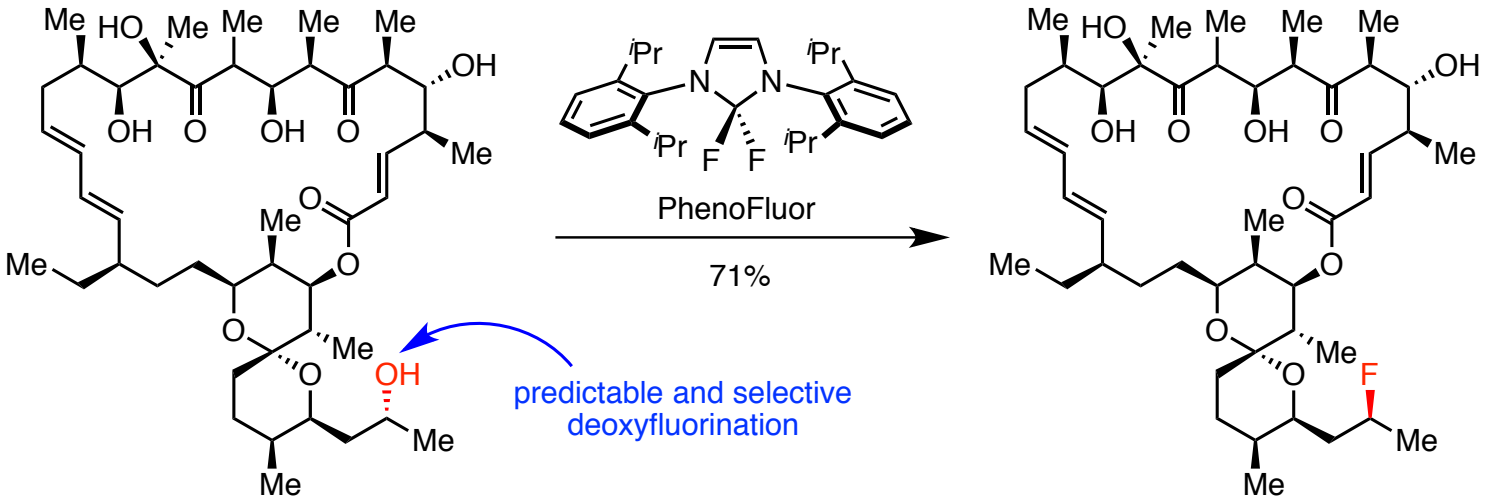
# Late-Stage Deoxyfluorination of Alcohols with PhenoFluor

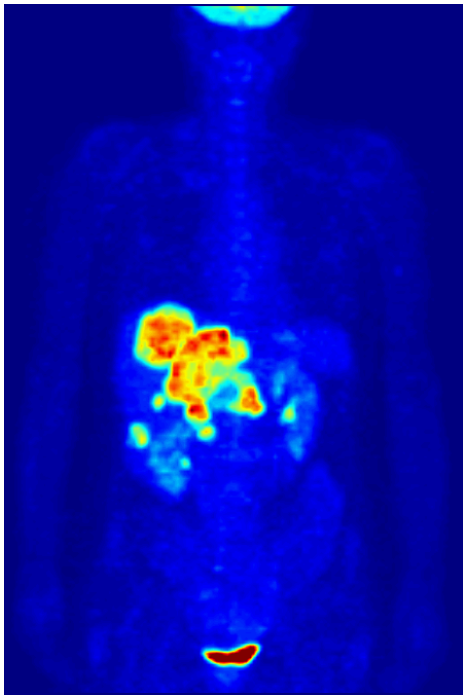
Sladojevich, F.; Arlow, S. I.; Tang, P.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *ASAP*
DOI: 10.1021/ja3125405

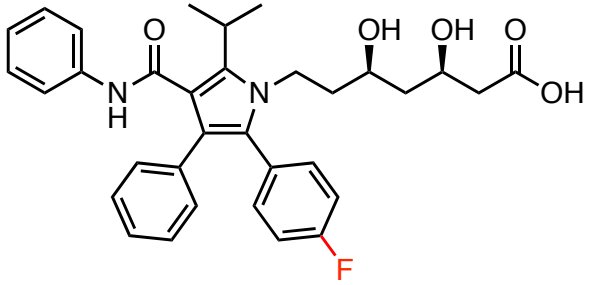



Kara George Rosenker
Current Literature
23 February 2013

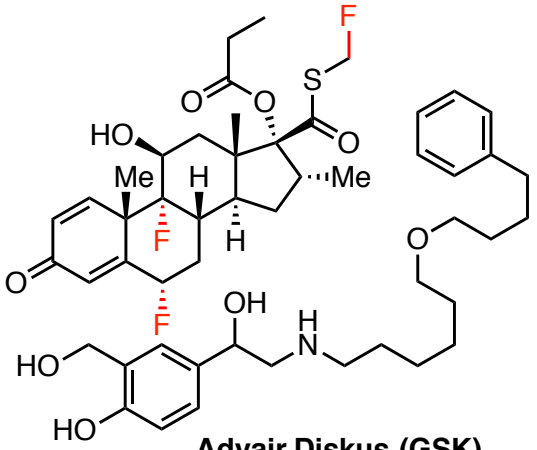
# Fluorine in Medicinal Chemistry

- The carbon fluorine bond plays an integral role in agrochemicals, pharmaceuticals, materials, and imaging
- Approximately 20% of all pharmaceuticals contain fluorine
- Strategies for the introduction of fluorine atoms in medicinal chemistry:
  - Metabolic stability by blocking metabolically labile sites
  - Modulate the physicochemical properties such as lipophilicity or basicity
  - Enhance binding affinity to a target protein
- Non-natural $^{18}F$ is the most commonly used positron-emitting isotope for molecular positron emission tomography (PET) imaging in oncology

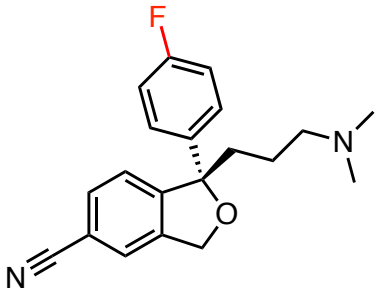





**Lipitor (Pfizer)**
$7.7 billion (2011)




**Advair Diskus (GSK)**
$4.6 billion

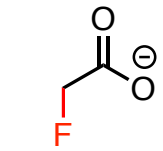



**Lexapro**
**(Forest Laboratories)**
$2.9 billion (2011)

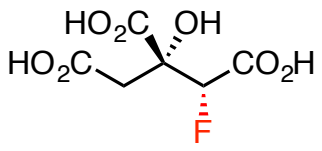
(a) Vitaku, E.; Ilardi, E.A.; Njarðarson, J.T. Top 200 Pharmaceutical Products by US Retail Sales in 2011. (b) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (e) Jens Langner, J.; *retrieved from http://en.wikipedia.org/wiki/File:PET-MIPS-anim.gif#filelinks*

