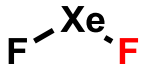
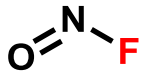
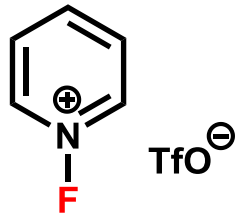
# Selectfluor™ mediated Organic Synthesis

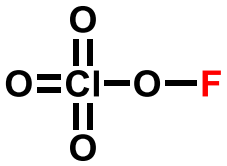
2016. 8. 27 Masaki Koshimizu

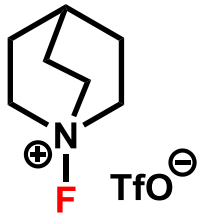
# Electrophilic Fluorinating Reagents

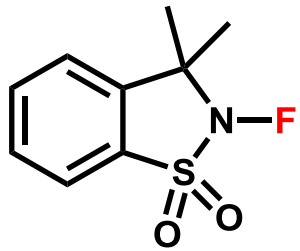



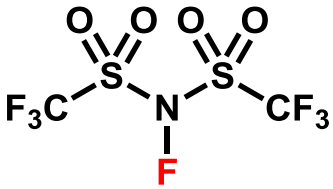



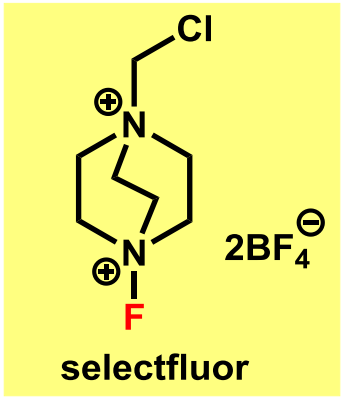



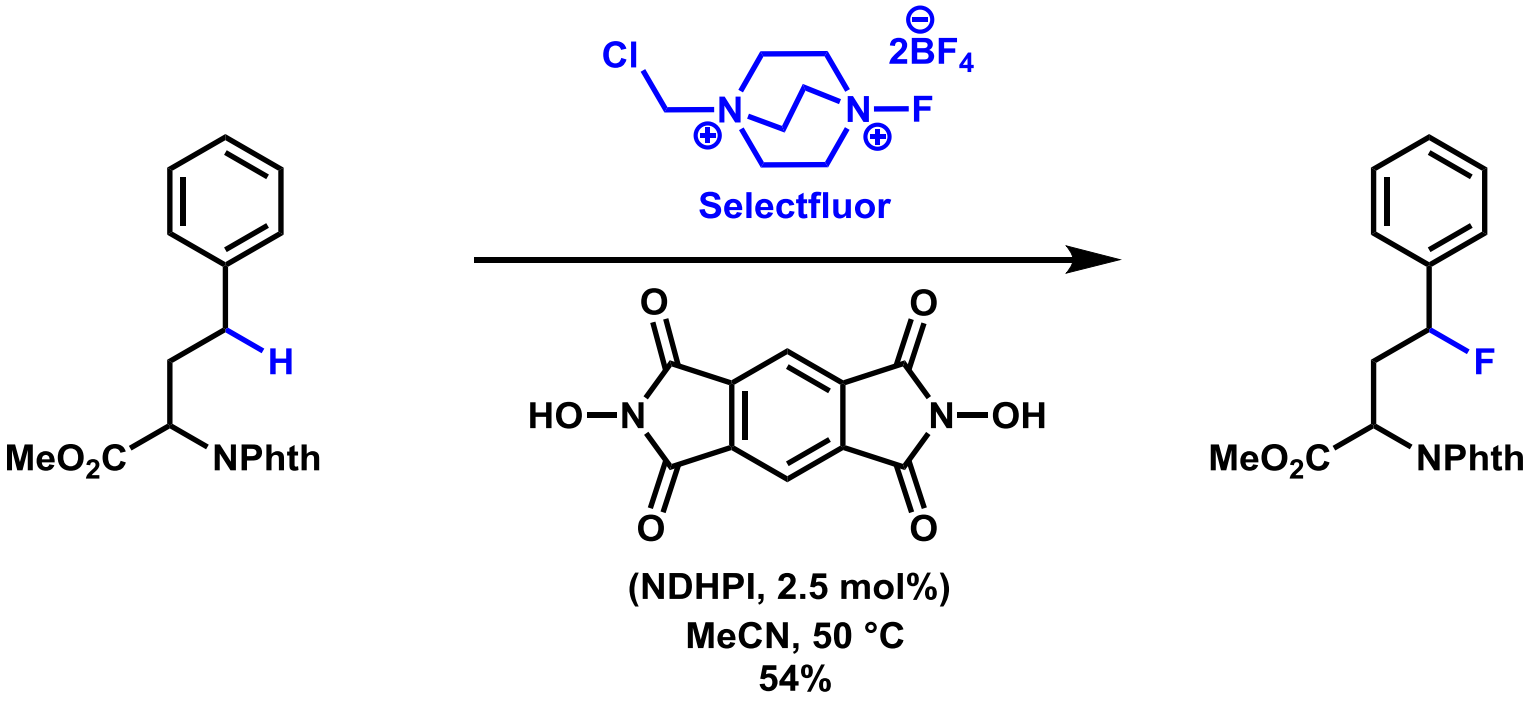







# Fluorination in Our Laboratory

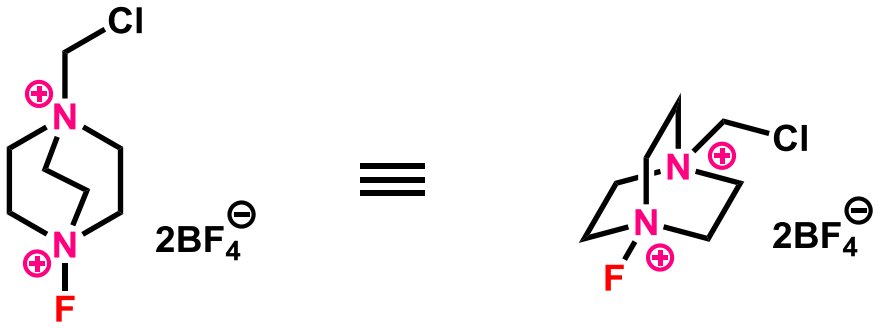





Amaoka, Y.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2013**, 15, 2160.

# Content

# Properties of Selectfluor

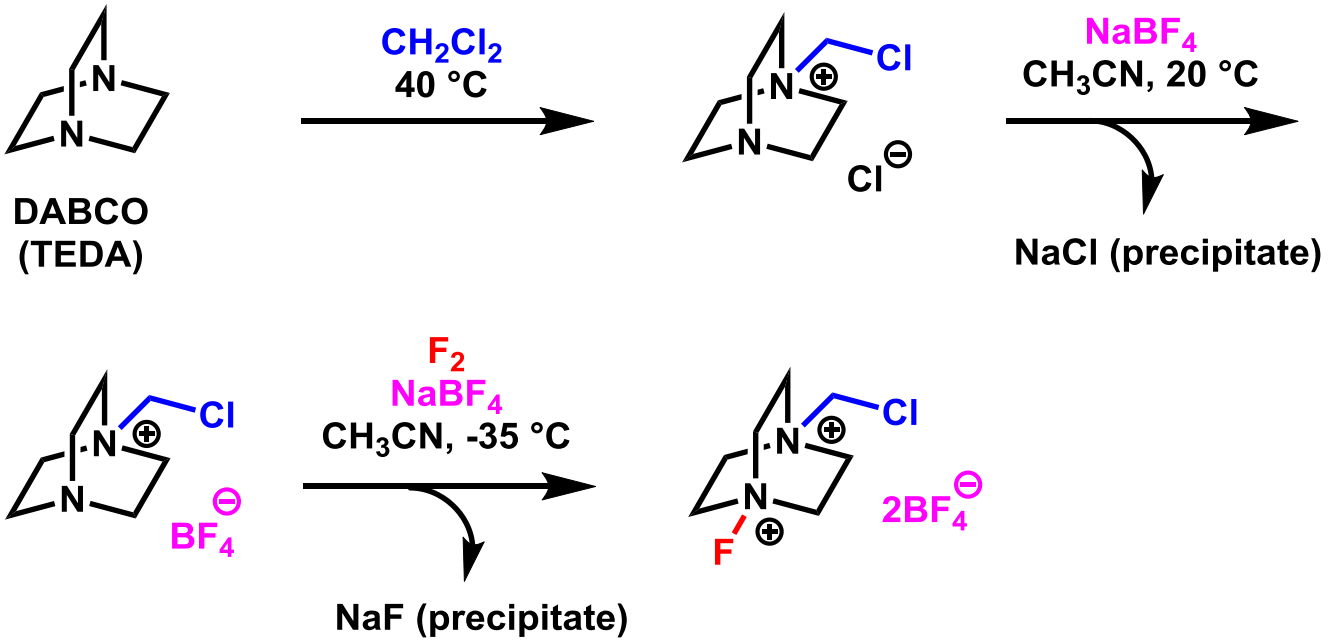



**Selectfluor, F-TEDA-$BF_4$**

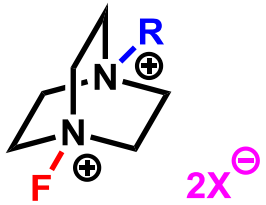
- **Non-hydroscopic crystalline**
- **Remarkable stable (up to 195 °C)**
- **Relatively harmless (oral $LD_{50}$ of 640 mg/kg for male adult rats)**
- **Commercially available (multi-ton scale)**

