UT-BATTELLE

Fluorine Transfer between Ionic Molecules: Exploring Nature's Approach to Fluoroorganic Synthesis

17th Winter Fluorine Conference

St. Petersburg, FL

Andrei A. Gakh, PhD
Oak Ridge National Laboratory

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Discovery Chemistry Project
an Overview

Discovery Chemistry Project

Objective

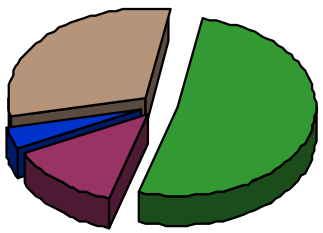
- **Synthesis and utilization of novel organic compounds by U.S. National Laboratories, chemical companies, and other government and non-government organizations.**

Approach

- **An international project offering the combination of expertise and resources of the participants in a team effort under the guidance and financial support of the Initiatives for Proliferation Prevention.**

Project-at-a-Glance

Resources



- Industry
- National Labs
- Universities
- International

Resources:

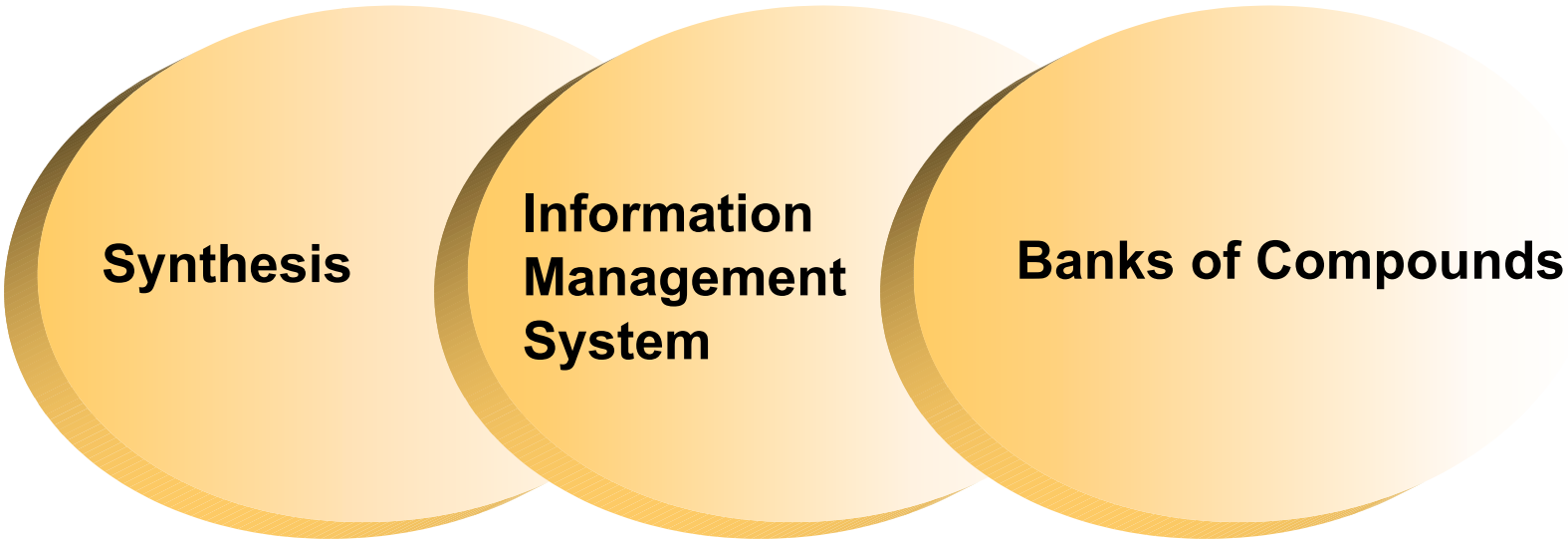
- **Industry: 52%**
- **National Laboratories: 13%**
- **Universities: 4%**
- **International Collaborators: 31%**

Major USG Funding:

- **US DOE, National Nuclear Security Administration**
  - **Initiatives for Proliferation Prevention**

Major Research Directions

Discovery Chemistry Project



More than 60% of the resources are allocated to biological targets (biological discovery)

Recent example:

- **39,647 structures proposed**
  - **11,248 structures accepted**
    - **6,217 compounds prepared**
    - **5,981 passed quality control**
    - **5,624 screened**
      - **127 active compounds identified**
        - **32 active leads selected**

Yield: 0.081% (active leads)

Human cost: >70 FTE (or > 2 FTE to develop an active lead)

Complexity of Biological Targets

GABA Receptors

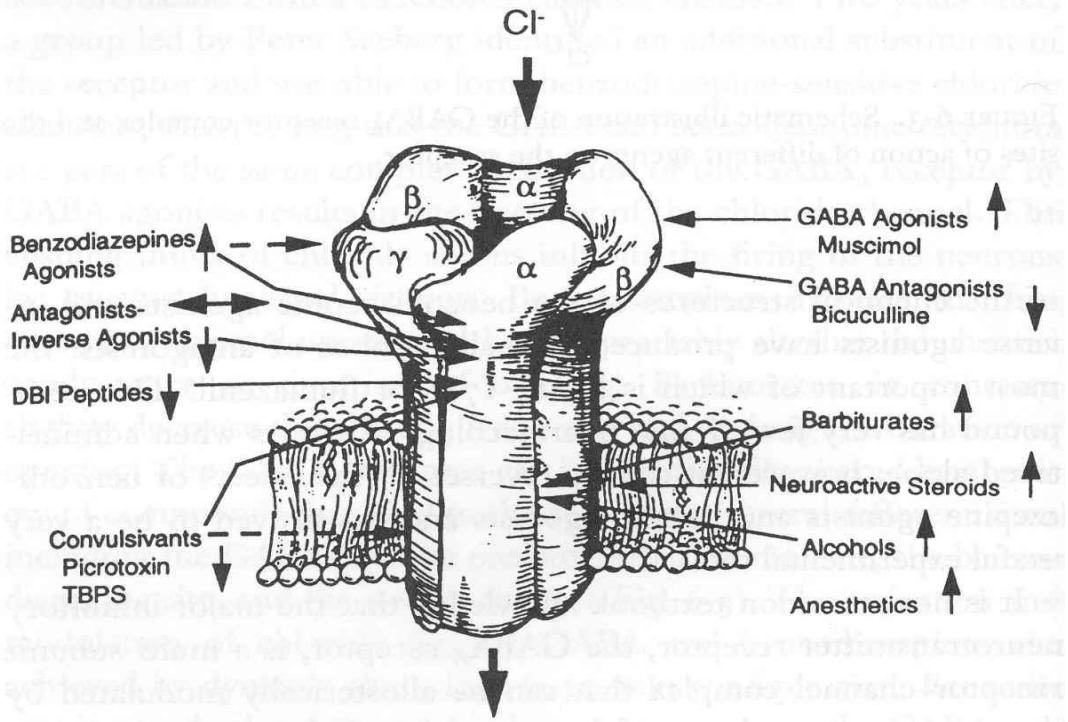
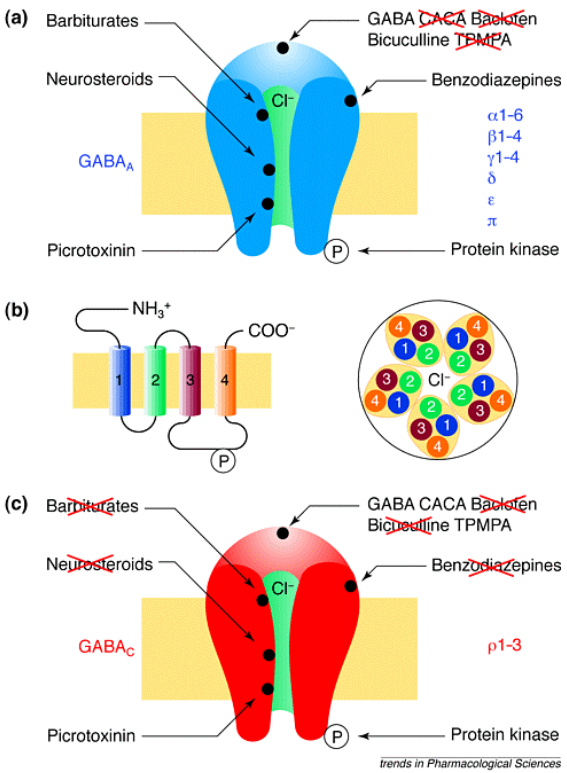