# Carbon-Fluorine Bond Formation

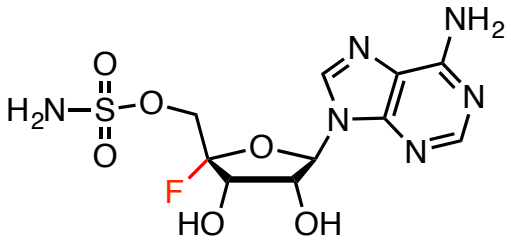
- Despite fluorine's importance, carbon-fluorine bond formation still represents a formidable synthetic challenge
- Only 21 biosynthesized natural molecules containing fluorine are known and no fluoroperoxidase is known
- Conventional fluorination reactions are generally limited to very simple molecules, with reliable fluorination of more complex molecules at specific positions being difficult
- New methods to incorporate fluorine into complex organic molecules are crucial to the progress of the field



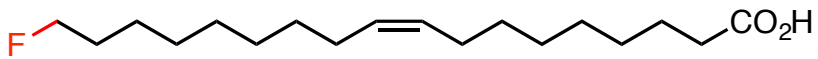

**fluoroacetate**




**fluorocitrate**




**nucleocidin**




**ω-fluoro-oleic acid**


Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637.
Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
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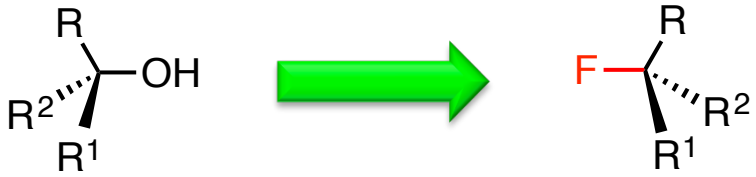



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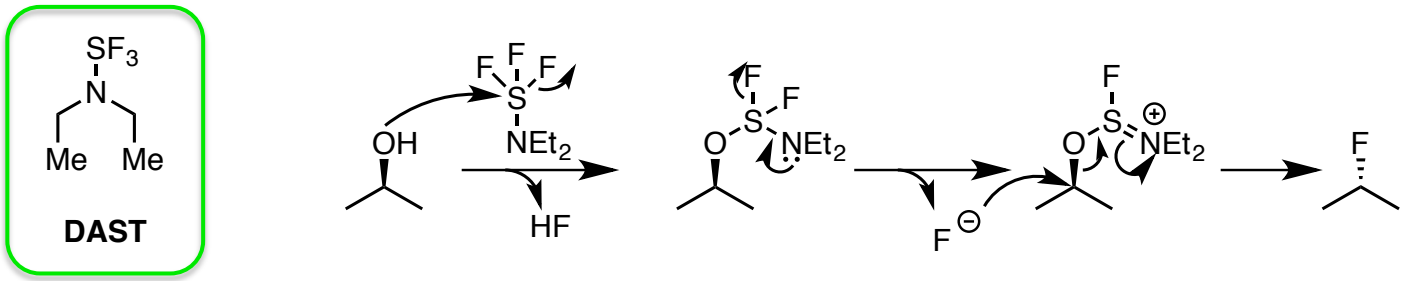
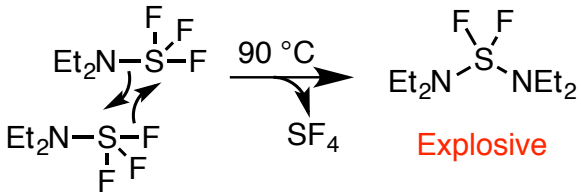
# Deoxyfluorination Reagents: DAST and Deoxo-Fluor®

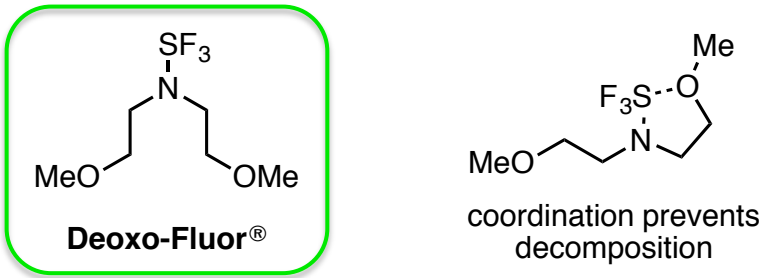
- Reported by Middleton in 1975 as the first bench-stable deoxyfluorinating reagent and a useful alternative to $SF_4$




- DAST suffers from poor thermal stability and potentially hazardous scale-up



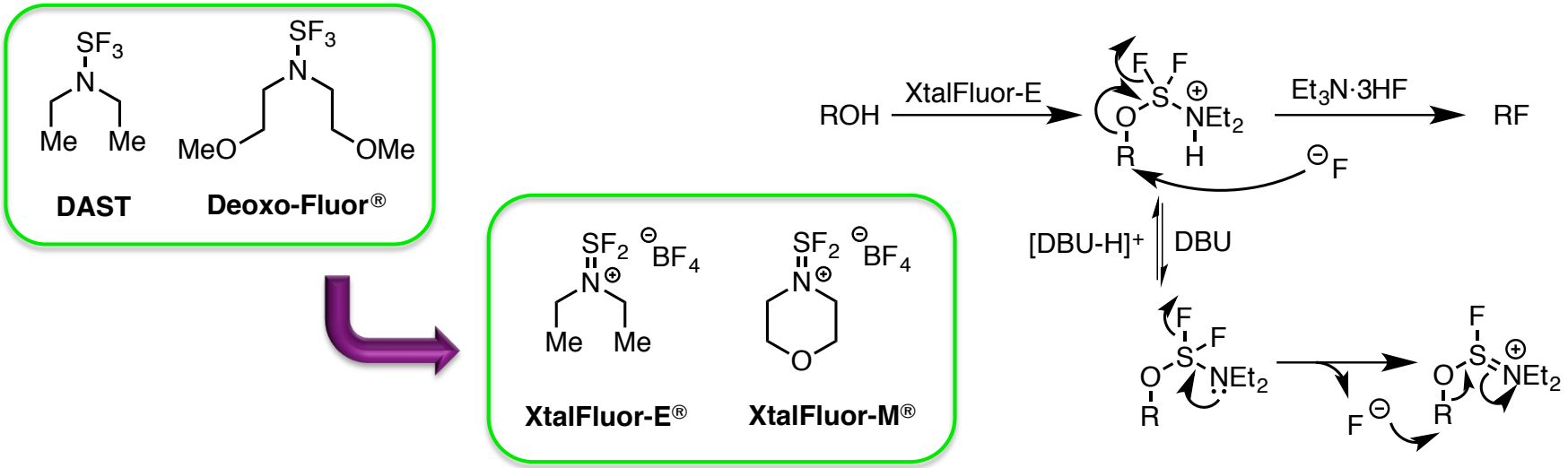

- Deoxo-Fluor® was introduced in 1999 and is a significant competitor to DAST for deoxyfluorination reactions due to its improved thermal stability





Middleton, W.J. *J. Org. Chem.* **1975**, *40*, 574.
Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048.
Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M. *Chem. Commun*. **1999**, 215.