- **Soluble in only few polar solvents as a dication (MeCN, DMF, $H_2O$, $MeNO_2$)**

# Preparation of Selectfluor




**F-TEDA-X derivatives**



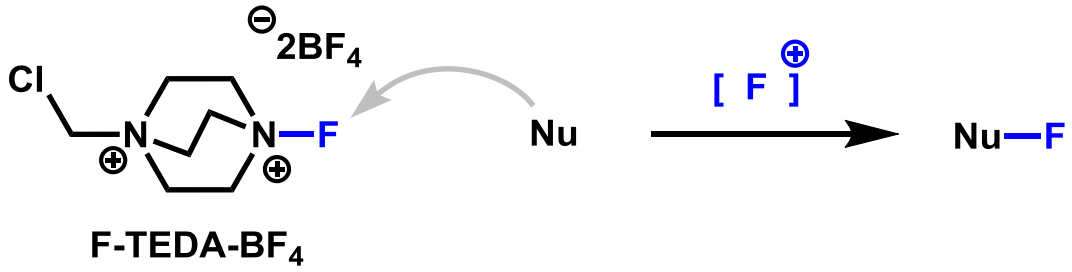

R = Me, $CH_2Cl_2$, Et, $CH_2CF_3$, $C_8H_{17}$
X = TfO, $BF_4$, $PF_6$, $FSO_3$

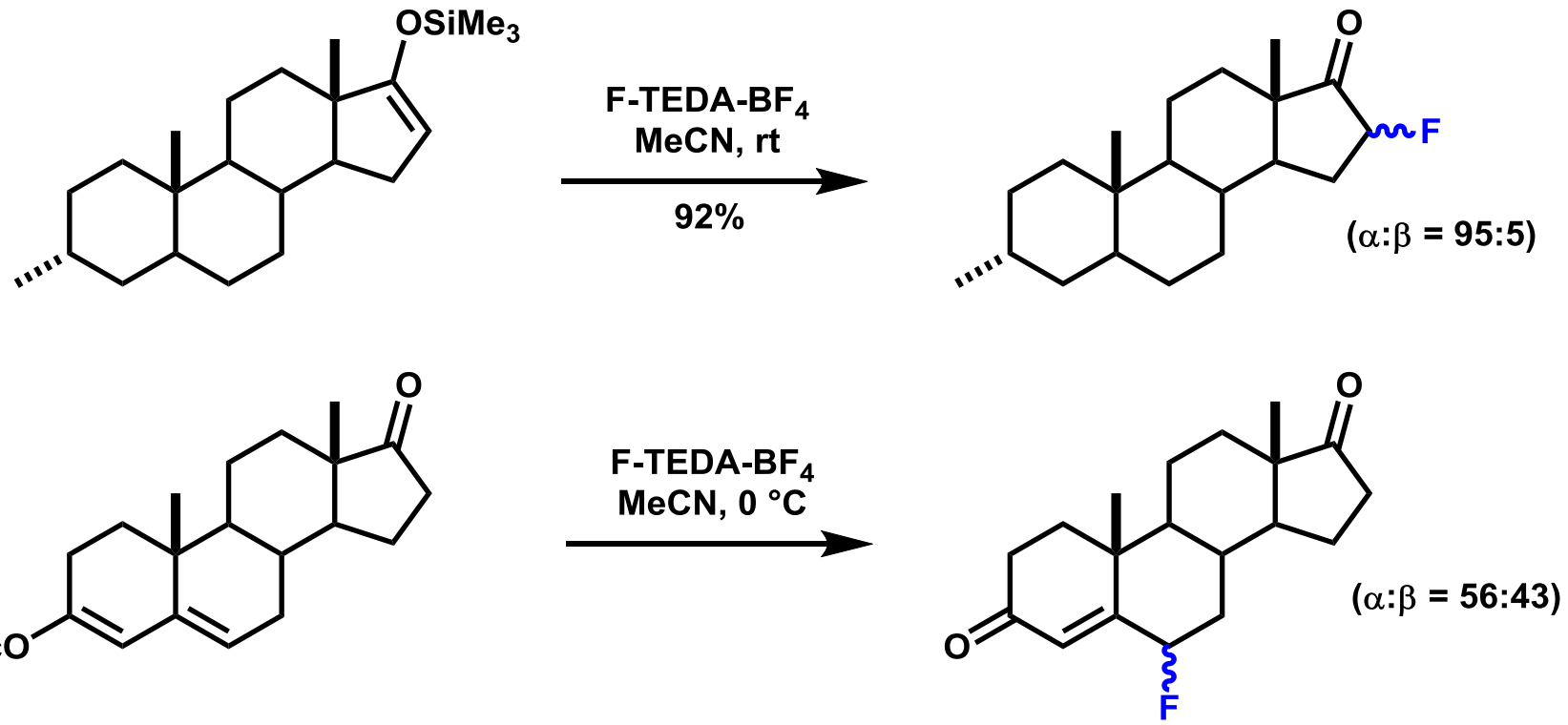


Hart, J. J.; Syvret, R. G. *J. Fluorine. Chem.* **1999**, 100, 157.

# Content

# Fluorination of Carbonyl Functionalities

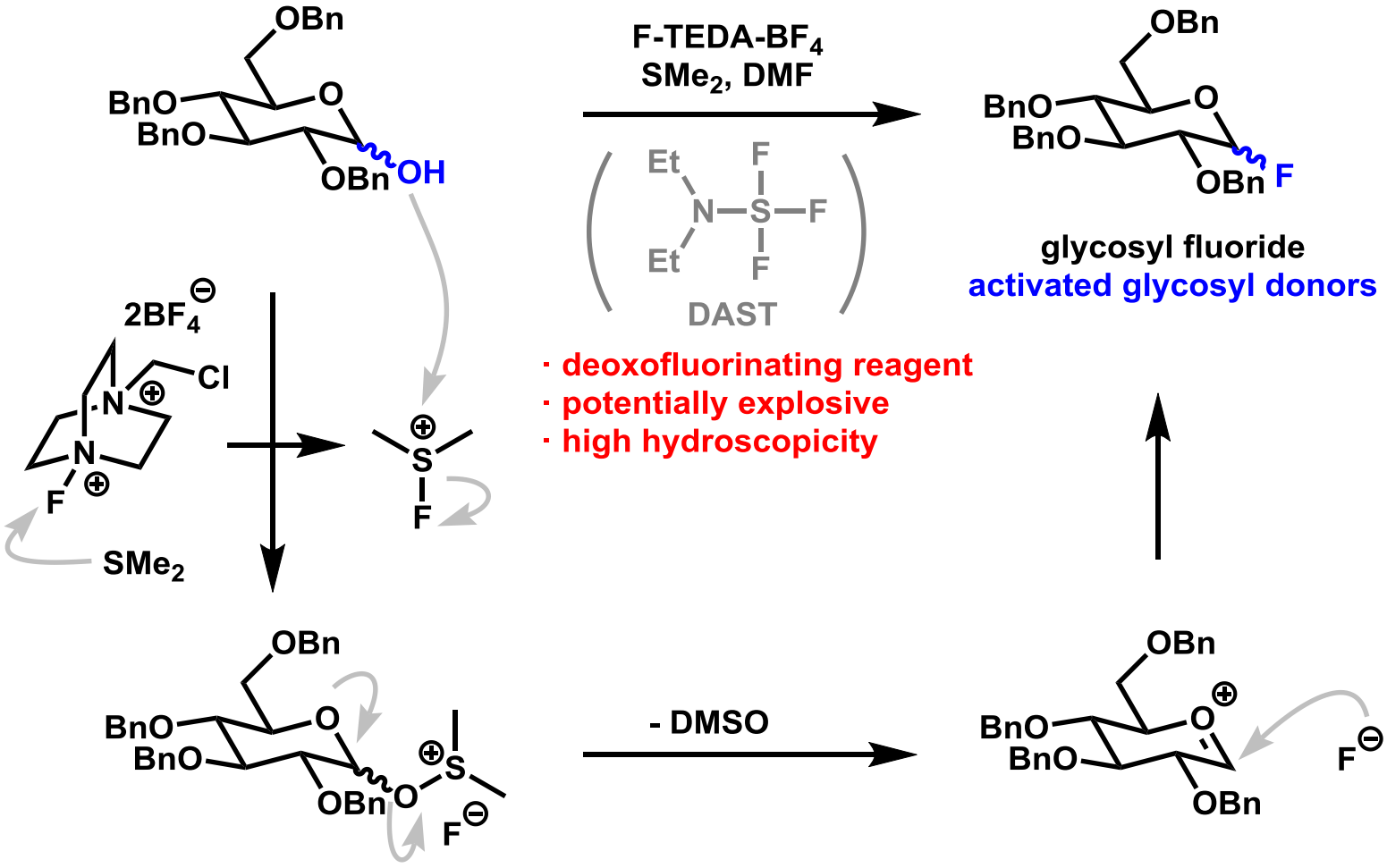





Ge, P.; Krik, K. L. *J. Org. Chem.* **1997**, 62, 3340.