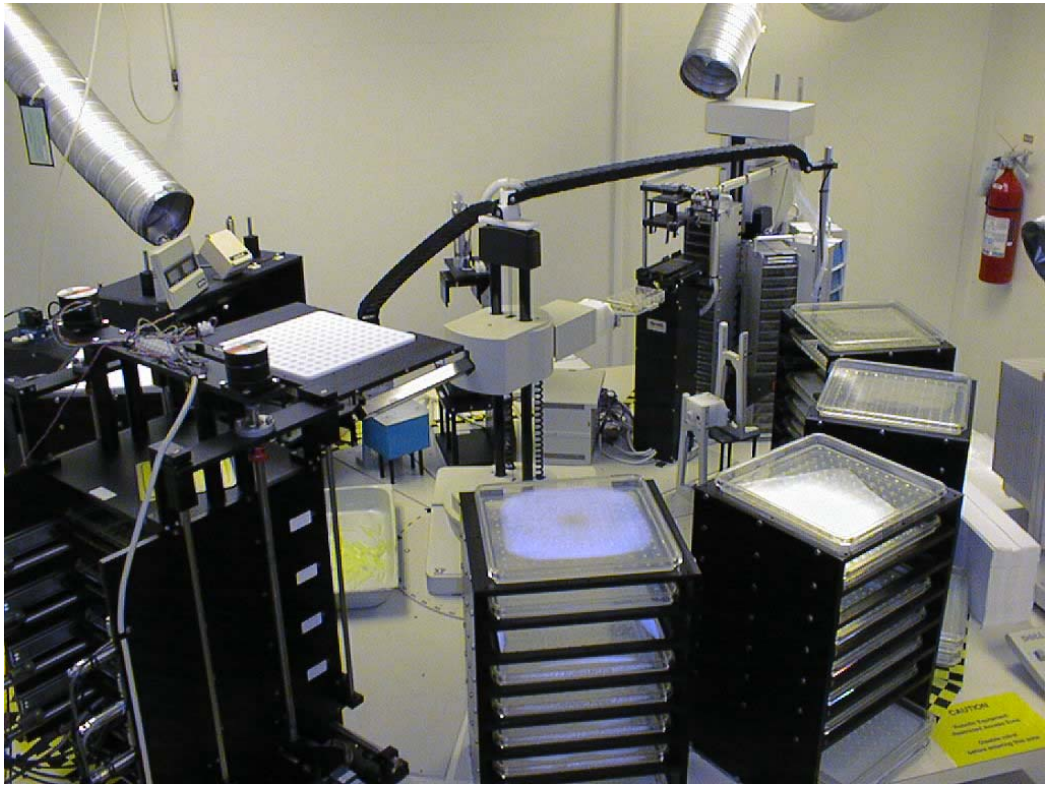
FIGURE 6-4. Schematic illustration of the $GABA_A$ receptor structure con-



The $GABA_A$ receptor is a pentamer consisting of various combinations of alpha, beta, and gamma subunits. Together these subunits form the chloride (Cl^-) ionophore (channel). The receptor also contains other binding sites (e.g., for benzodiazepines and barbiturates). These binding sites influence the frequency at which the channel opens and the duration of time the channel remains open in response to $GABA_A$, respectively. $GABA_B$ and $GABA_C$ receptors have different binding sites compared to $GABA_A$.

High Throughput Screening

Discovery Chemistry Project



The robot photo (courtesy of American Cyanamid Co.) shows the well plates with recombinant yeast containing a gene expressing a receptor and a marker gene. If a compound binds to the receptor the marker gene results in a color change so the actives can be easily picked out. The robot is capable of testing several hundred compounds per week.

Accelerated Discovery

Discovery Chemistry Project

- Objective: increasing odds of finding an active ligand
- Approach: utilization of fluoroorganic compounds*

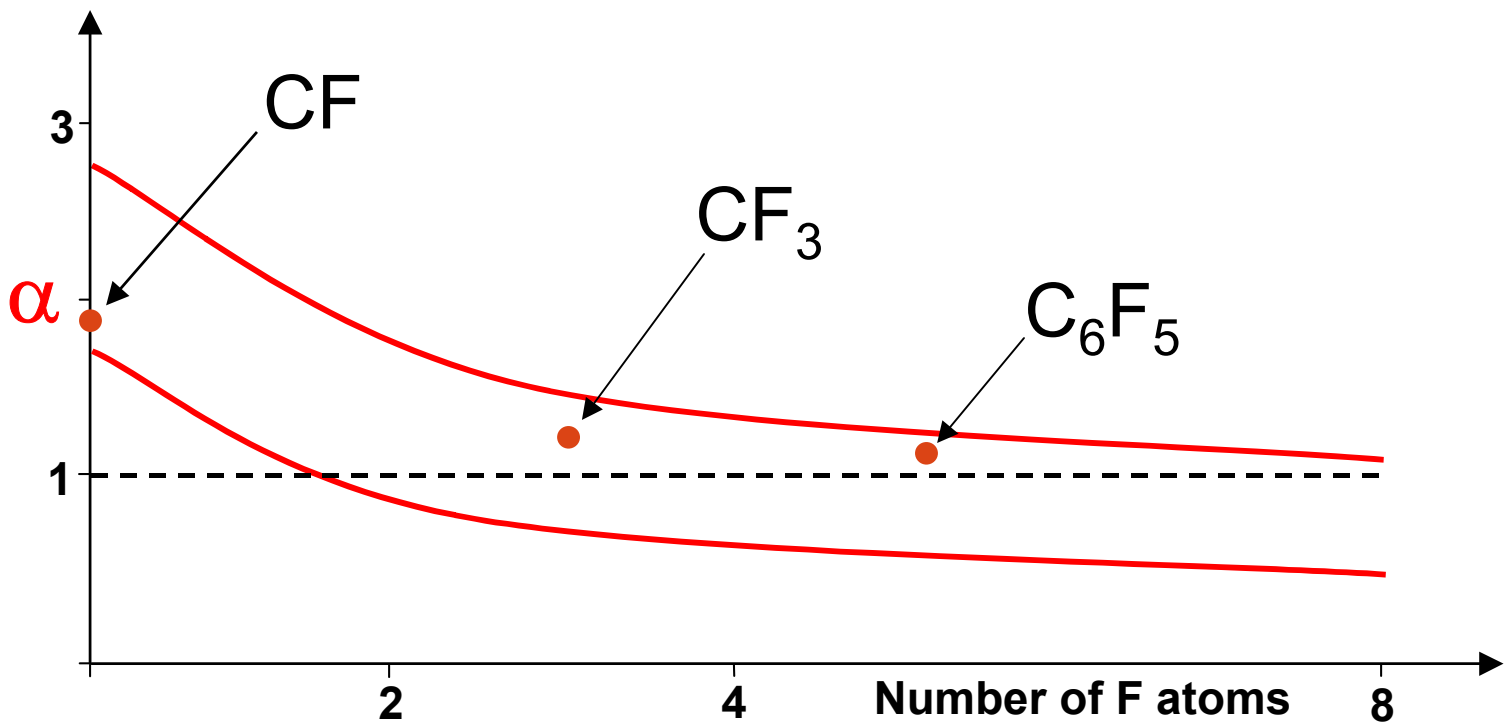
Screened Compounds	Active Compounds
➢Total Number:	➢Total Number:
• 6,217	• 127
➢With Fluorine:	➢With Fluorine:
• 421	• 15
• 6.7% (S_T)	• 11.8%(S_F)