# Deoxyfluorination Reagents: XtalFluor-E® and XtalFluor-M®

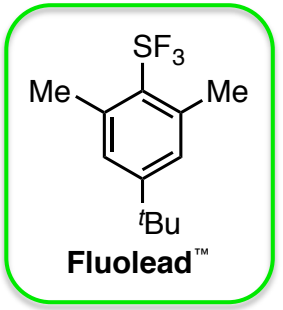



- In 2009, Courturier and co-workers reported the preparation and use of XtalFluor-E® and XtalFluor-M®
- XtalFluor-E® and XtalFluor-M® are crystalline reagents that are relatively safe and cost-efficient to prepare
- The reactions require the addition of either an HF•amine reagent or DBU for efficient transformation
- The XtalFluor® reagents are typically more selective and reduce the levels of elimination side products often observed with DAST and Deoxo-Fluor®

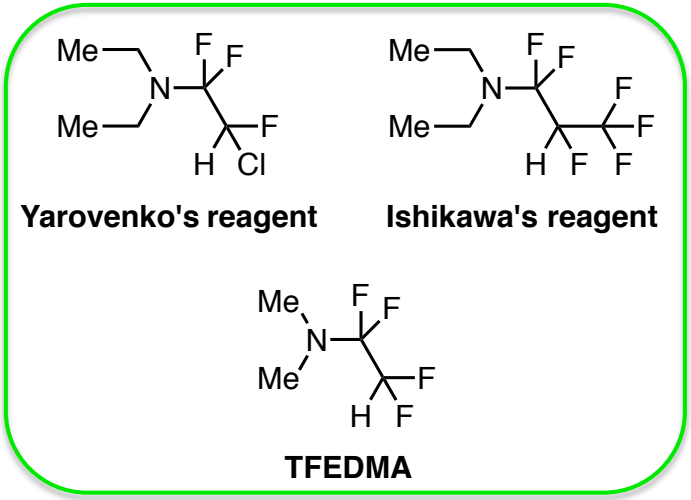
L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401.
Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050.

# Deoxyfluorination Reagents: Fluolead™ and TFEDMA, Yarovenko's and Ishikawa's reagents

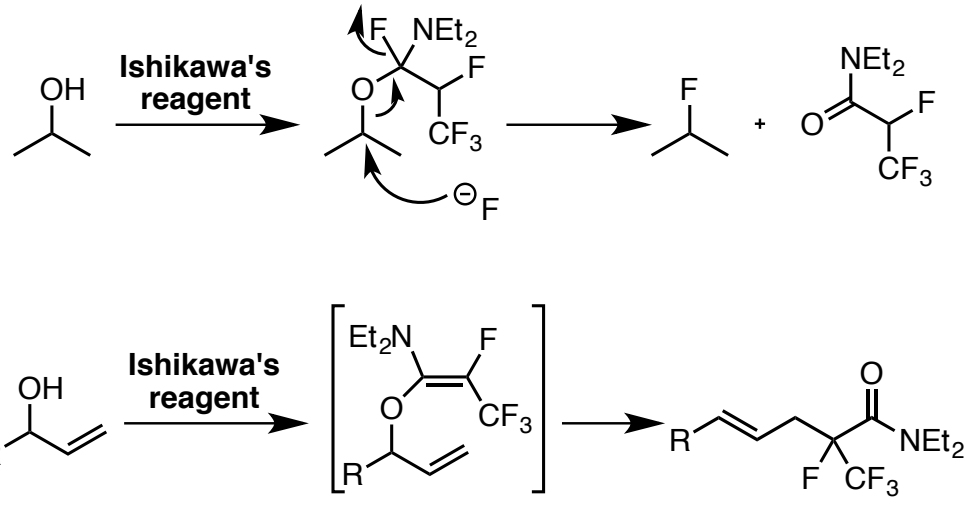
- In 2010, Umemoto and co-workers introduced the second generation $PhSF_3$, which is marketed as Fluolead™
- More chemically stable than $PhSF_3$, and more more thermally stable than DAST because of the stronger C-S bond in Fluolead™
- Ishikawa's, Yarovenko's, and TFDMA reagents fluorinate a wide range of primary and secondary alcohols to provide alkyl fluorides
- There reagents are generally prepared by the addition of $Et_2NH$ to the corresponding halogenated alkene
- This group of reagents can suffer from formation of ester and amide side products



**Fluolead™**

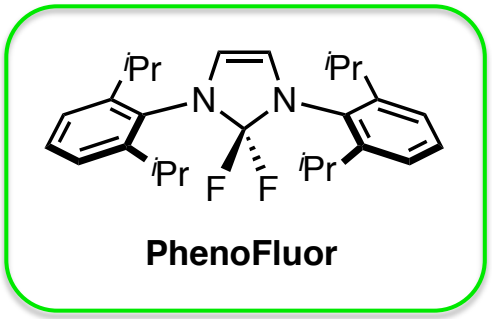


**Yarovenko's reagent** **Ishikawa's reagent** **TFEDMA**



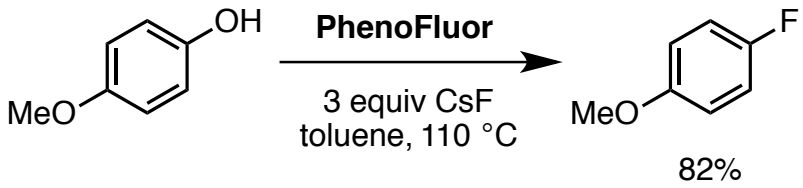

(a) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, *132*, 18199. (b) Takaoka, A.; Iwakiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3377. (c) Petrov, V. A.; Swearingen, S.; Hong, W.; Petersen, W. C. *J. Fluorine Chem.* **2001**, *109*, 25. (d) Yarovenko, N. N.; Raksha, M. S. *Zh. Obshch. Khim.* **1959**, *29*, 2159.