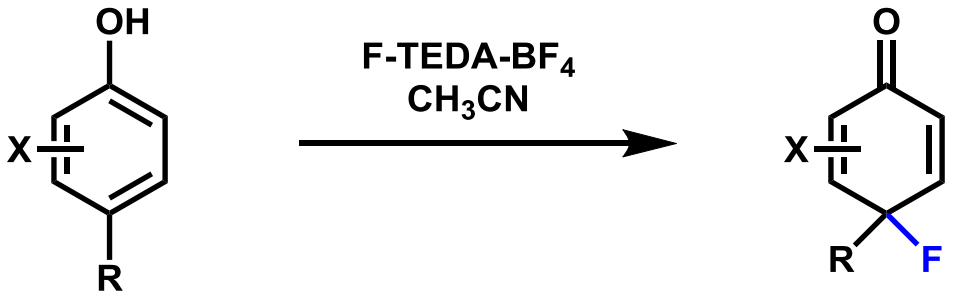
# Synthesis of Glycosyl Fluoride

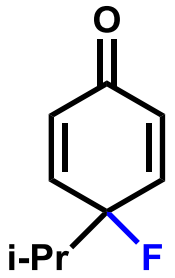





Burkart, M. D.; Zhang, Z.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, 119, 11743.

# Electrophilic Fluorination of Phenols

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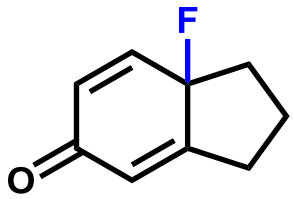


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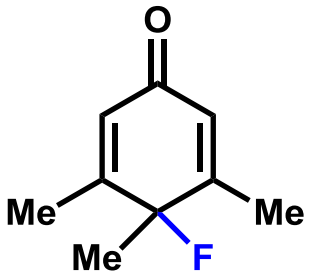


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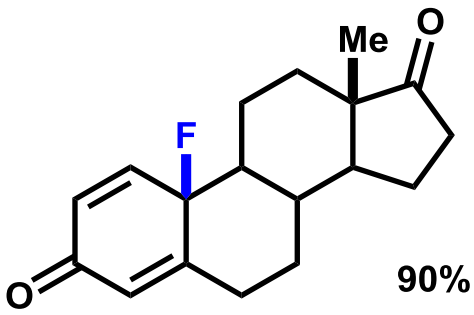


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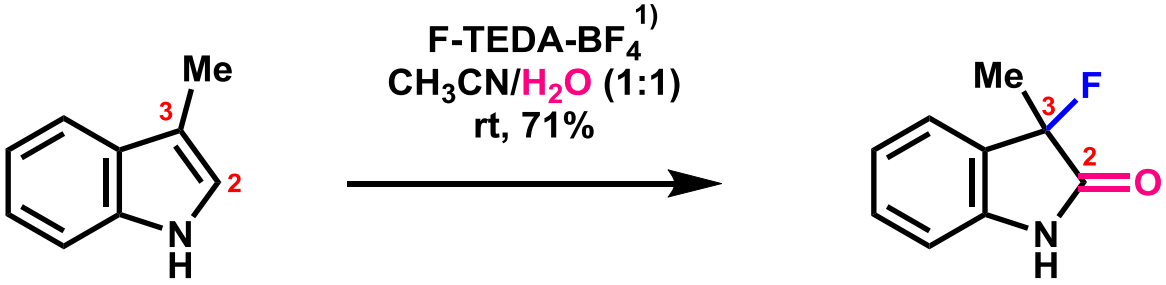
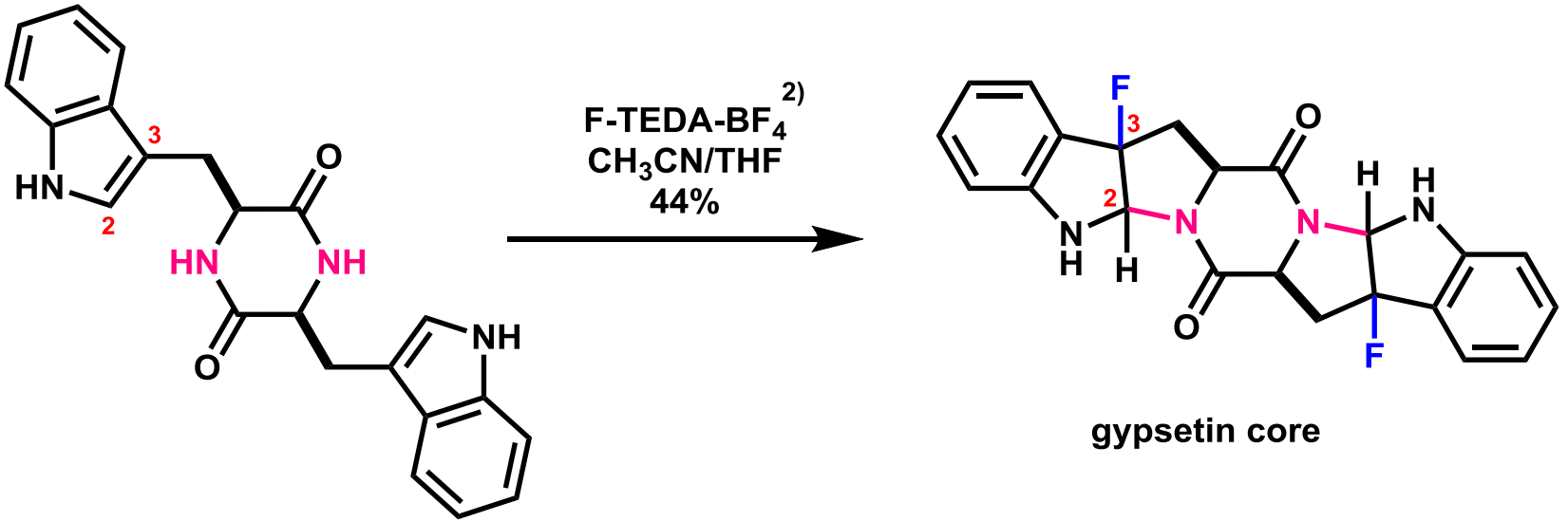
Stavber, S.; Jereb, M.; Zupan, M. *Synlett.* **1999**, 1375.

# Electrophilic Fluorination of Indoles




3-fluorooxindole

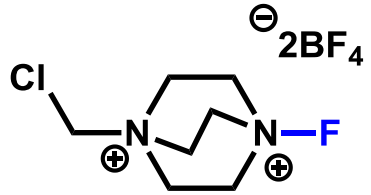



gypsetin core

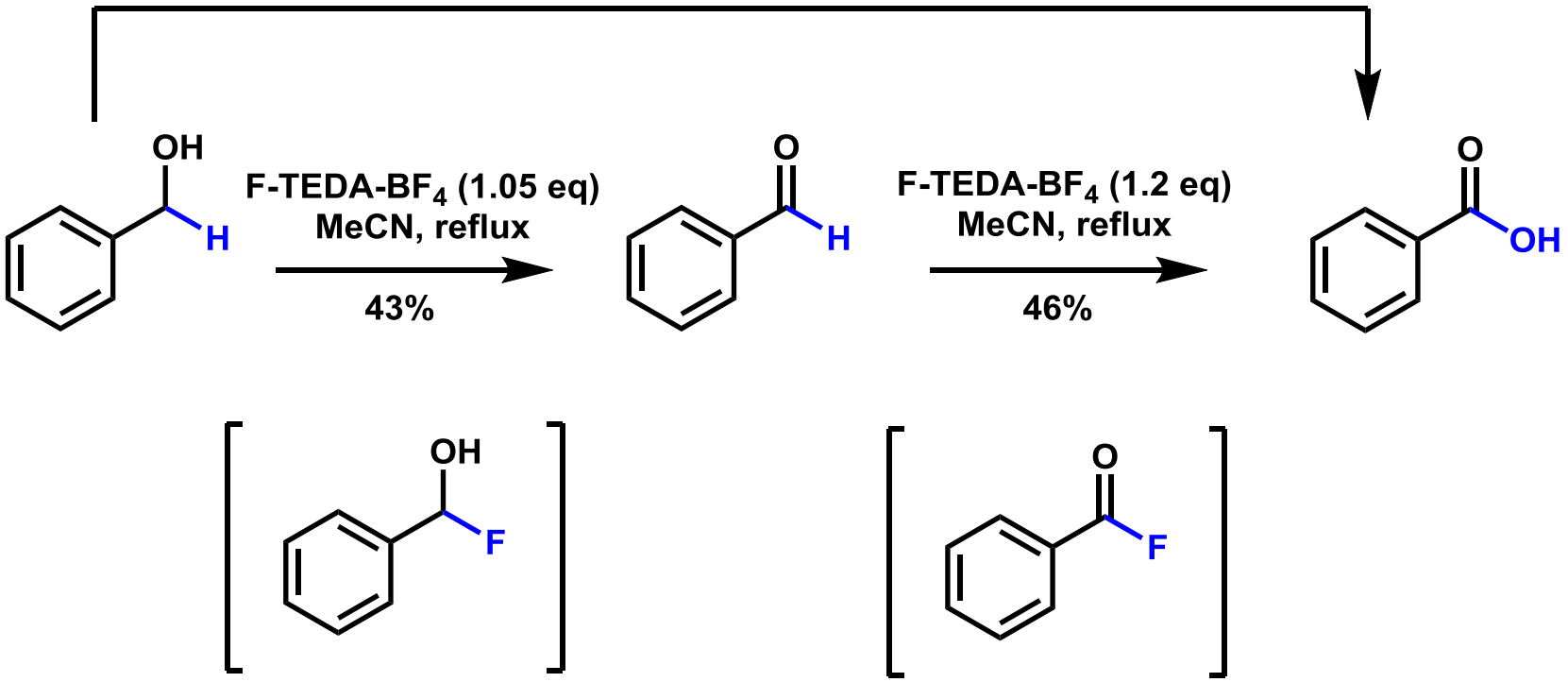
1) Takeuchi, T.; Tarui, T.; Shibata, N. *Org. Lett.* **2000**, 2, 639.
2) Shibata, N.; Tarui, T.; Doi, Y.; Kirk, K. L. *Angew. Chem. Int. Ed.* **2001**, 40, 4461.