"Acceleration Factor" $\alpha = S_F/S_T = 1.76$

*Can be accomplished without a significant loss of diversity

Further Improvements

Acceleration Factor



Acceleration coefficient α is affected by the number of fluorine atoms in a molecule. In this particular study the use of more than 3 fluorine atoms is counter-productive and actually reduces chances to find an active molecule.

Fluorine in Biological Systems

Discovery Chemistry Project

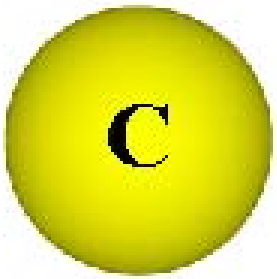
- **General considerations**
  - Naturally-occurring fluoroorganic molecules are very rare (less than 0.1% of all halogenated compounds); no common biological defense mechanisms exist to neutralize these xenobiotics
  - The sizes of fluorine atoms and other biogenic second-row elements (O/N/C) are similar; enzymatic recognition is not always effective
  - C-F bond strength is comparable to C-C bond strength; fluorine atoms are usually retained in molecules during biochemical transformations
  - Polar character of many fluorinated fragments may facilitate interactions with active sites of some protein-based receptors
- **Fluorine effects**
  - Unique; other halogens did not improve performance in our tests
  - Nonspecific in nature with respect to a molecular structure or a mode of bioaction

Fluorine and Other Biogenic Elements

A Comparative Overview

Van der Waals radii (Å), bond energies (KJ/mol) and electronegativities (Pauling units) are taken from A. Bondi (1964) and A.J. Gordon and R.A. Ford (1972)

~1.2 Å
C-H
~420 kJ
~2.2 PU



~1.7 Å
C-C
~350 kJ
~2.5 PU

~1.6 Å
C-N
~290 kJ
~3.1 PU

~1.5 Å
C-O
~360 kJ
~3.5 PU

~1.4 Å
C-F
~490 kJ
~4.1 PU

~1.8 Å
C-Cl
~330 kJ
~2.8 PU

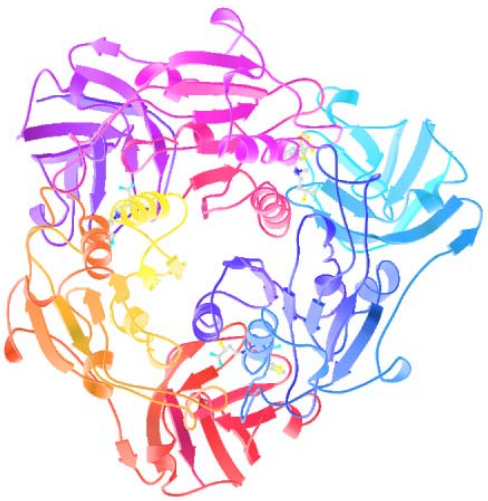
Synthesis of Fluoroorganic Compounds

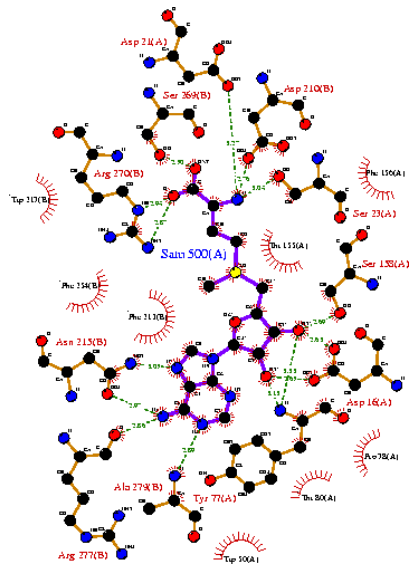
Discovery Chemistry Project

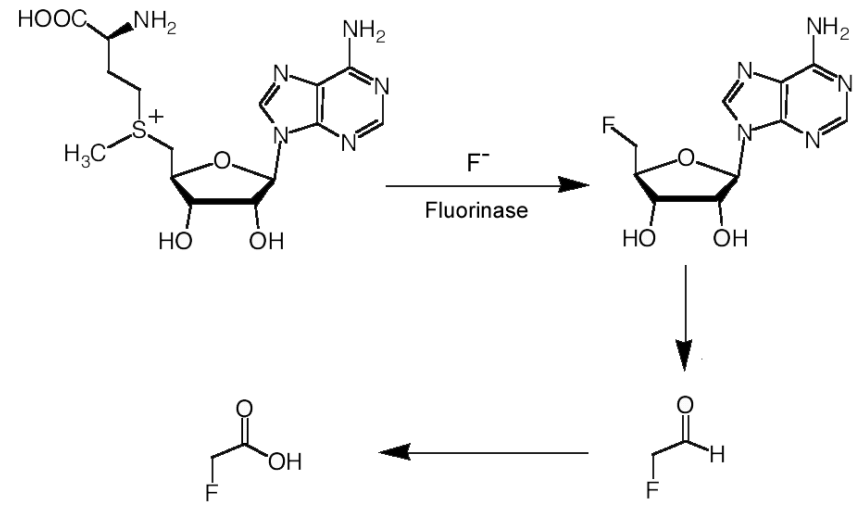
- **Electrophilic fluorination**
  - Elemental fluorine
  - N-F and O-F compounds
  - XeF_2 and other hypervalent fluorides
- **Nucleophilic fluorination via fluorodenitration**
  - Activated nitroaromatics
  - Nitroaliphatic and -heterocyclic compounds
- **From fluorinated blocks**
  - Functionalized -F, $-CF_2-$, $-CF_3$ and $-OCF_3$ compounds

Fluorine Biosynthesis

Adenosyl-Fluoride Synthase (Fluorinase)







Fluorinase (ca. 32000 Dalton)

1) O'Hagan, D., Schaffrath, C., Cobb, S.L., Hamilton, J.T. and Murphy, C.D. Biosynthesis of an organofluorine molecule. Nature 416 (2002) 279.
2) Dong, C., Huang, F., Deng, H., Schaffrath, C., Specner, J.B., O'Hagan, D. and Naismith, J.H. Crystal structure and mechanism of a bacterial fluorinating enzyme. Nature 427 (2004) 561-565.