# Deoxyfluorination Reagent: PhenoFluor




**PhenoFluor**

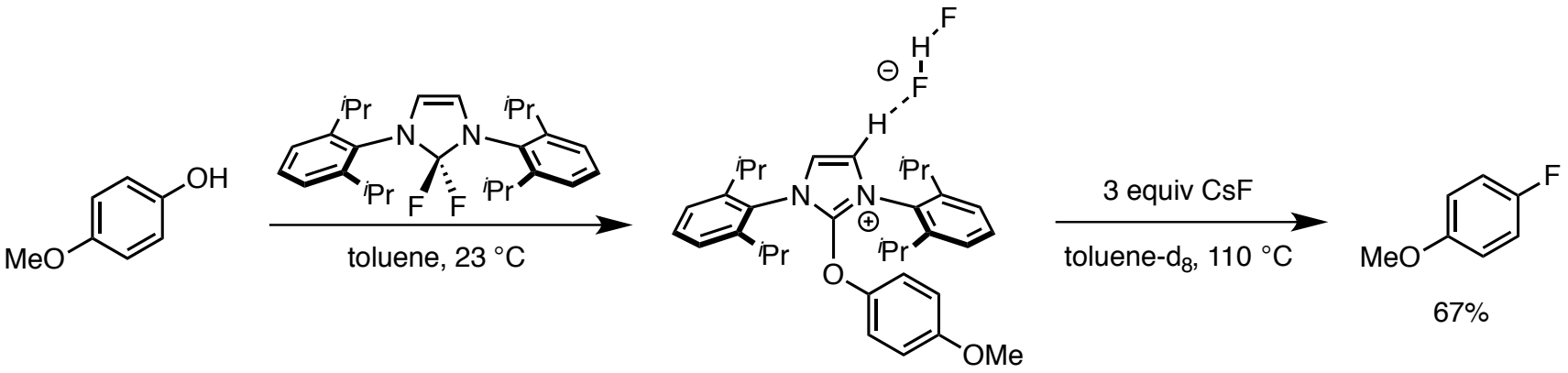
- PhenoFluor was first reported by Ritter and co-workers in 2011 for deoxyfluorination of phenols
- PhenoFluor is commercially available from Sigma-Aldrich
- PhenoFluor is a crystalline, nonexplosive solid that can be handled in air, but hydrolyzes upon prolonged storage in a wet atmosphere
- PhenoFluor can be stored in a dry toluene solution for at least 2 months without detectable decomposition

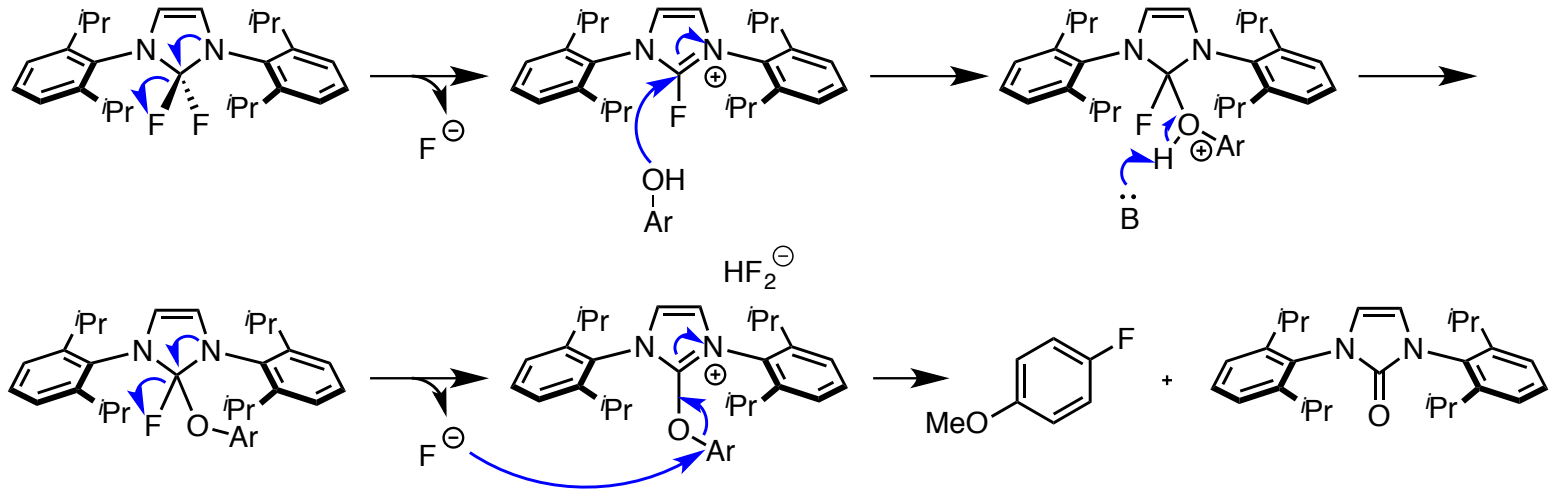



Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482-11484.
Tang, P.; Wang, W.; Ritter, T. WO 2012/142162

# PhenoFluor: Proposed Mechanism

- Ritter and co-workers propose that the mechanism for fluorination proceeds via a 2-phenoxyimidazolium bifluoride salt

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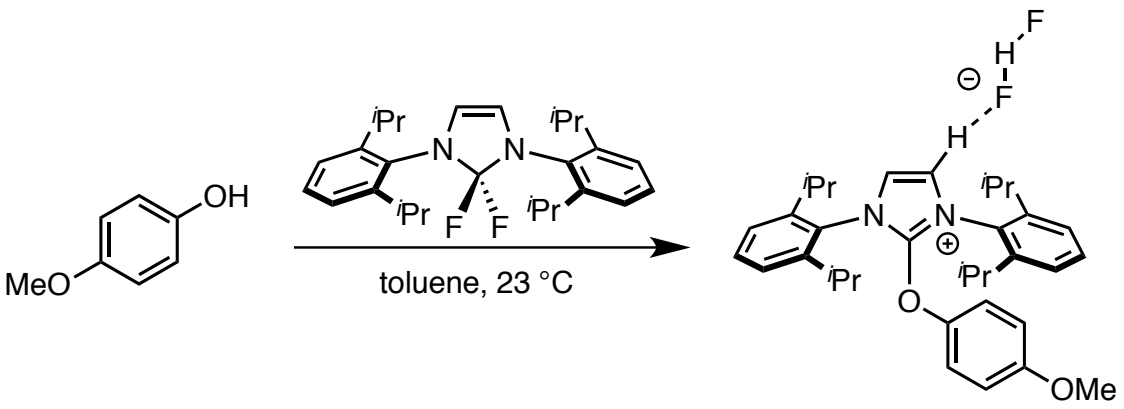