# Content

# Oxidation of Benzilic Alcohols




**F-TEDA-$BF_4$ (2.2 eq), MeCN, reflux, 87%**

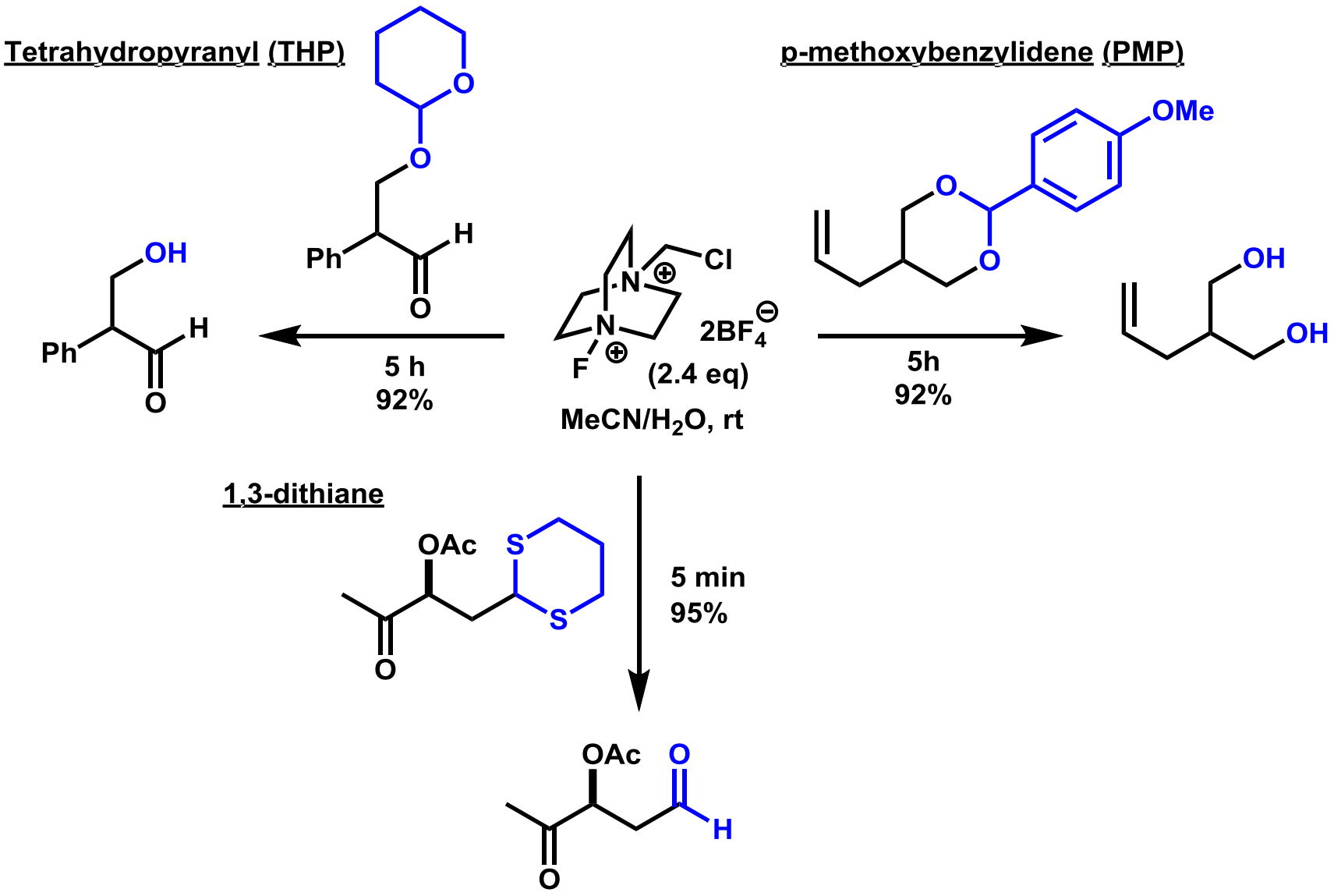



**Oxidation at benzylic position initiated by a single electron transfer (SET)**



Banks, R. E.; Lawrence, N. J.; Popplewell, A. L. *Synlett.* **1994**, 831.

# Protecting-Group Removal

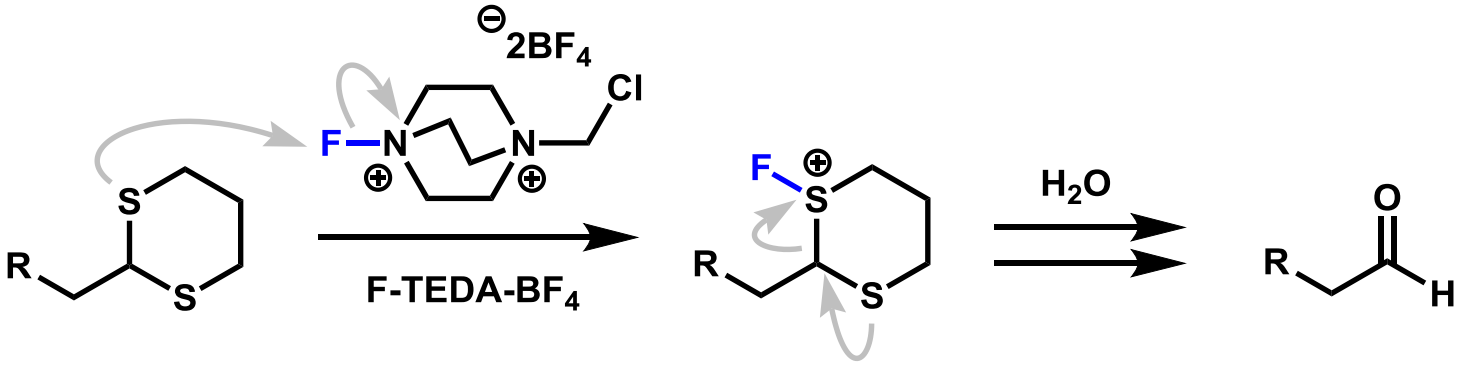




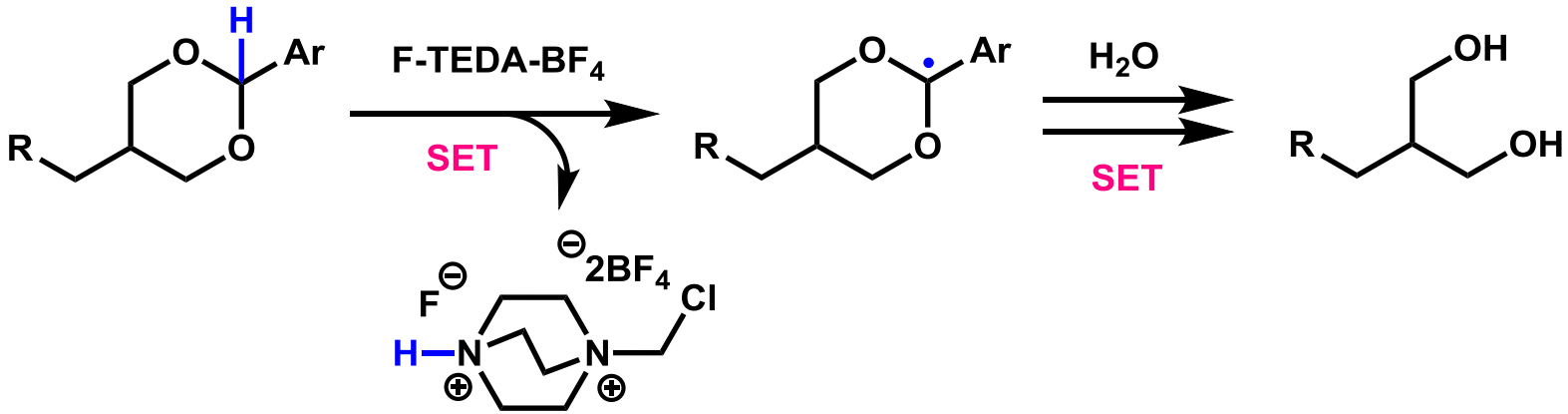

Liu, J.; Wong, C.-H. *Tetrahedronlett.* **2002**, 43, 4037.