Flurine Transfer: Ionic Structures

Possible Variants

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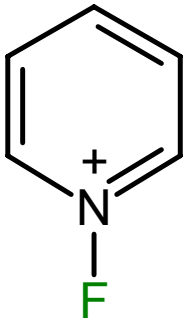
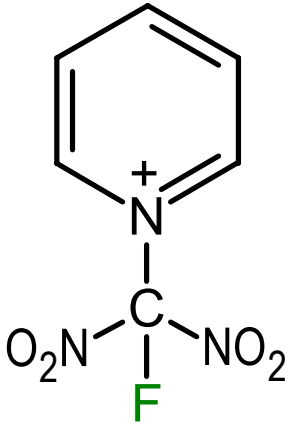
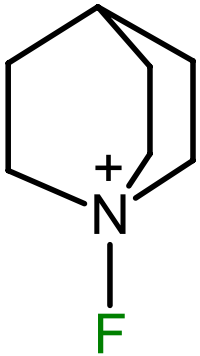
- **Possible variants of cation-anion and anion-anion interactions:**
  - Cationic electrophilic fluorinating agents and anionic nucleophiles (e.g., fluorinated ammonium or immonium salts and carbanions)
  - Anionic electrophilic fluorinating agents and anionic nucleophiles (e.g., fluoxysulfate salts and various C- and N-anions)
  - Anionic sources of fluoride ions and cationic substrates (e.g., bifluirides and quaternary ammonium salts)