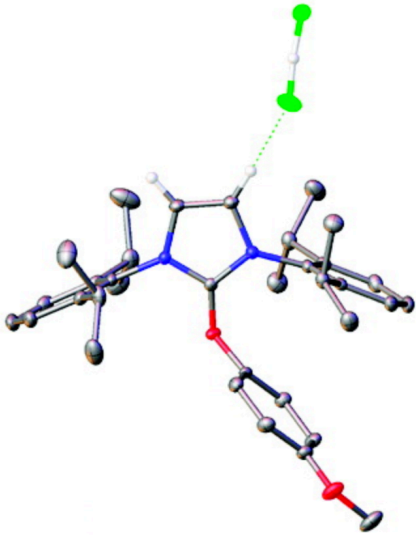

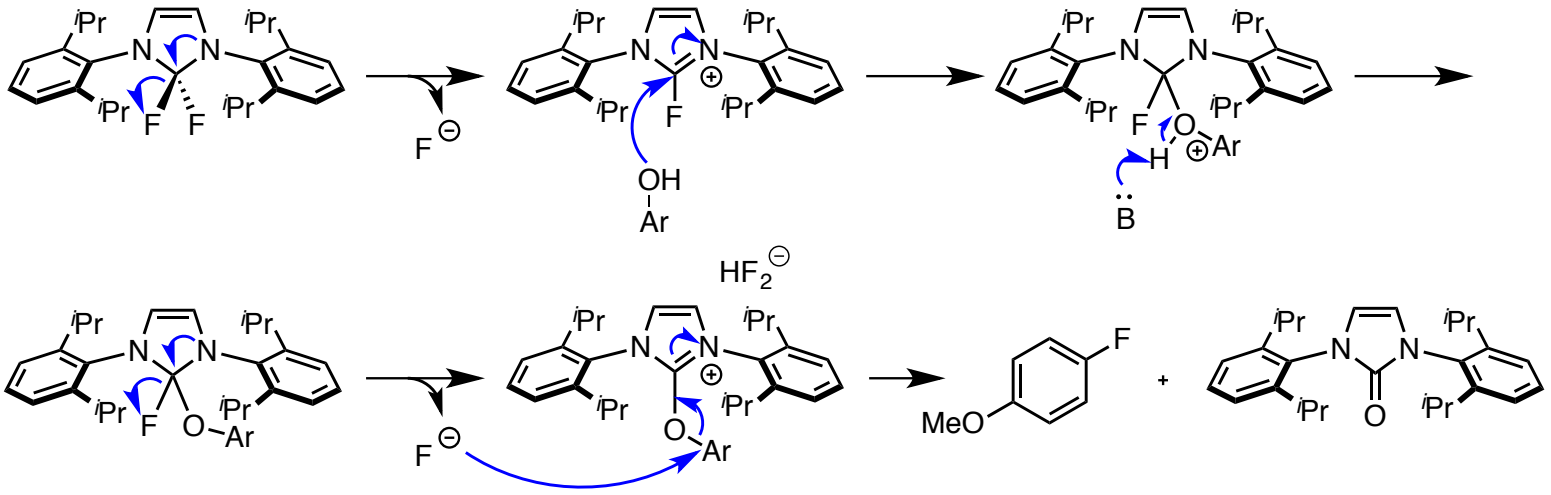


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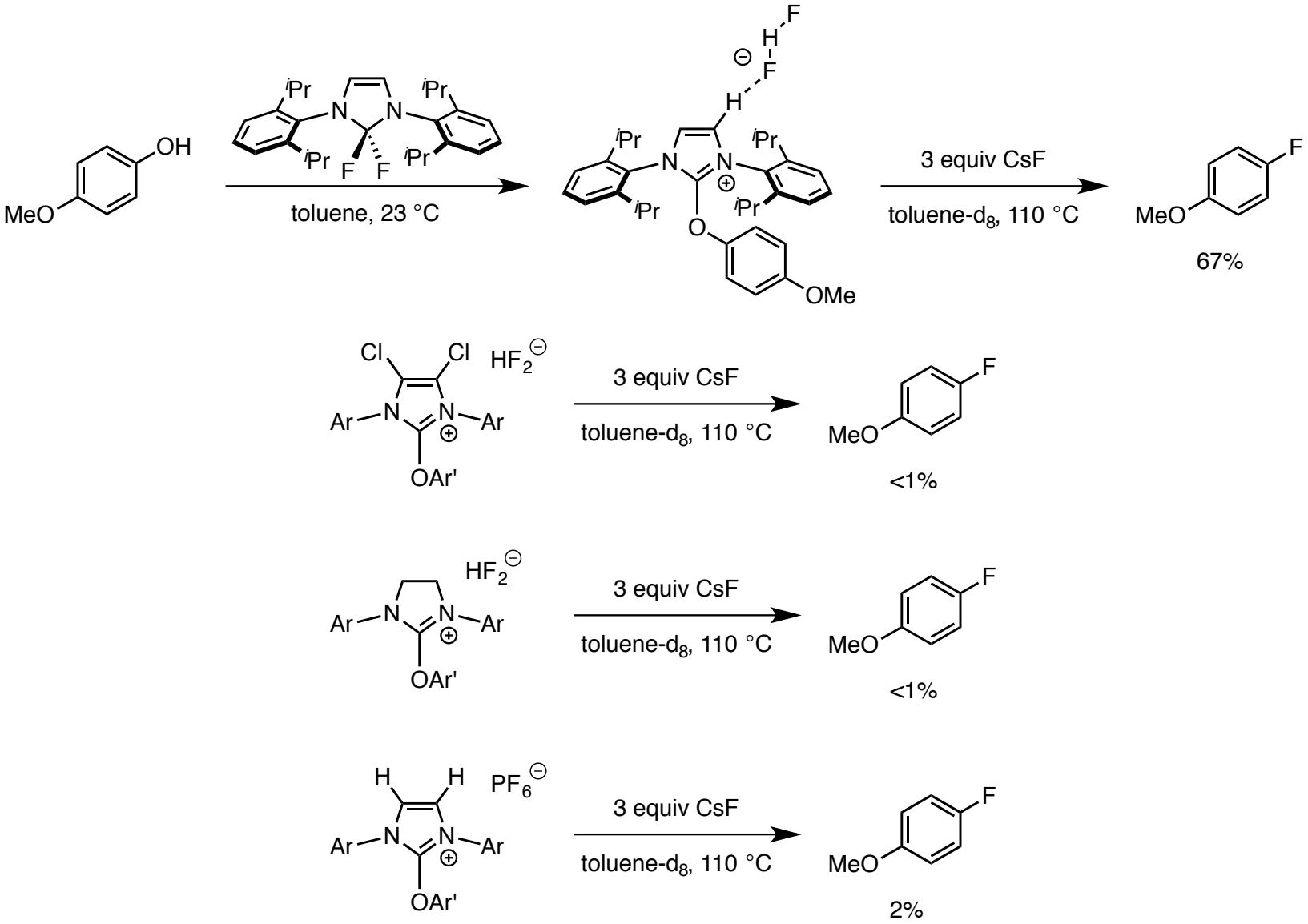
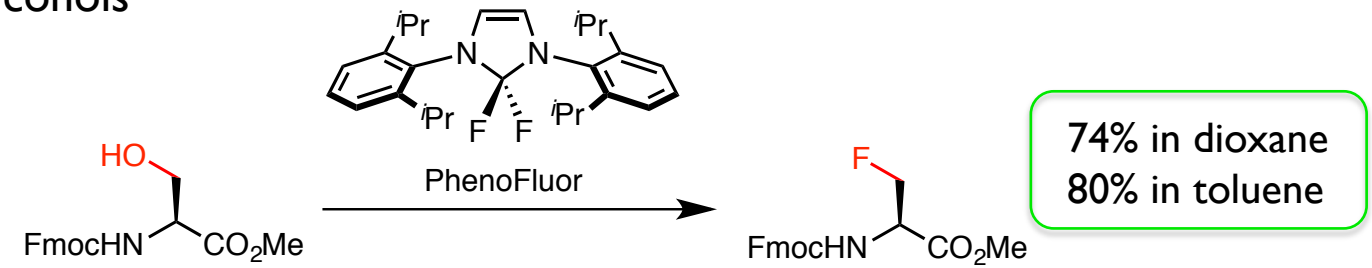
# PhenoFluor: Hydrogen Bonding