# Proposed Mechanism

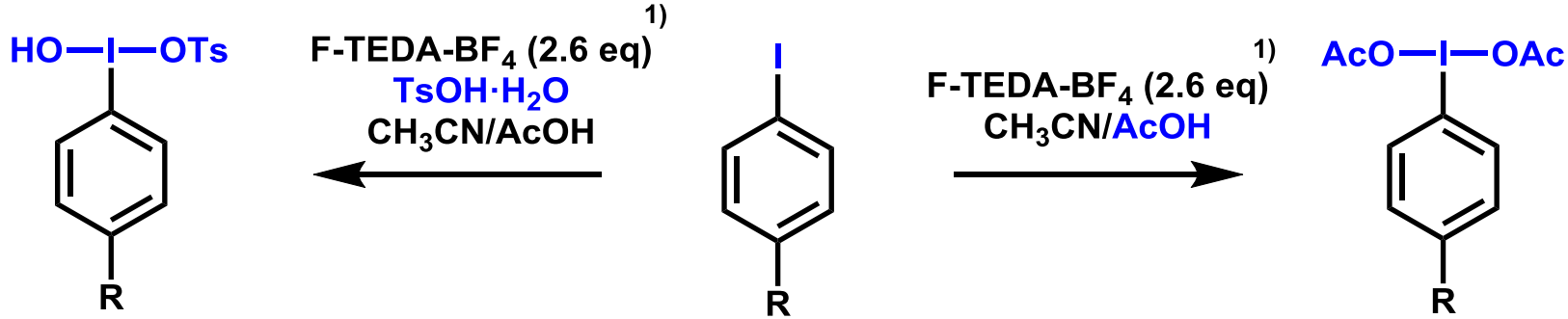
**Cleavage of thioacetal**



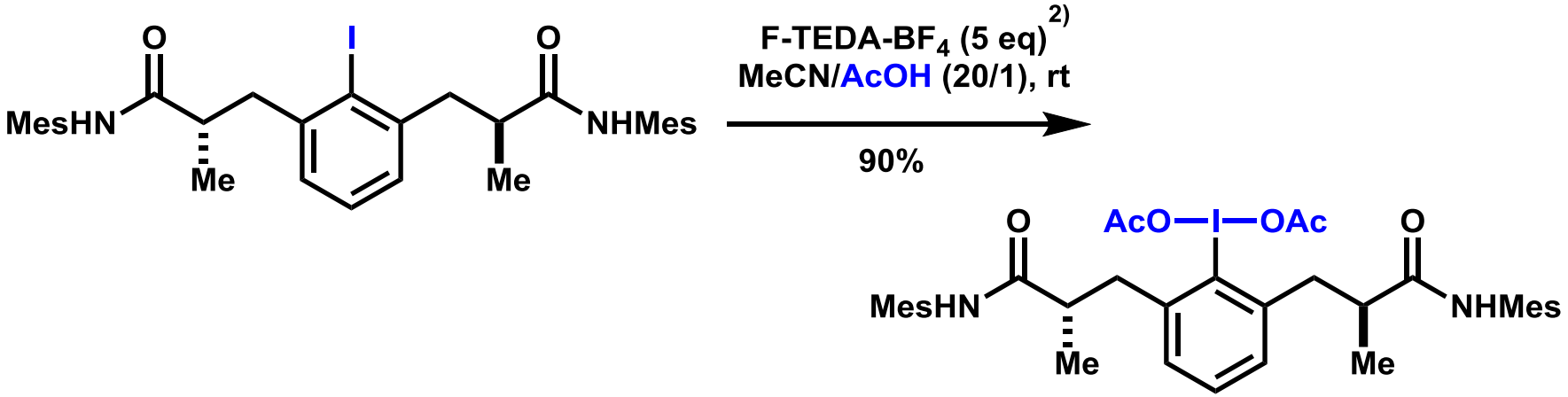

**Cleavage of acetal (proposed)**



# Preparation of Hypervalent Iodine(III) Compounds




Koser's reagents

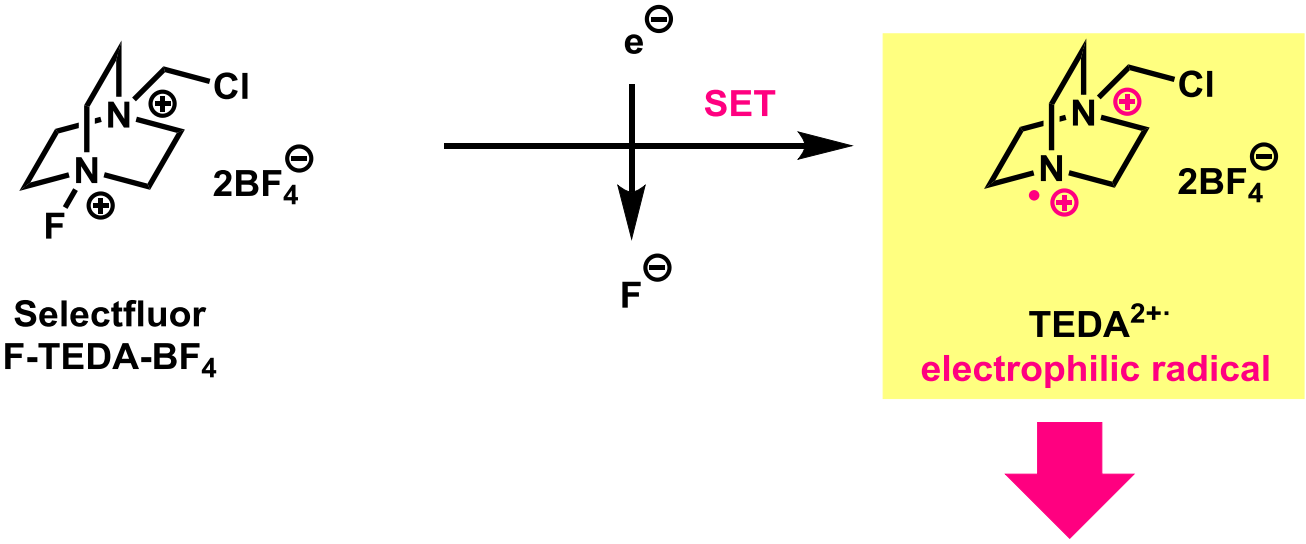



chiral hypervalent iodine (III) reagent


1) Ye, C.; Twamley, B.; Shreeve, *Org. Lett.* **2005**, 7, 3961.
2) Uyanik, M.; Yasui, T.; Ishihara, K. *Tetrahedron*, **2010**, *66*, 5841.

# Content

# Doubly Cationic Radical TEDA$^{2+\cdot}$

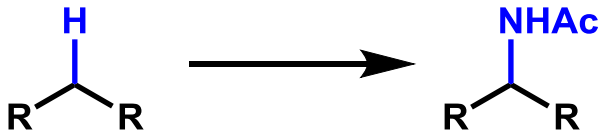



Selectfluor
F-TEDA-BF$_4$

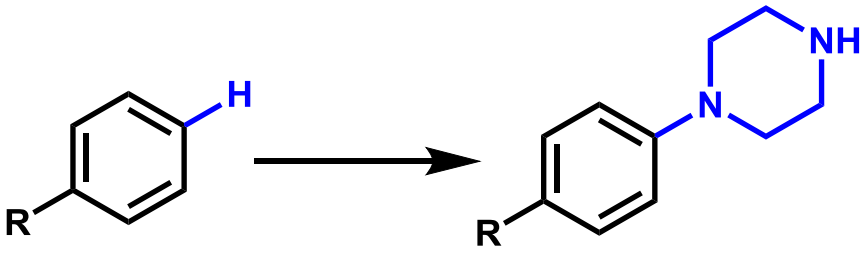
TEDA$^{2+\cdot}$
electrophilic radical

**Development of radical reactions**

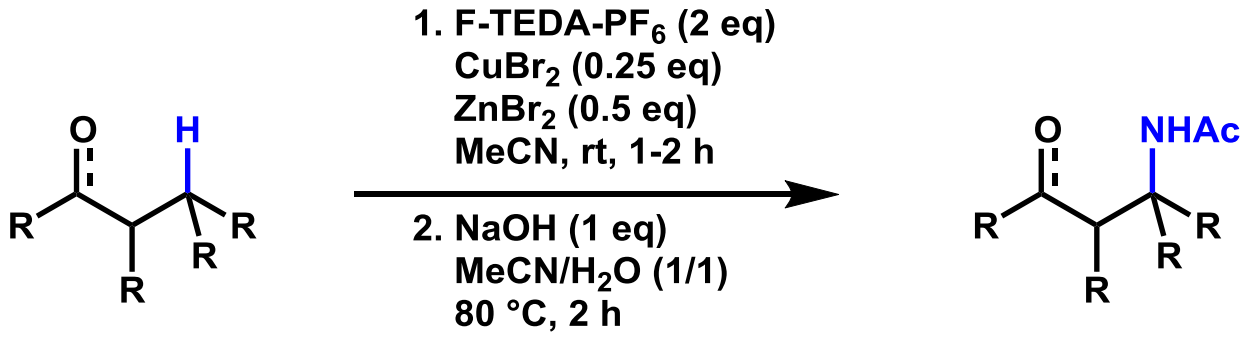
**Baran (2012)**
**C-H Amination of sp$^3$ carbon**

