4984

DAST

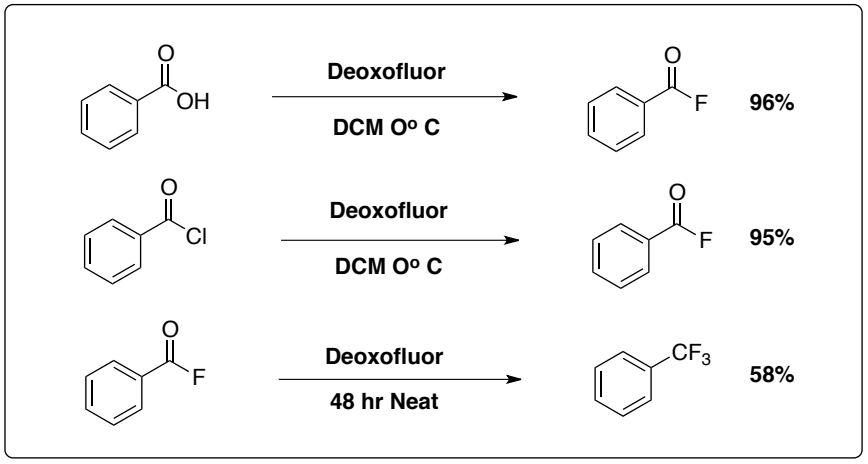
Reaction of DAST with Various Carbonyls



Prozonic, Chem. Commun. 1999, 215
Cheng, J. Org. Chem. 1999, 64, 7048
Shiji, 2001, 23, 296, Chem. Abstr. 136: 183600g

- Aldehydes and ketones can be converted to the difluorides
- Acids can be converted to the acid fluoride or trifluoromethyl at longer durations

Reactions with Acids

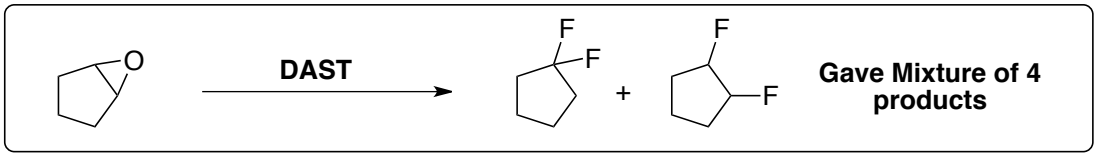


Prozonic, Chem. Commun. 1999, 215
Cheng, J. Org. Chem. 1999, 64, 7048

DAST

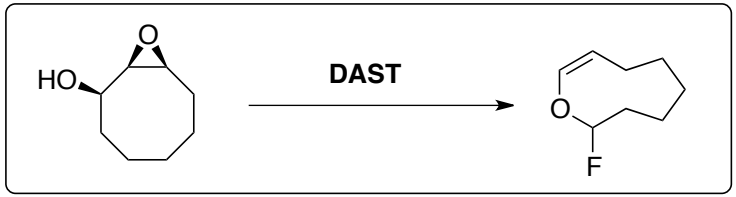
- Epoxides are difficult substrates

DAST With Epoxides



Hudlicky, Journal of Fluorine Chemistry, 36 (1987) 373-384

DAST Ring expansion

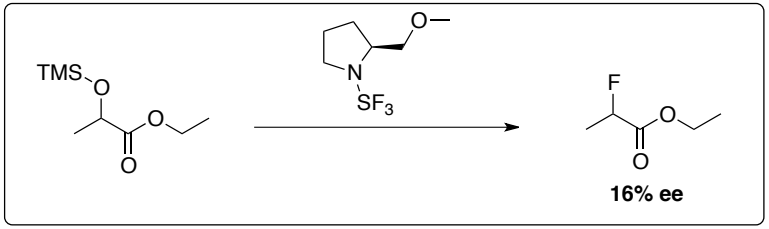


Gree, Org. Lett. 2002, 4, 451

- Unique c-c bond cleavage of epoxides

- Enantioselective nucleophilic fluorination with DAST – like compounds is ineffective