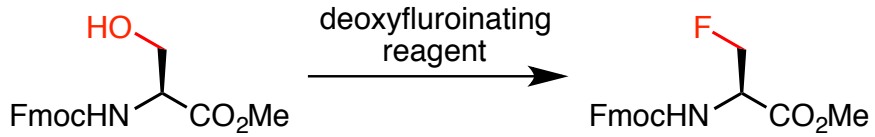


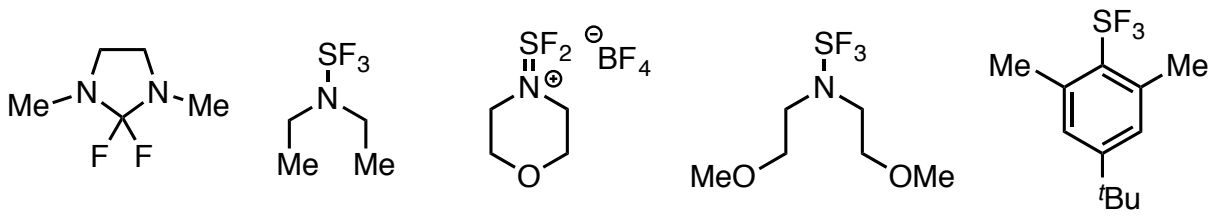

Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482-11484.

# Title Paper: Deoxyfluorination of Aliphatic Alcohols

- Modifications of the initial reaction conditions allowed for the deoxyfluorination of aliphatic alcohols




| | DFI | DAST | XtalFluor-M® | Deoxo-Fluor® | Fluolead™ |
|---|---|---|---|---|---|
| toluene | <1% | <1% | <1% | <1% | <1% |
| dioxane | 2% | 11% | <1% | 10% | <1% |
| reported optimized conditions | <1% | 3% | <1% | <1% | <1% |

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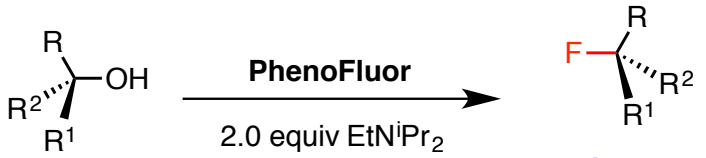
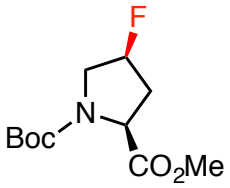
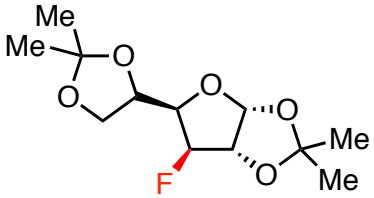


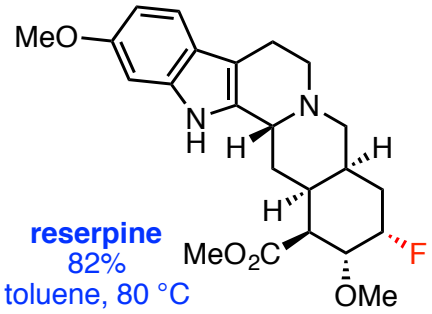

**parent compound**
yield%
solvent, temperature



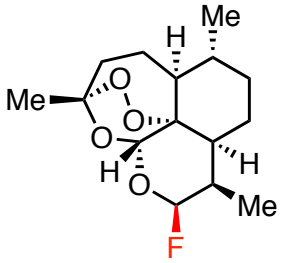

**(2*S*, 4*R*)-4-hydroxy-proline**
92%
toluene, 80 °C



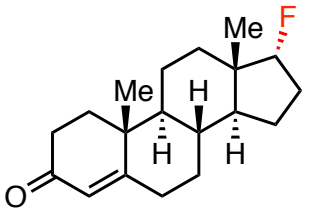

***D*-allofuranose**
83%
toluene, 80 °C



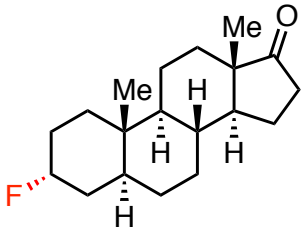

**reserpine**
82%
toluene, 80 °C



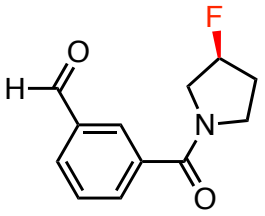

**artemisinin**
79%
toluene, 80 °C




**testosterone**
88%
toluene, 80 °C




***epi*-androterone**
84%
toluene, 80 °C




77%
toluene, 80 °C

- Chiral secondary alcohols could typically be deoxyfluorinated with inversion
- Carbonyl functional groups are well tolerated