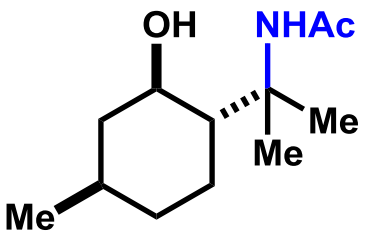



**Ritter (2016)**
**directly aryl piperizine synthesis**



# C-H Amination of Unactivated $sp^3$ Carbons

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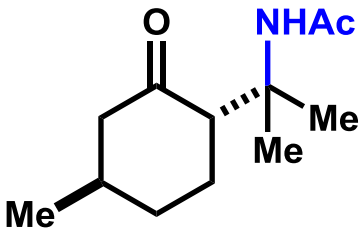


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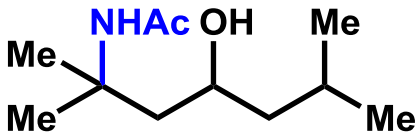


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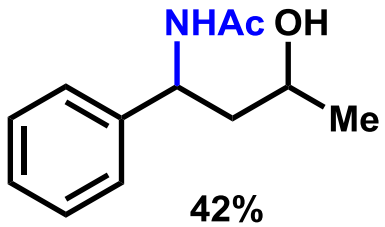


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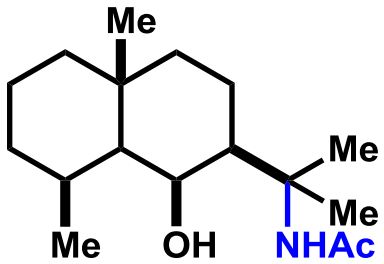
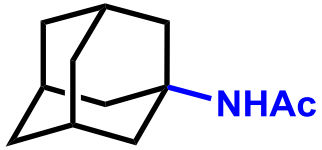



65%



Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, 134, 2547.

# C-H Amination of Hydrocarbon

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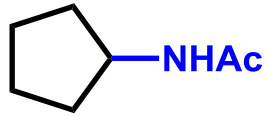


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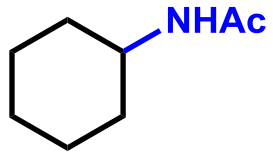


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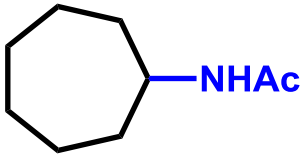


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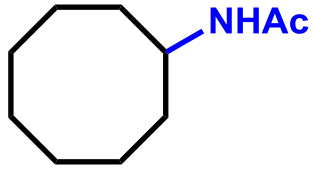


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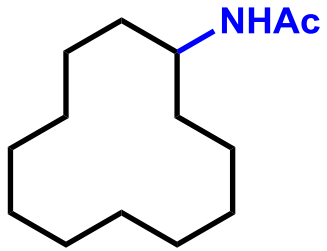


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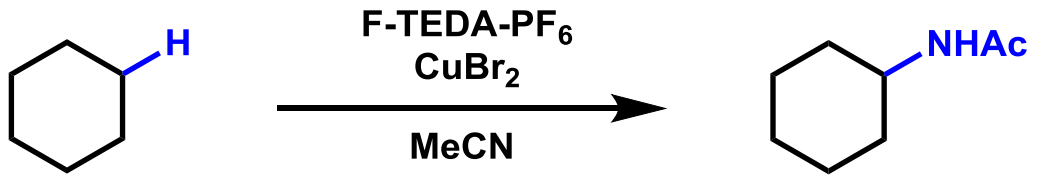
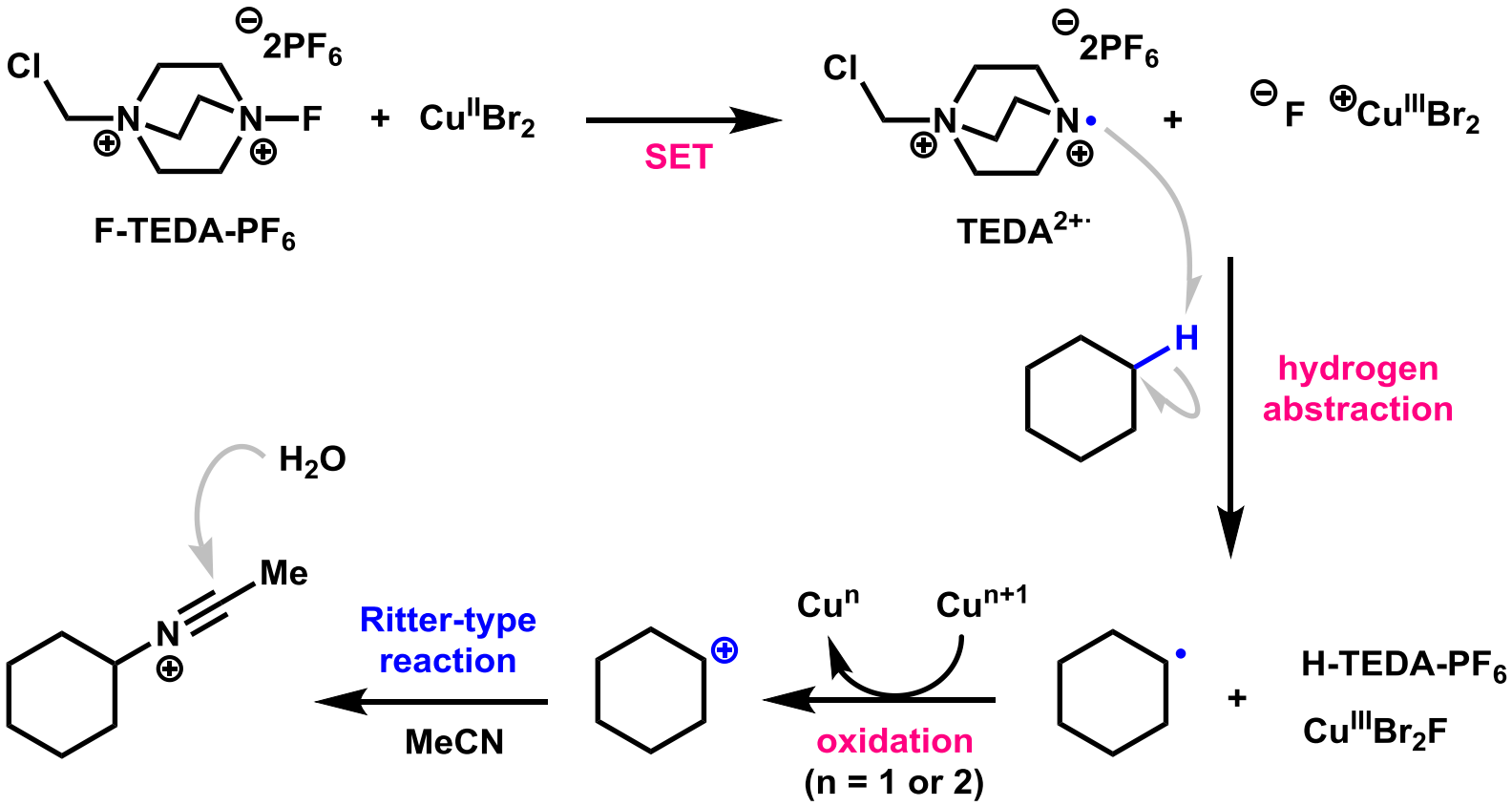
# Mechanistic Hypothesis