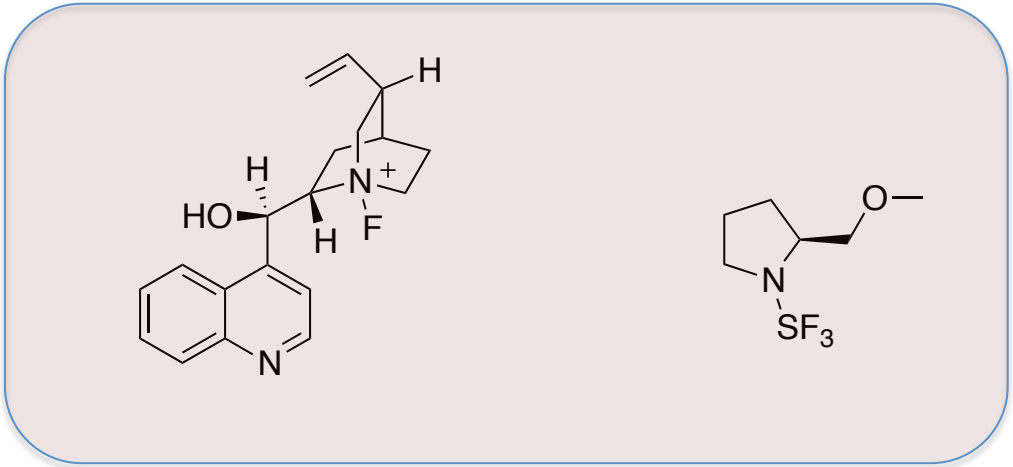
Enantioselective Variation



Sampson, J. Chem. Soc. Perkin Trans. I 1989, 1650

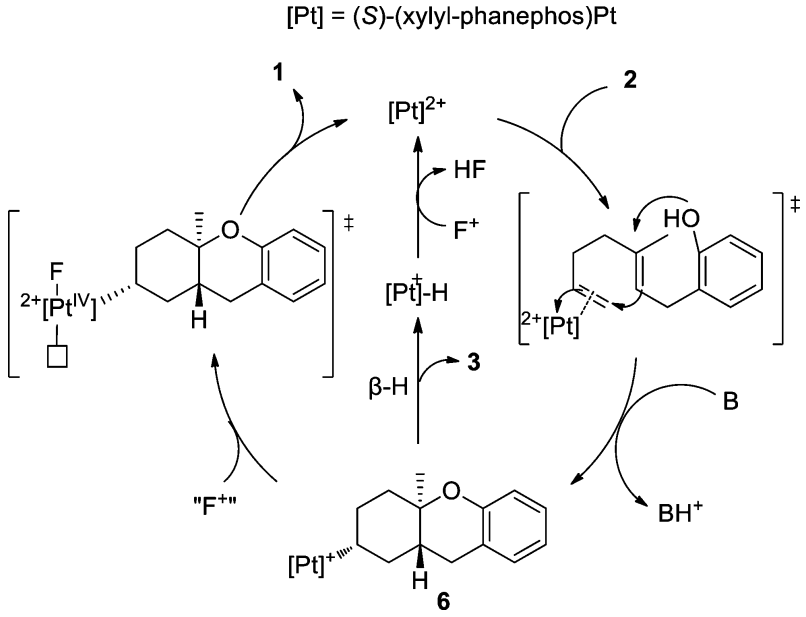
Metals in Fluorination

- Selectfluor and DAST can be used for a wide variety of fluorinations
- They are both much more mild and user friendly reagents than Fluorine gas
- Neither Selectfluor or DAST translated very well into an enantioselective process.