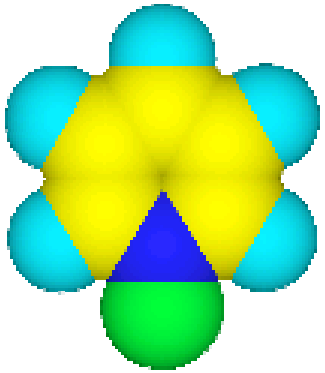
Fluorinated Heterocyclic Cations

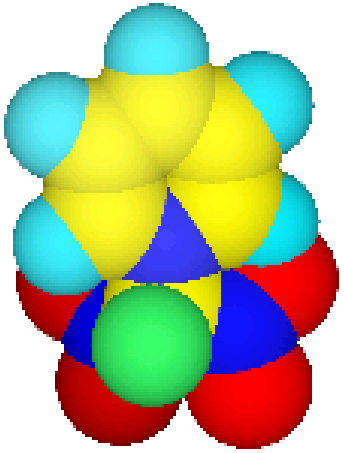
Structures

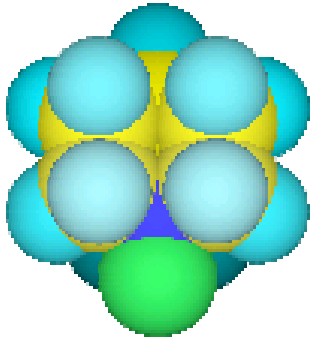






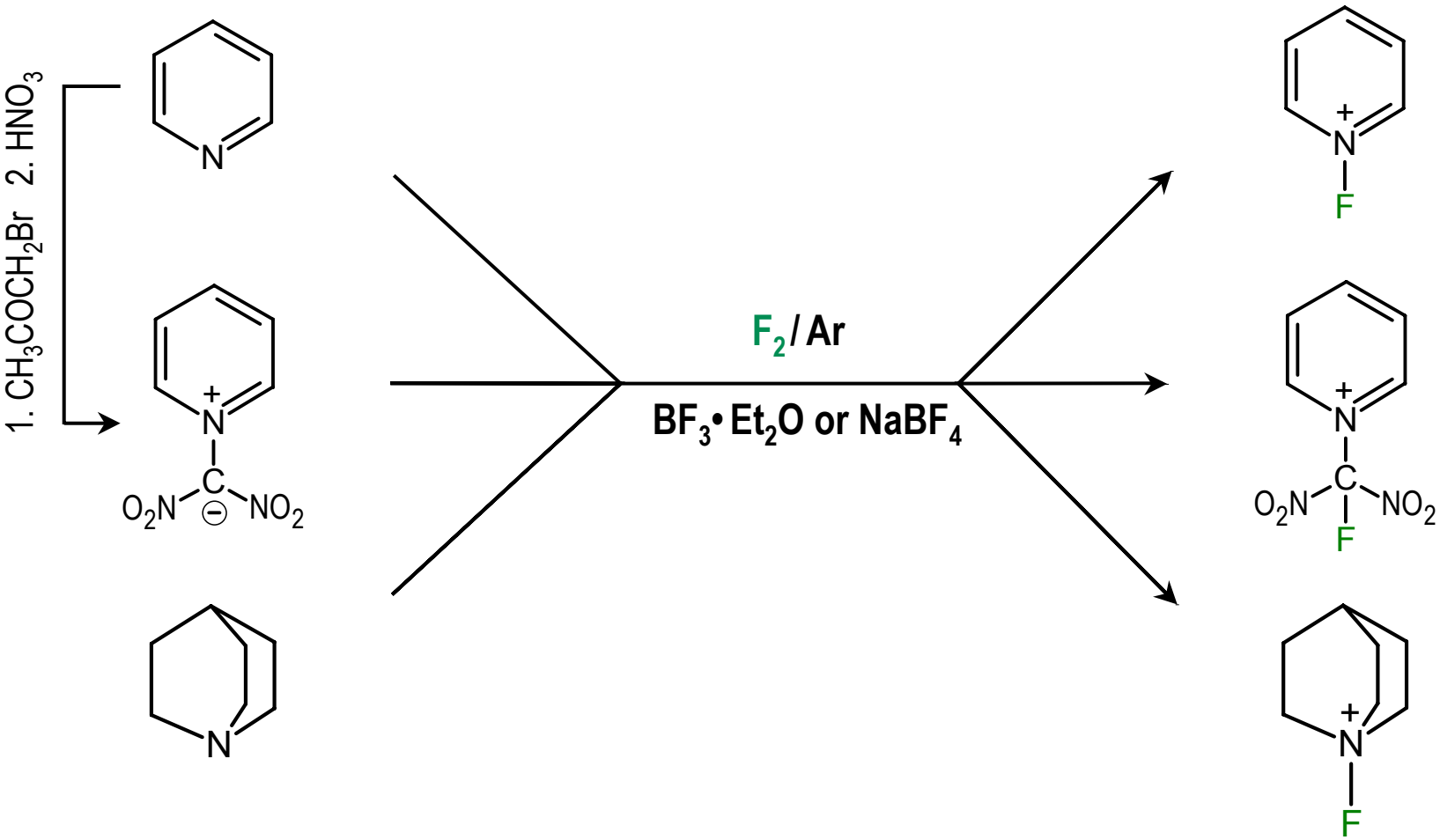






Fluorinated Heterocyclic Cations

Synthesis



Cation-Anion Reactions

Fluoroheterocyclic Cations and Nitro-carbanions

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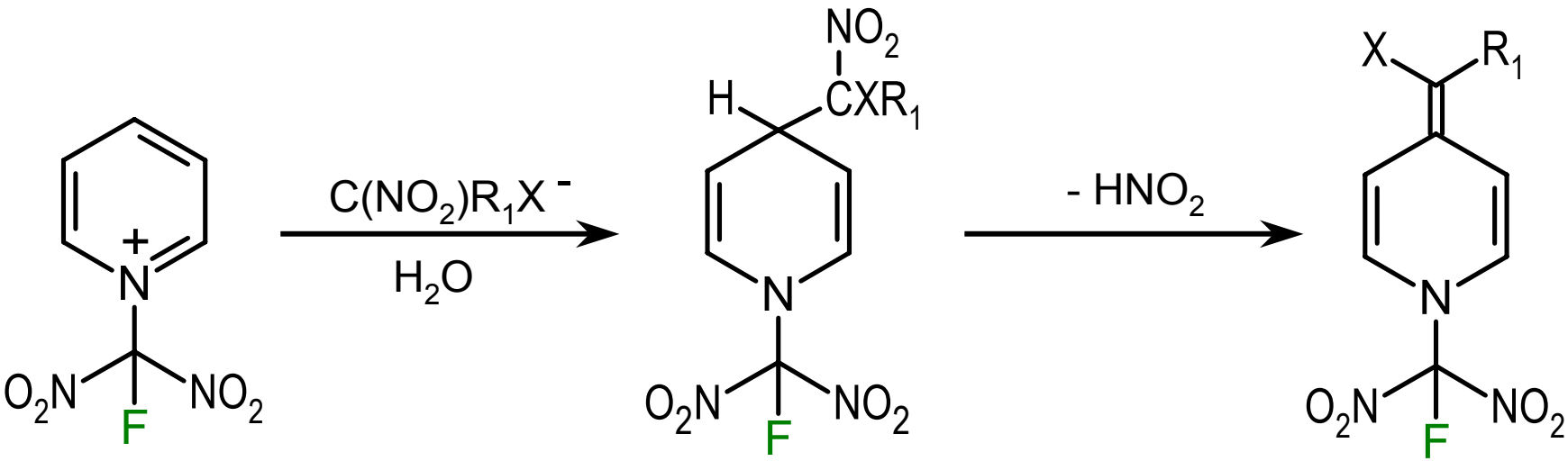
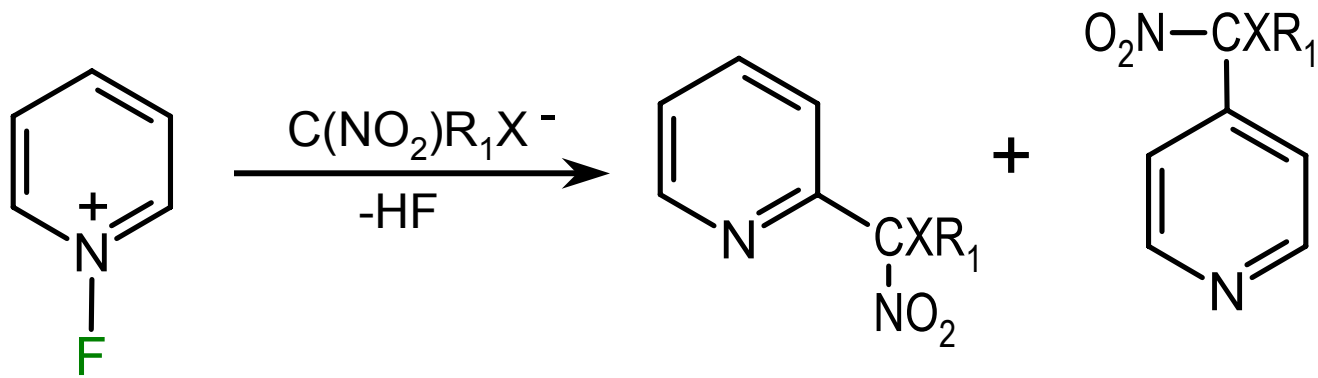
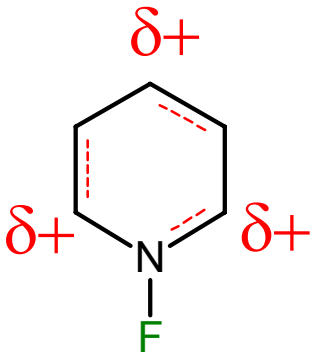


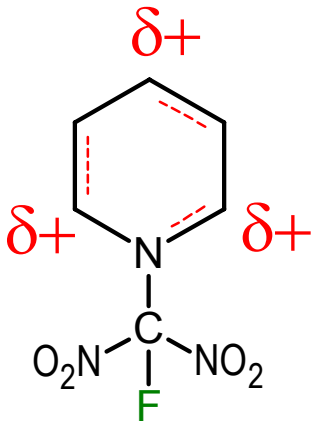


X = NO_2, CN, COOEt; R_1 = H, NO_2; $^-C(NO_2)_2CN$ - No Reaction

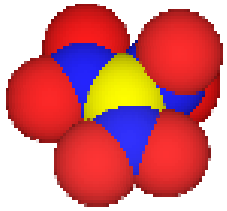
Fluoroheterocyclic Cations:
Ambident Electrophiles

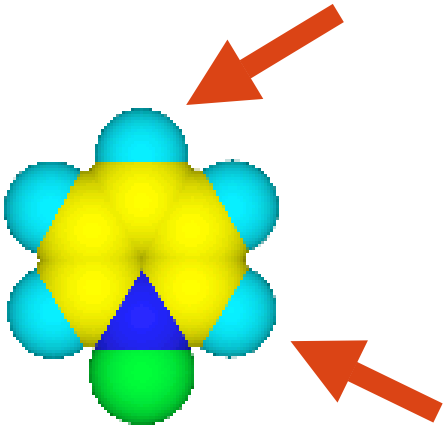
Discovery Chemistry Project

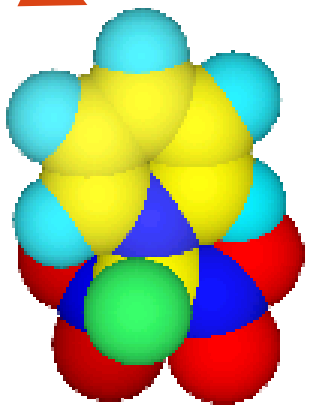




Nu⁻







(Blocked)

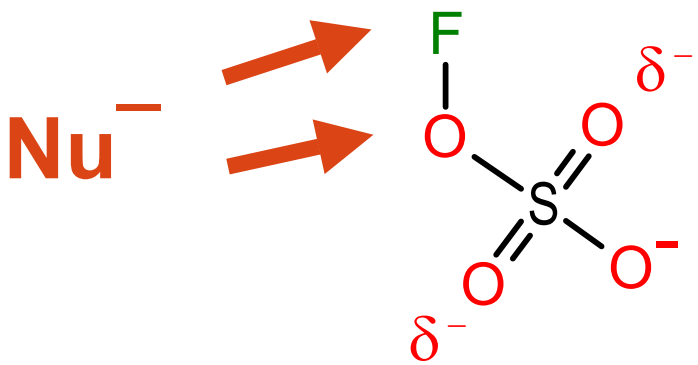
Fluoroxysulfate Anion:

A Possible Solution with Low Ambident Reactivity

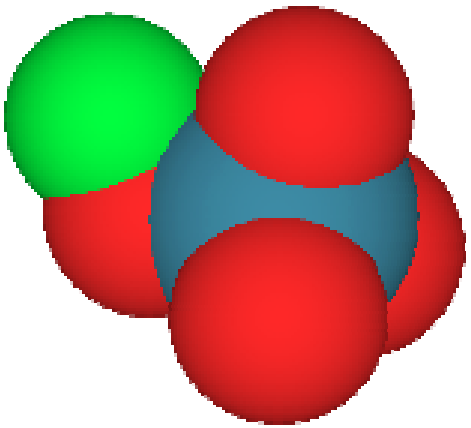
Discovery Chemistry Project

Synthesis:

$$SO_4^{2-} \xrightarrow[H_2O]{F_2 / Ar} FOSO_3^-$$



Structure of $FOSO_3^-$:



Ambident electrophilic properties of $FOSO_3^-$(O versus F) towards anions are less notable due to higher electronegativity of O compared to N and C as well as favorable negative charge distribution suppressing potential attack of anionic nucleophiles on SO_4 fragment. Ambident behavior is more pronounced in the cases of electroneutral double bonds.

Fluoroxysulfates, $FOSO_2O^- M^+$

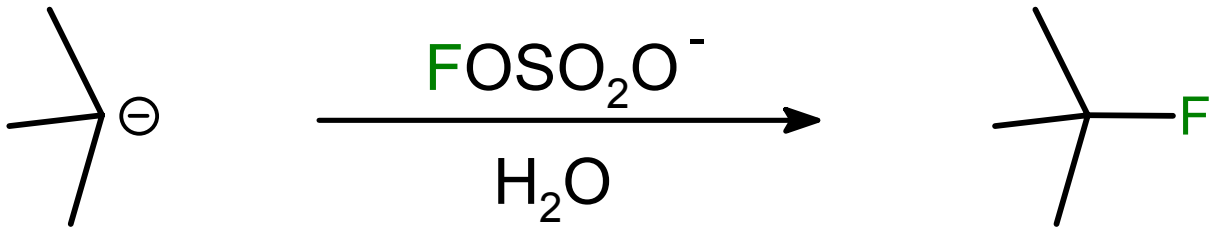
Unique Anionic Electrophilic Fluorinating Agents

Discovery Chemistry Project

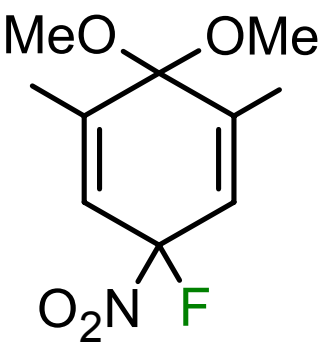
- **Advantages**
  - Can be produced *in situ* from inexpensive chemicals (elemental fluorine and sulfates) on a multi-kilogram scale using modified industrial equipment
  - Very potent electrophilic fluorinating agent
  - Good solubility in water
  - "Titration-like" mode of action - many reactions can be completed in seconds with 95-97% yield
  - Relatively mild exothermic effects during the reactions
- **Disadvantages:**
  - Thermally unstable (require cryogenic equipment for solution storage)
  - Can be used only in water or CH_3CN, not in water-ethanol mixtures
  - Strong oxidizer

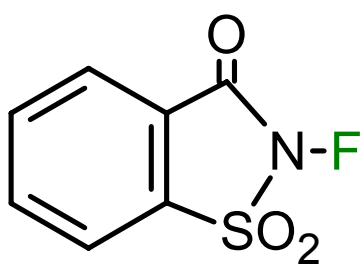
Electrophilic Fluorination in Water

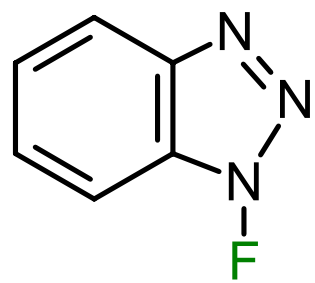
C- and N-anions with $FOSO_2O^- M^+$

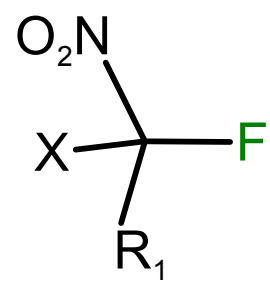


32-97%*





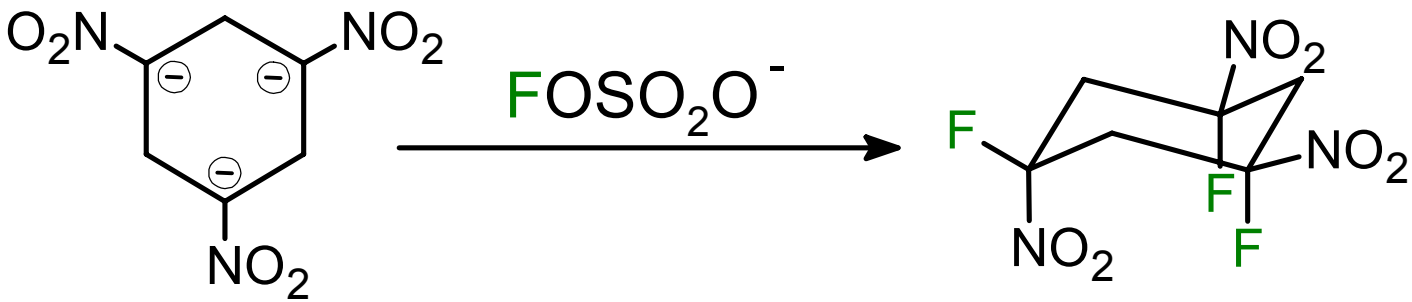




*In many cases yields can be improved in CH_3CN, particularly for anions with pKa > 5