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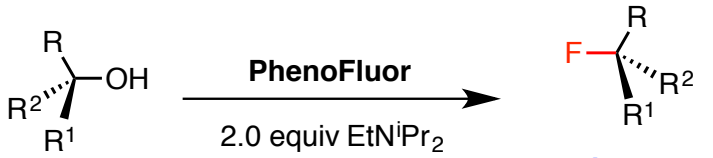
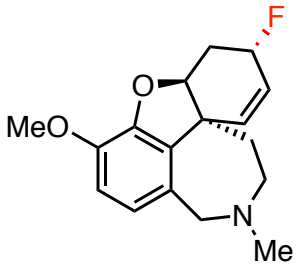
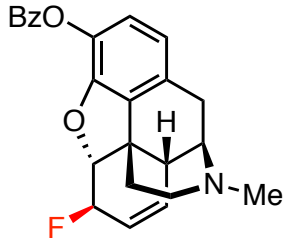


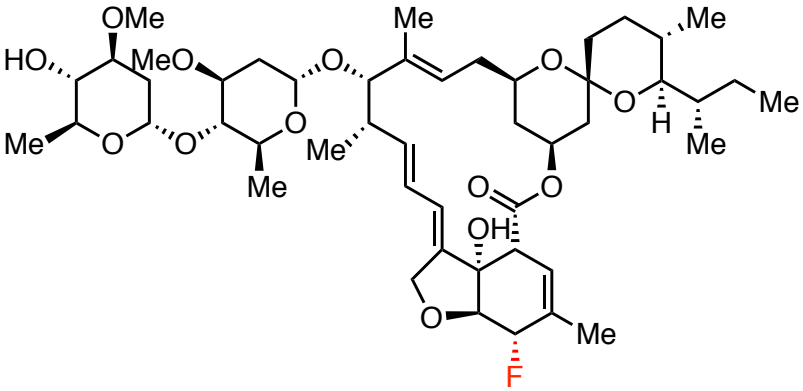

**parent compound**
yield%
solvent, temperature



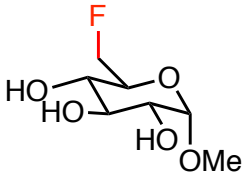

**galantamine**
80%, 10:1 dr
toluene, 80 °C



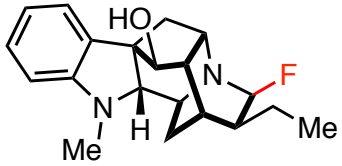

**morphine**
80%
$CH_2Cl_2$, 23 °C




**ivermectin $B_{1a}$**
41%
toluene, 50 °C




**methyl α-D-glucopyranoside**
43%
dioxane, 80 °C

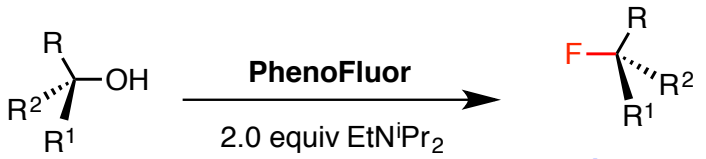



**ajmaline**
30%
$CH_2Cl_2$, 50 °C

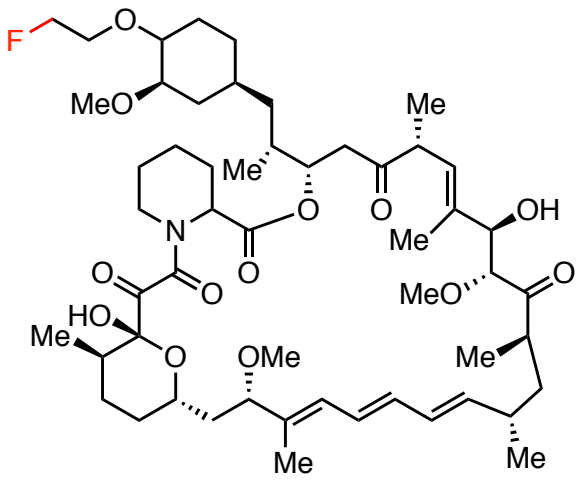
- Secondary allylic alcohols afforded allylic fluorides consistent with an $S_N2$ mechanism
- Deoxyfluorination is site-selective and predictable

Sladojevich, F.; Arlow, S. I.; Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *ASAP.* DOI: 10.1021/ja3125405

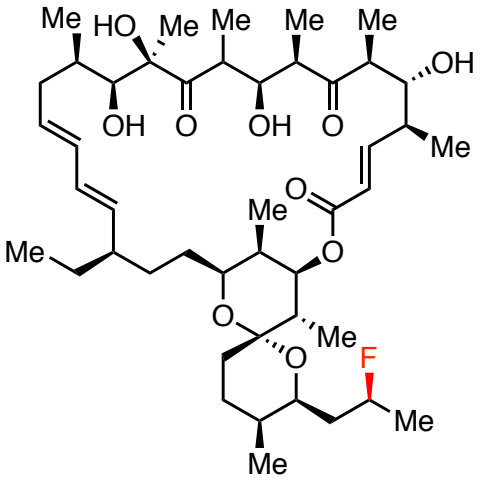
# Title Paper: Site-Selective Late-Stage Deoxyfluorination of Alcohols