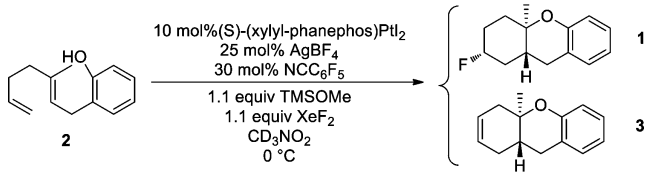
Electrophilic Fluorination With Pt

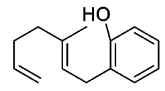
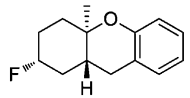
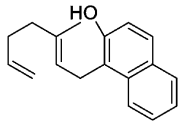
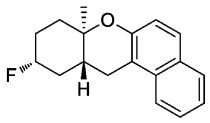
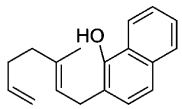
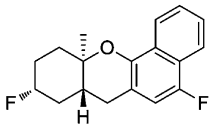
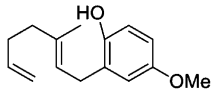
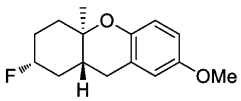
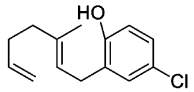
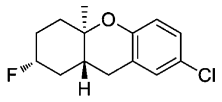
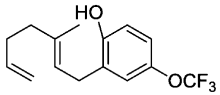
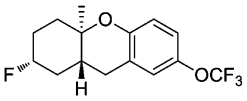
Scheme 2. Proposed Catalytic Cycle for Electrophilic Fluorination



- Fluorination outcompetes B-hydride elimination!

Table 2. Catalytic Electrophilic Fluorination[a]



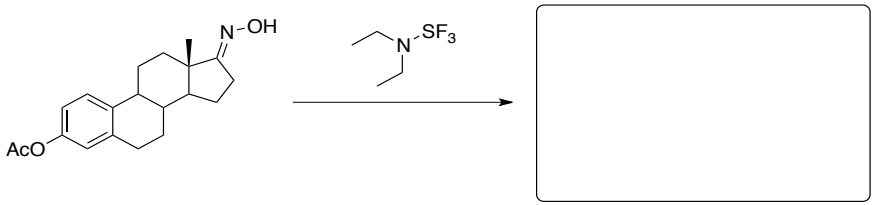
Entry	Polyene	Product	Yield **1** (%ee)[b]	Yield **3**[c]
1			67% (75)	14%
2			67% (73)	15%
3[d]			49% (86)	15%[e]
4			56% (81)	16%
5			60% (87)	13%
6			68% (83)	24%

Questions?

Thanks!
Questions for me?

Questions for you

1) Mechanism and Product



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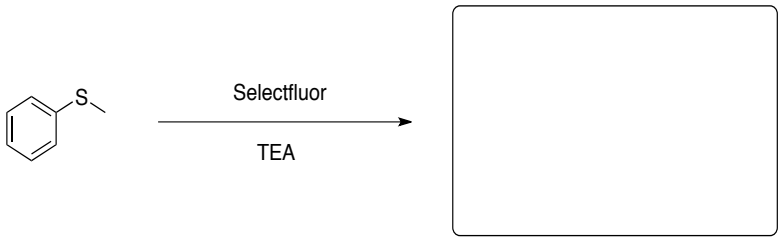
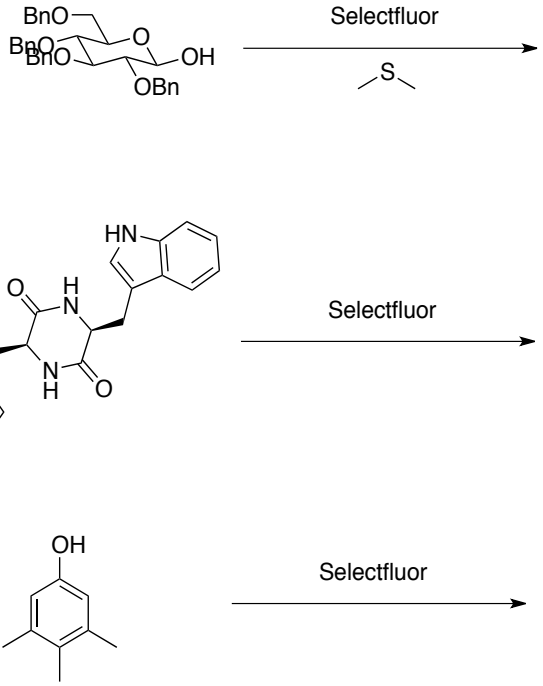
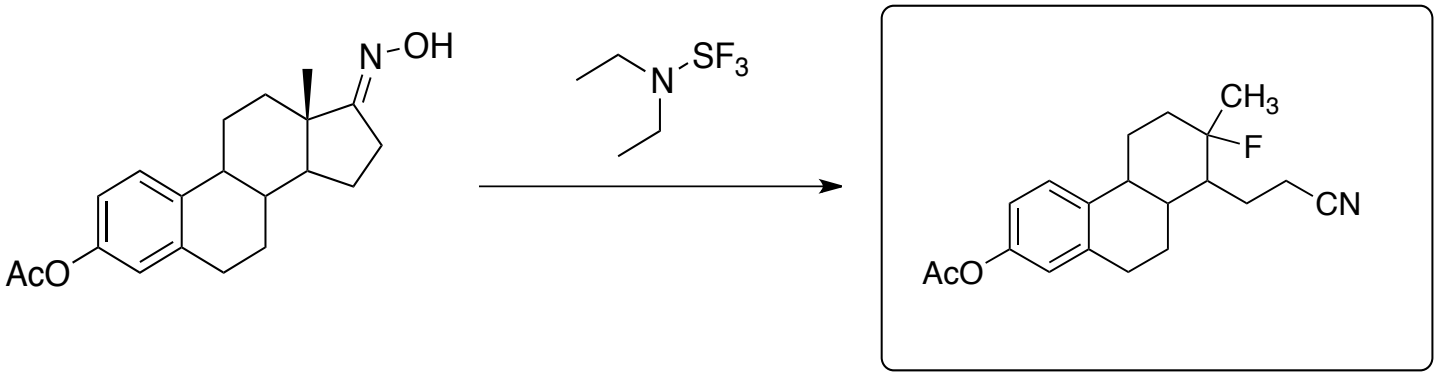