Fluorination with $FOSO_2O^- M^+$

Poly-anions

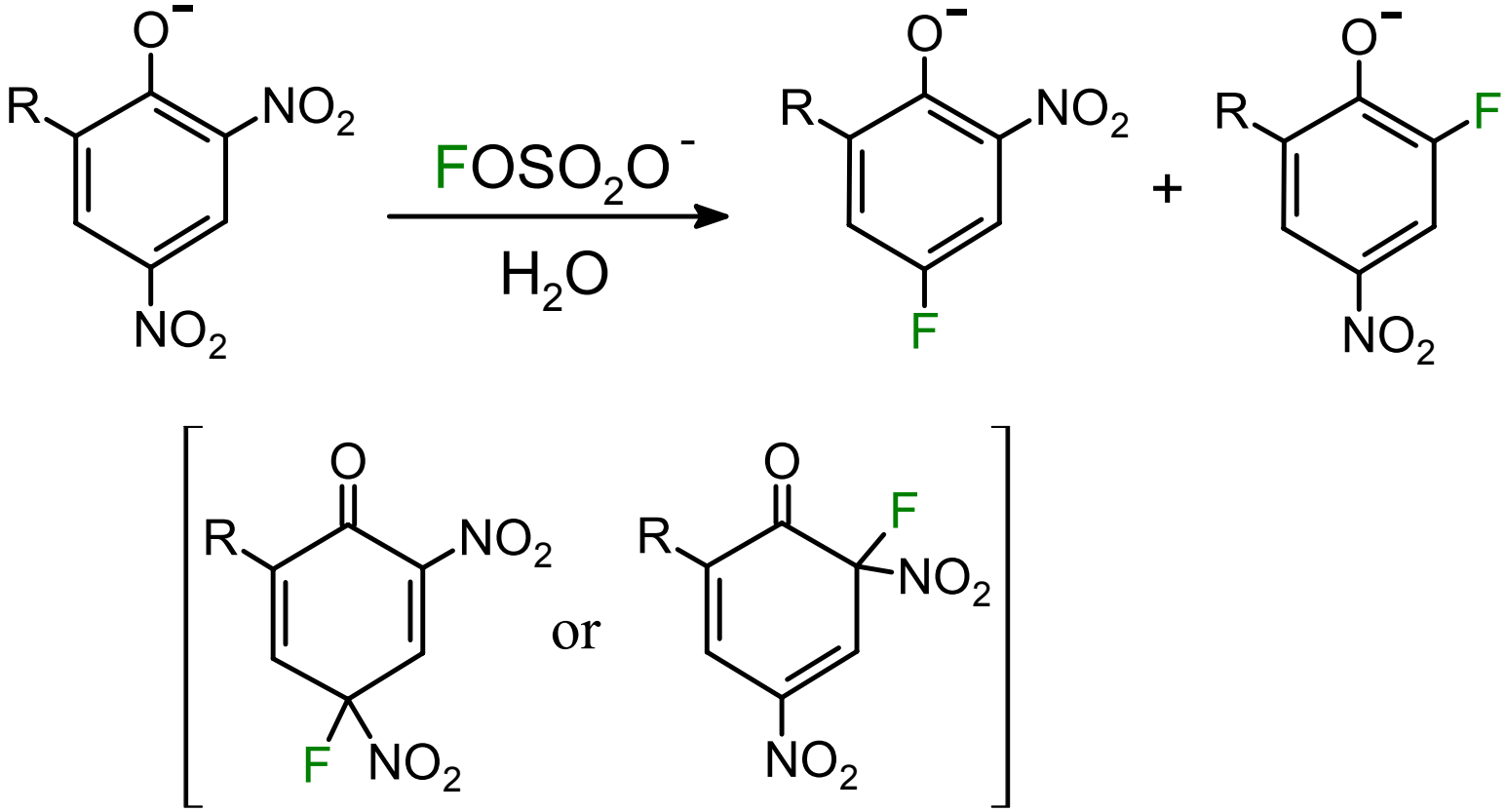


42%*

*in CH_3CN

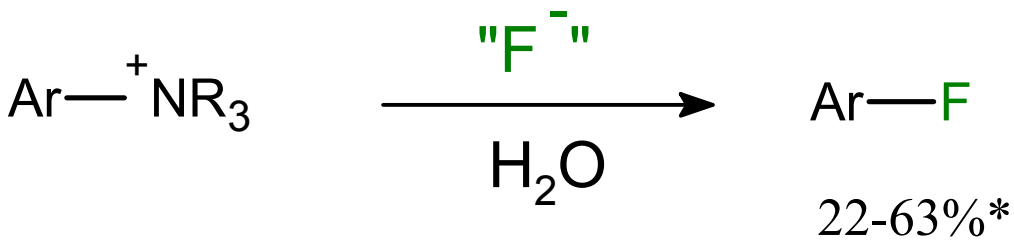
Fluorodenitration with $FOSO_2O^- M^+$

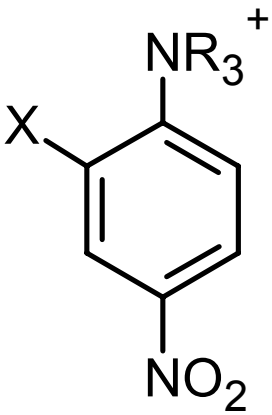
Nitrophenolates

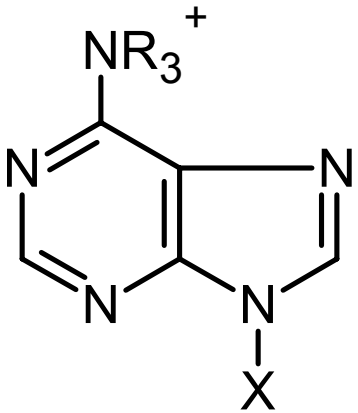


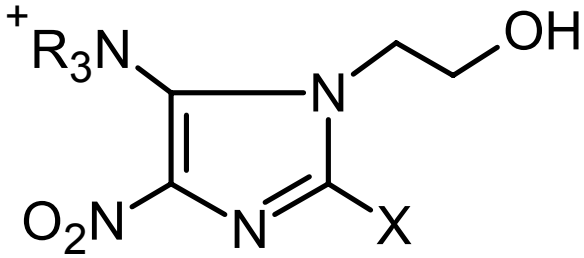
Nucleophilic Fluorination

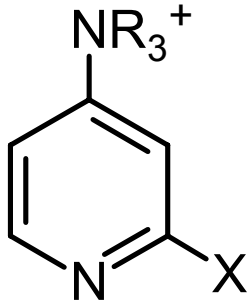
Via Quaternary Salts







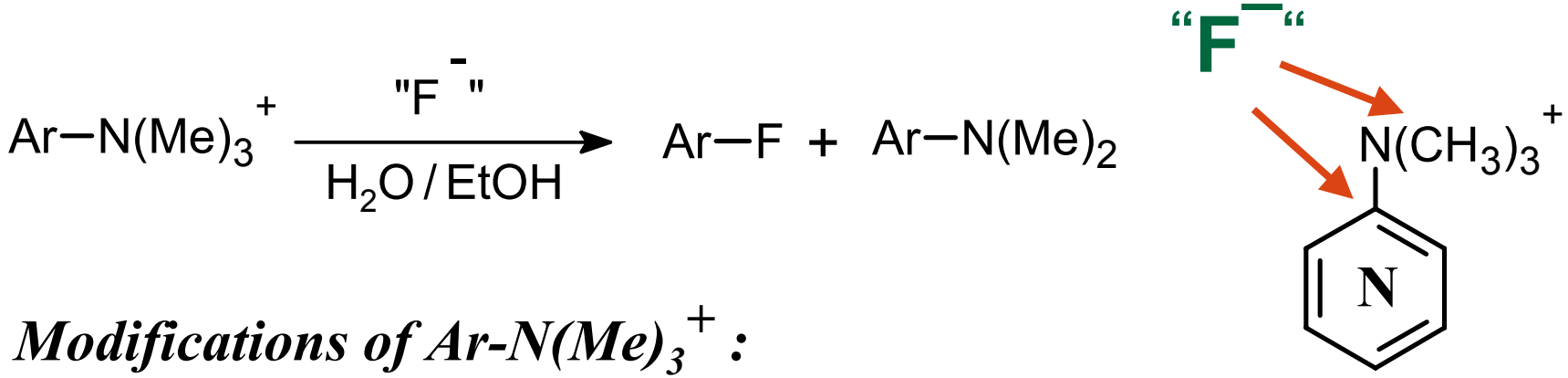




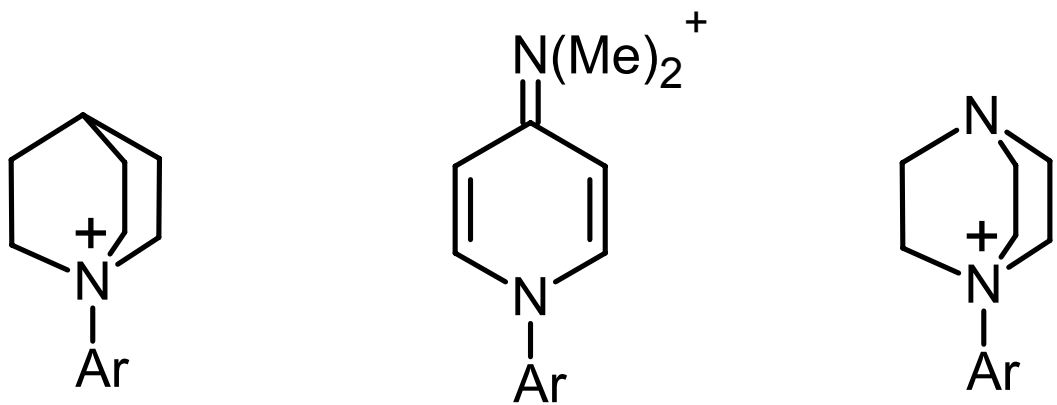
Side Reactions

Nucleophilic Fluorination of Ar-N(Me)$_3^+$ Salts

Discovery Chemistry Project



Modifications of Ar-N(Me)$_3^+$:



The best results were achieved with Ar-N(Me)$_3^+$

Sources of "F^-"

Discovery Chemistry Project

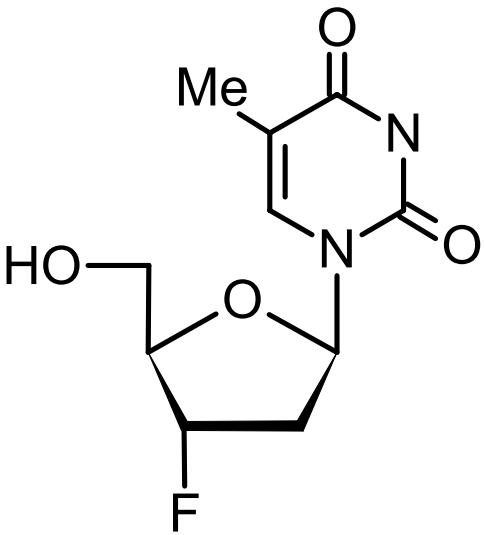
PF_6^- BF_4^- SiF_6^{2-} AlF_6^{3-} HF_2^- $F^- \cdot nH_2O$

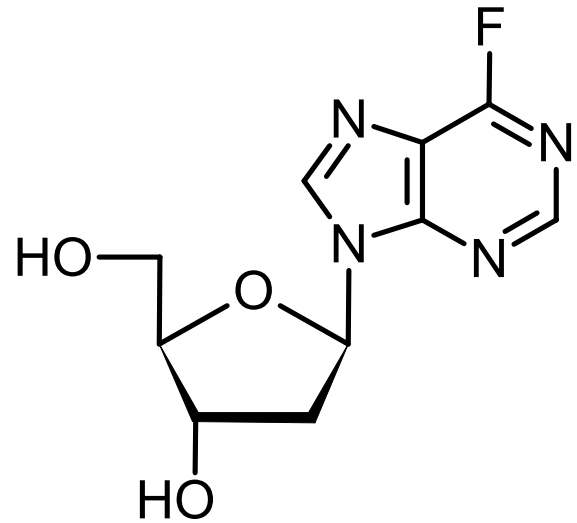