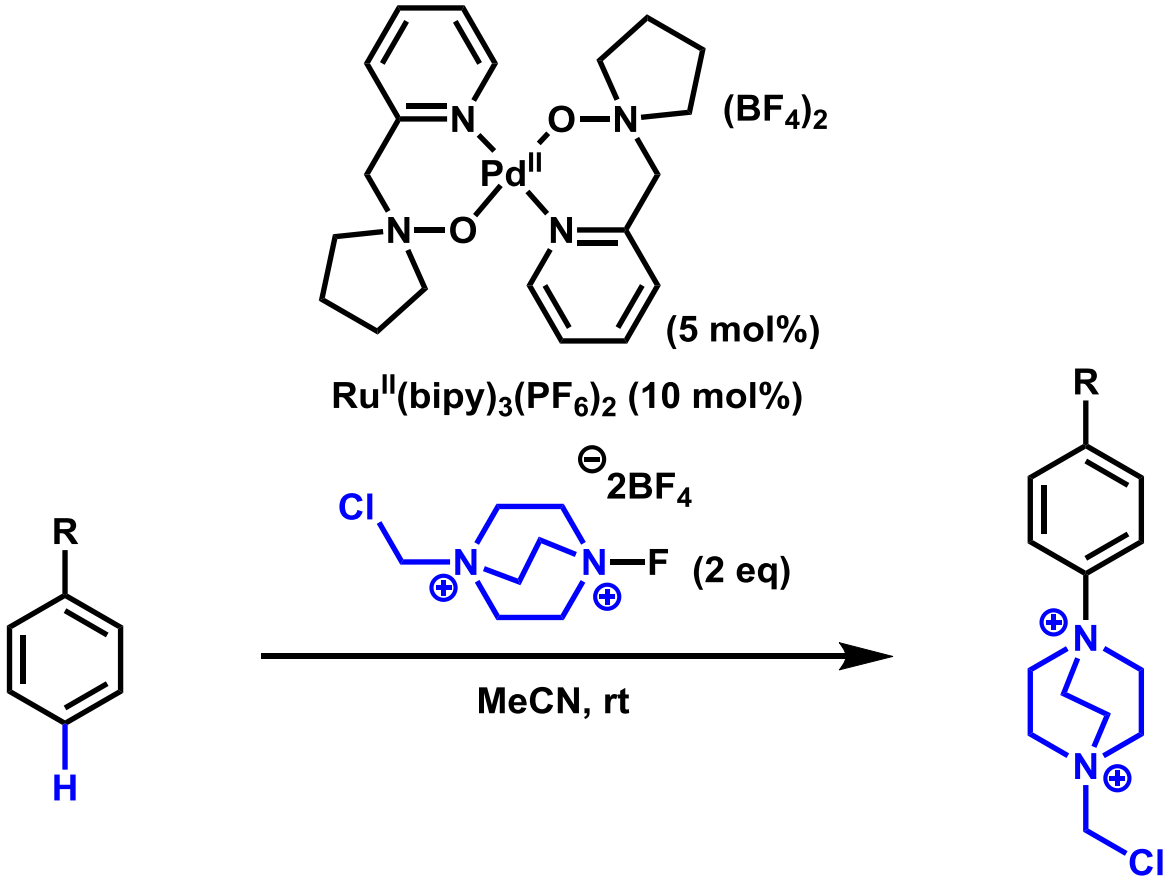



KIE: $k_H/k_D$ = 3.5

TEMPO (5 eq) inhibited the reaction completely.



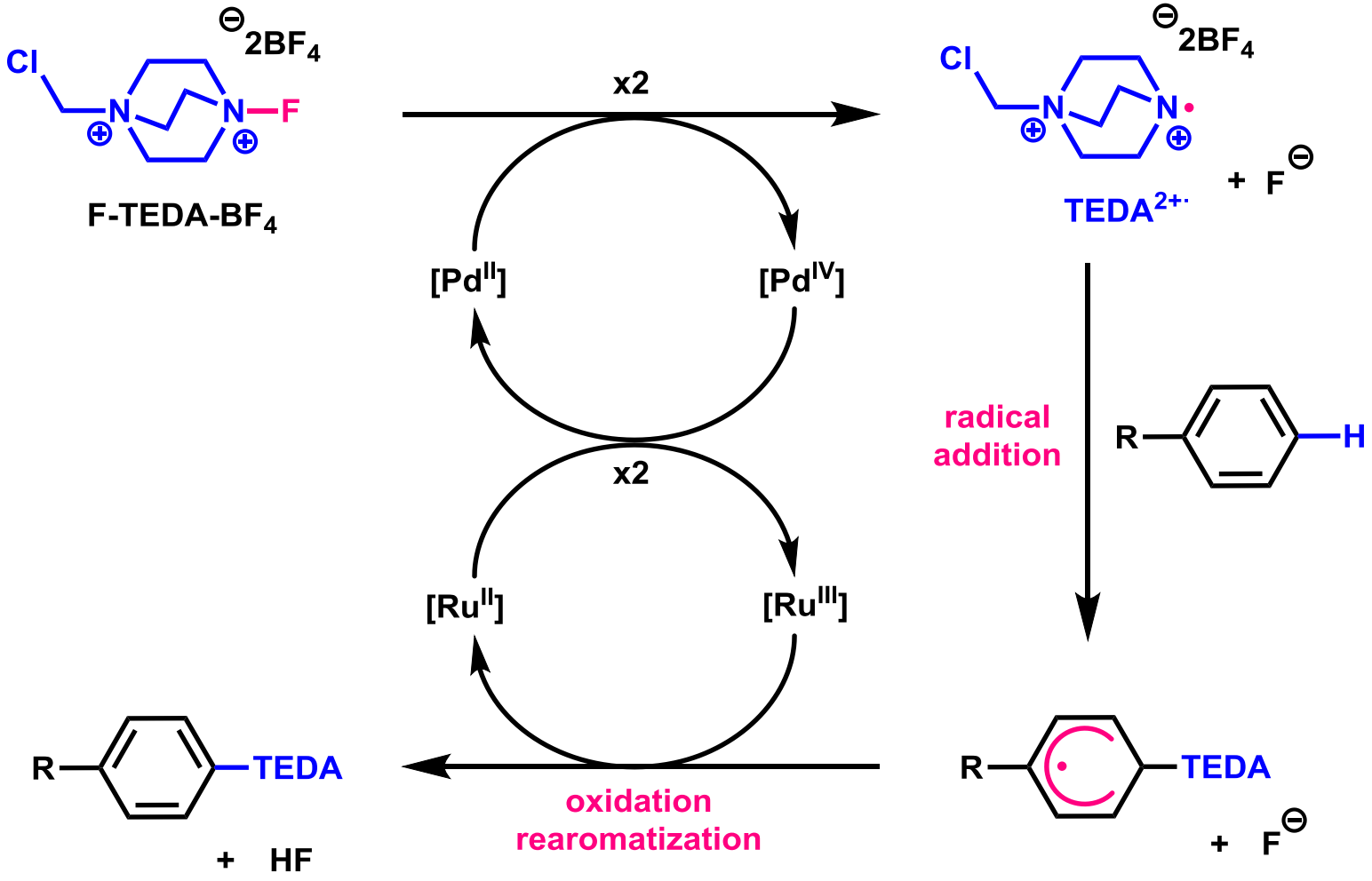
# Radical Aromatic Substitution






Boursalian, G. B.; Ham, W. S.; Mazzotti, A. R.; Ritter, T. *Nature. Chem.* **2016**, 8, 810.