3) Products

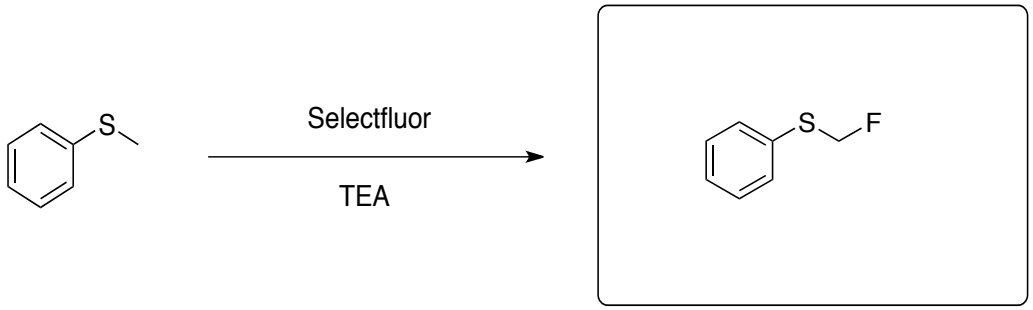


Answers

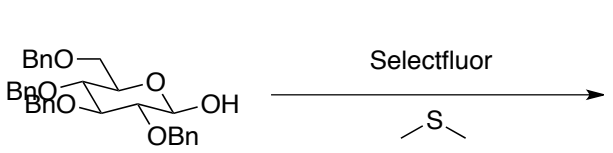


Richards, Tetrahedron Letters, 2000, 41, 9351

Answers



Answers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BnO
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OH
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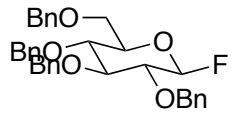
Selectfluor
S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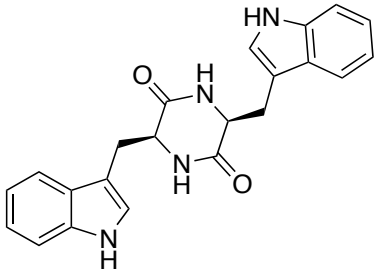
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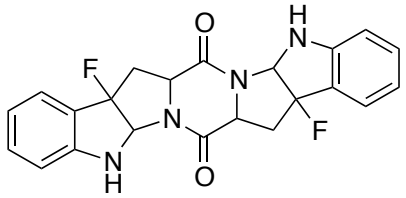
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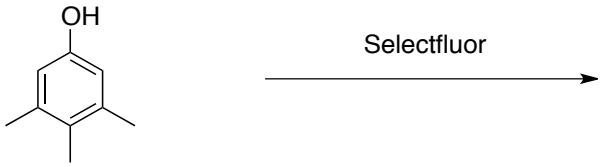
OH
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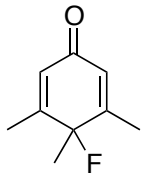
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