**parent compound**
yield%
solvent, temperature




**everolimus**
83%
$CH_2Cl_2$, 23 °C

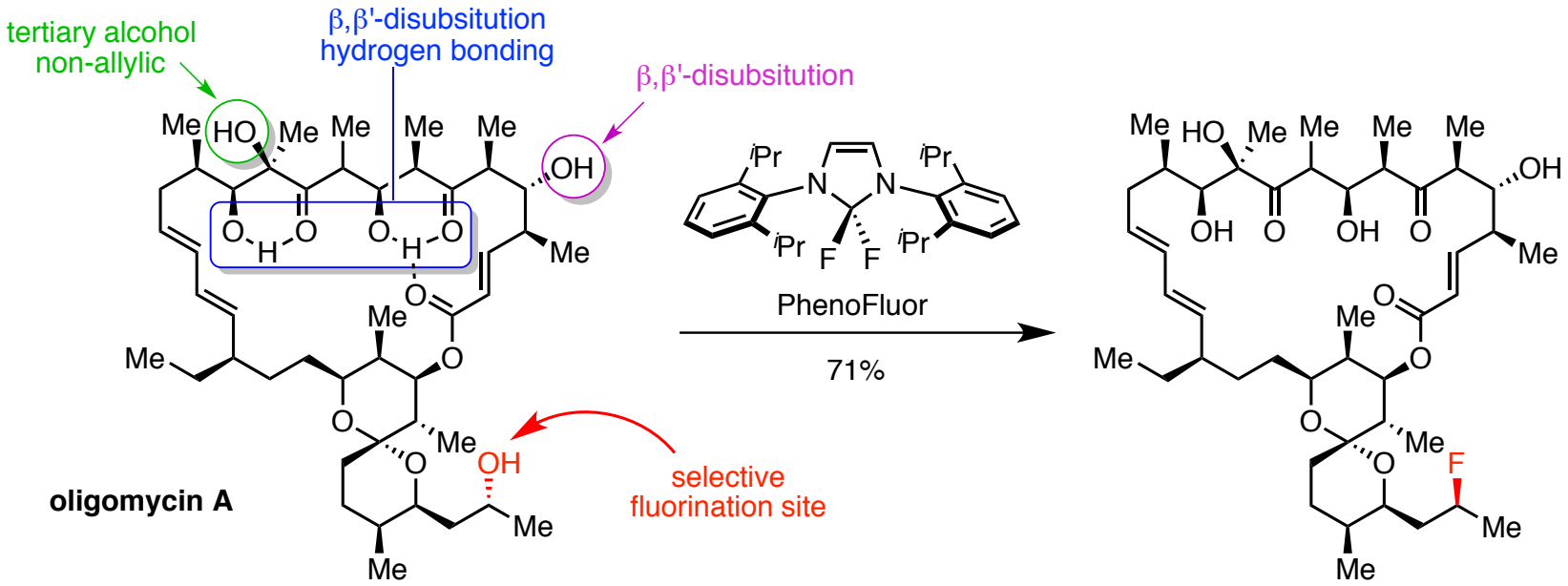



**oligomycin A**
71%
$CH_2Cl_2$, 23 °C to 0 °C

- Deoxyfluorination can be carried out at room temperature, allowing for fluorination of temperature sensitive substrates
- KF was not required

Sladojevich, F.; Arlow, S. I.; Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *ASAP.* DOI: 10.1021/ja3125405

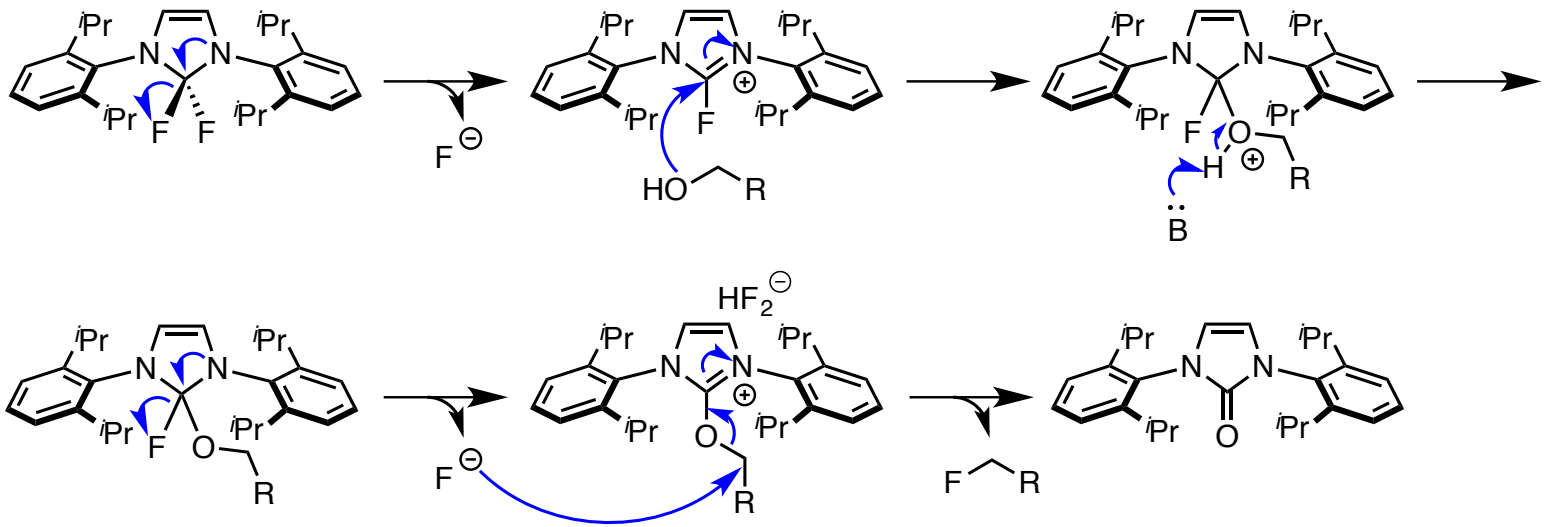
# Title Paper: Site-Selective Late-Stage Deoxyfluorination of Alcohols




- Primary alcohols are selectively deoxyfluorinated
- Secondary alcohols react slower or not at all when they are β,β'-dibranched, unless it is allylic
- Hydroxyl groups engaged in hydrogen bonding are not reactive
- Tertiary alcohols do not react, unless they are allylic

Sladojevich, F.; Arlow, S. I.; Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *ASAP.* DOI: 10.1021/ja3125405

# Deoxyfluorination with PhenoFluor: Mechanistic Considerations

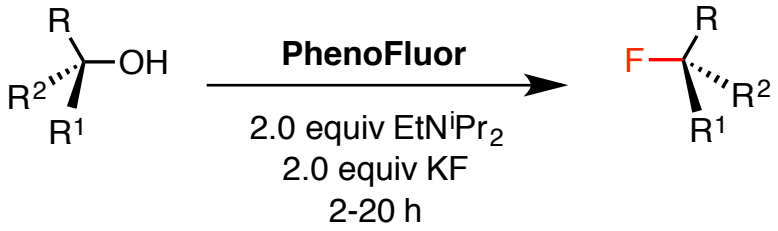



- The formation of elimination products could be reduced by increasing the reaction temperature from 23 °C to 80 °C
- The addition of DIPEA was beneficial to shorten the reaction time
- KF was found to reduce side products resulting from elimination, but was not generally required for the reaction to proceed

Sladojevich, F.; Arlow, S. I.; Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *ASAP.* DOI: 10.1021/ja3125405

# Conclusions and Outlook

- A general method for selective, late-stage deoxyfluorination of complex aliphatic alcohols has been developed




- The substrate scope and functional group tolerance of this methodology surpass all others reported to date
- PhenoFluor has a better safety profile and higher chemoselectivity than other deoxyfluorination reagents
- One drawback is the molar mass (427 g/mol), which is convenient for subgram- and gram-scale reactions, but is wasteful for larger-scale reactions
- Extending this method to late-stage $^{18}F$ radiolabeling would be useful for positron emission tomography (PET) applications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