Nucleophilicity and Basicity

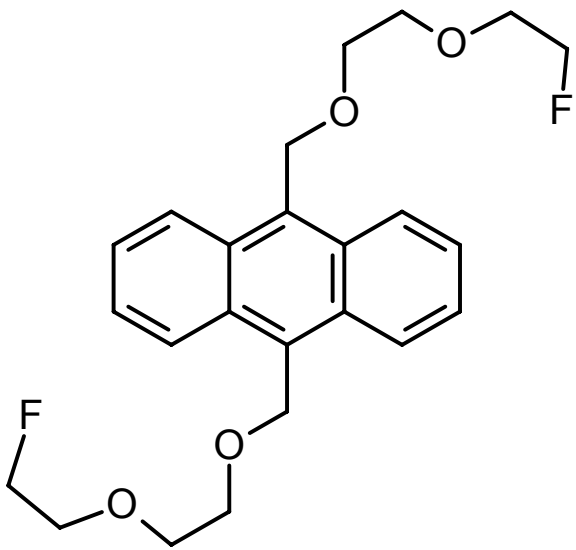
The best results were achieved with HF_2^- and AlF_6^{3-} in $EtOH/H_2O$

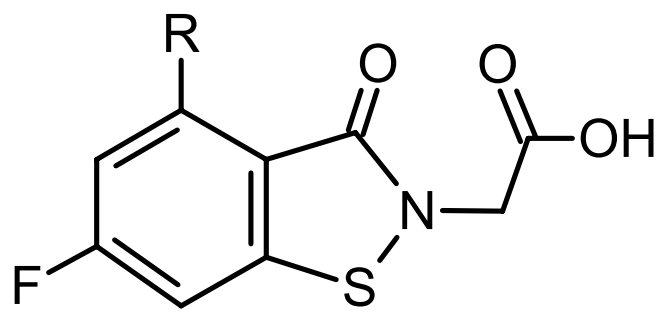
Additional Examples

Fluoroorganic Compounds









Acknowledgements

Discovery Chemistry Team and Collaborators

Dr. A.S. Astrat'ev
K.T. Barry
Dr. Ad Bax
Dr. P.V. Bonnesen
Prof. J.C. Bryan
Dr. AC Buchanan
M.N. Burnett
Dr. D.J. Coughlin
V.P. Chernyshov
Dr. E.W. Hagaman
D.A. Harkins
Dr. W. Heilman
M.A. Janney
Dr. P.G. Kislitsin
Prof. A.L. Klibanov
T. Laudeman
Dr. D.W. Noid
Dr. M. Raikhstadt
Dr. A. Yu. Romanovich
Dr. R.S. Sachleben
Dr. A.V. Samet
Dr. V.V. Semenov
Dr. A.M. Shestopalov
Dr. M.A. Sigman
Dr. V.B. Sokolov
Dr. T. Spraggins
Dr. Y. Sterlelenko
Dr. B.G. Sumpter
Dr. S. Trepalin
L.D. Trowbridge
Prof. A.A. Tuinman
Dr. S.G. Zlotin

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