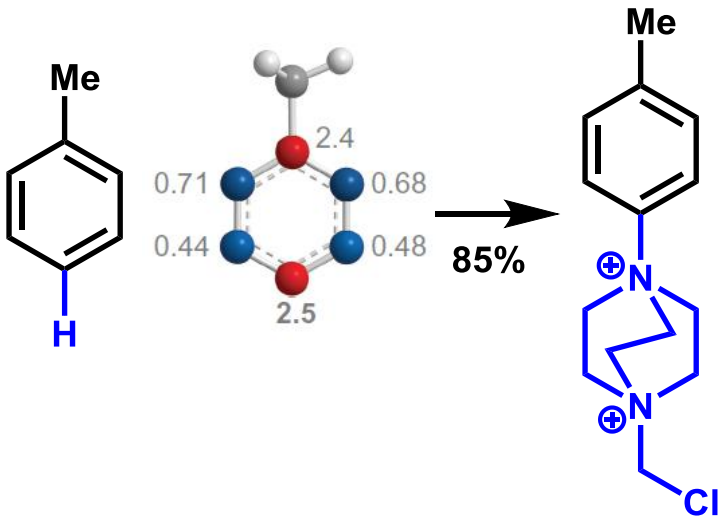
# Mechanistic Hypothesis

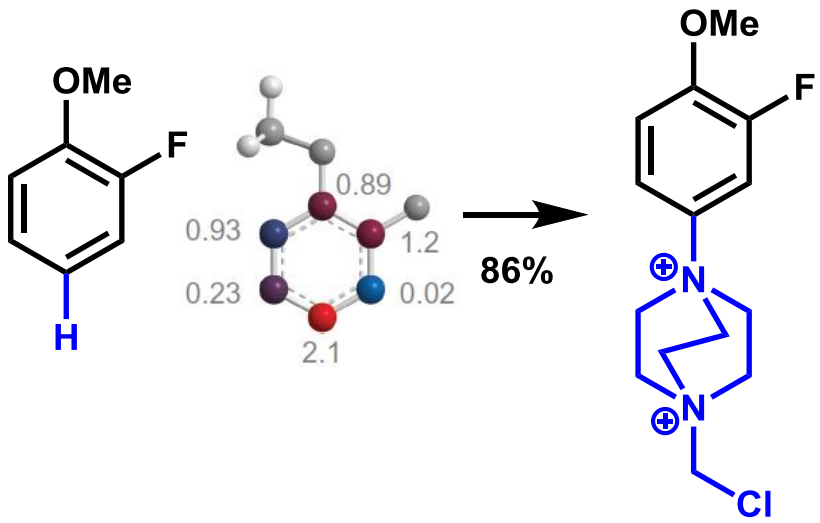


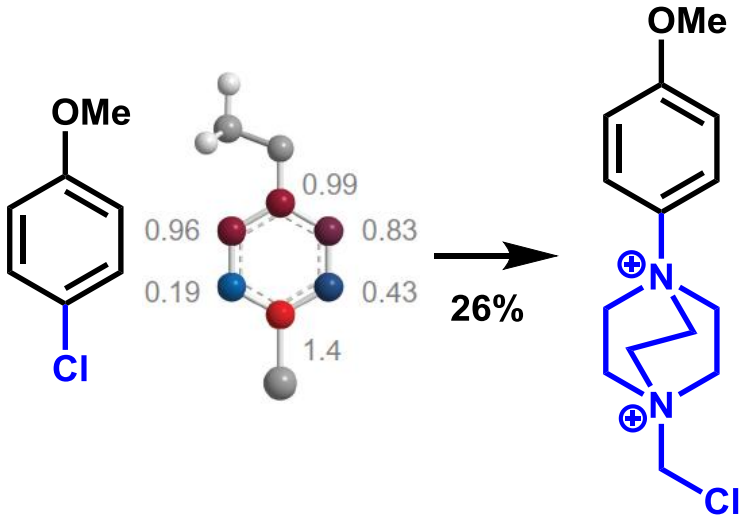
# Predictable Regioselectivities

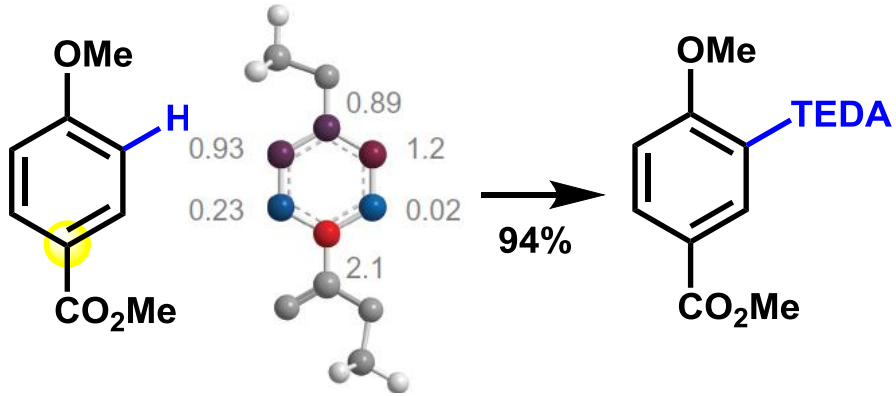
Fukui index (reactivity)

low high



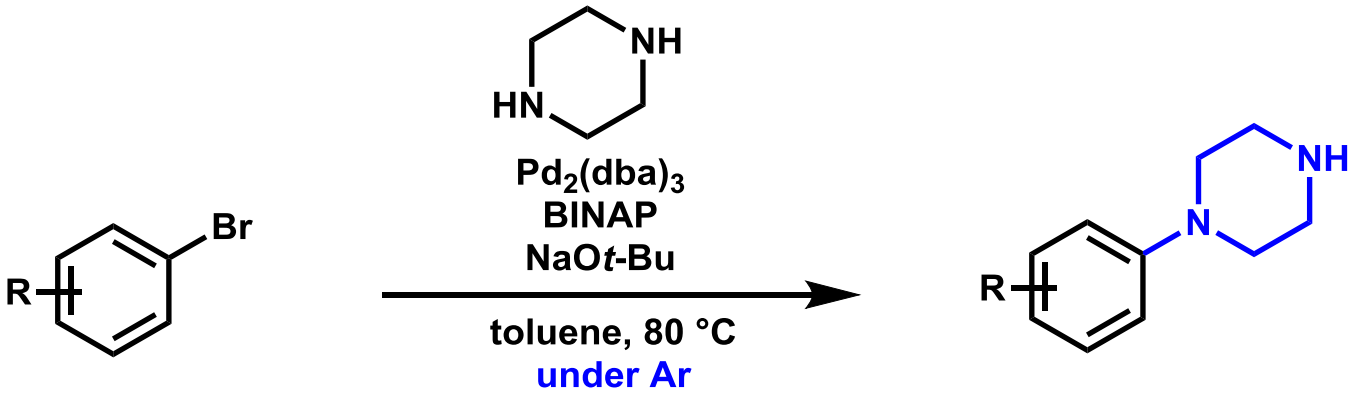



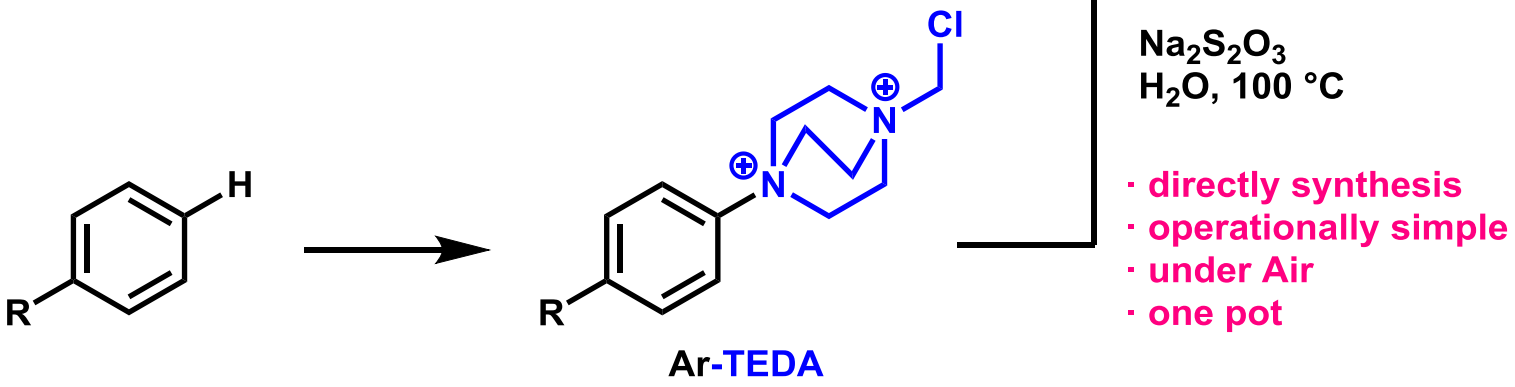
# Synthesis of Aryl Piperazines

**Buchwald-Hartwig coupling**



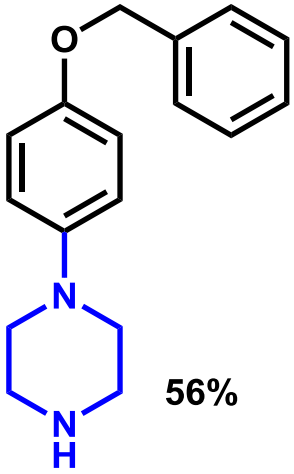

**pharmaceutically important motif**

**This reaction sequence**

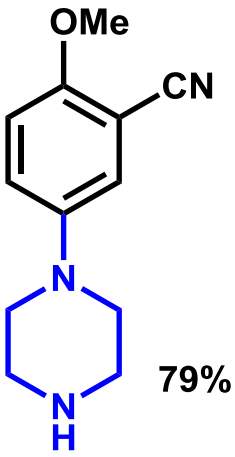



- directly synthesis
- operationally simple
- under Air
- one pot

# Substrate Scope




56%

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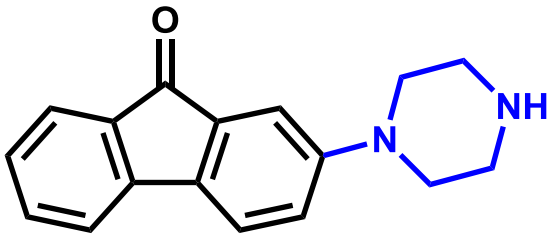


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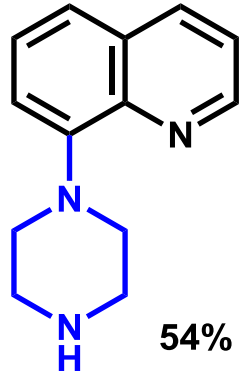


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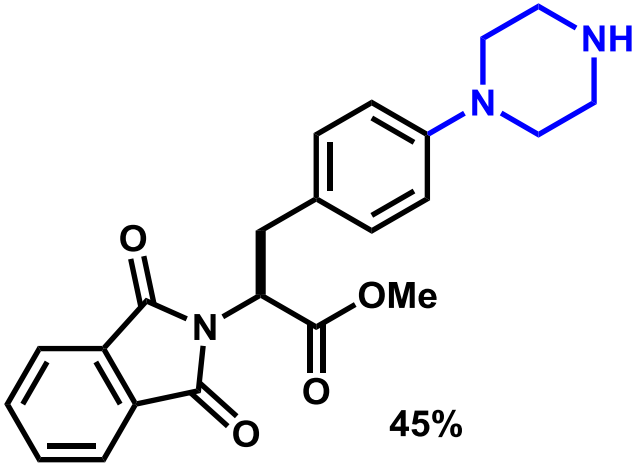


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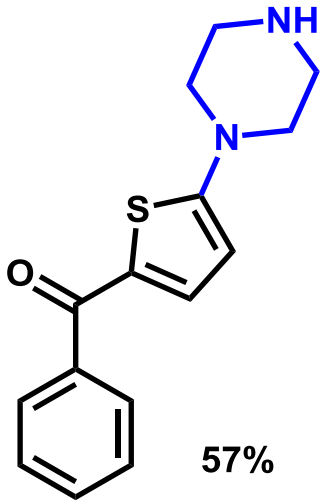


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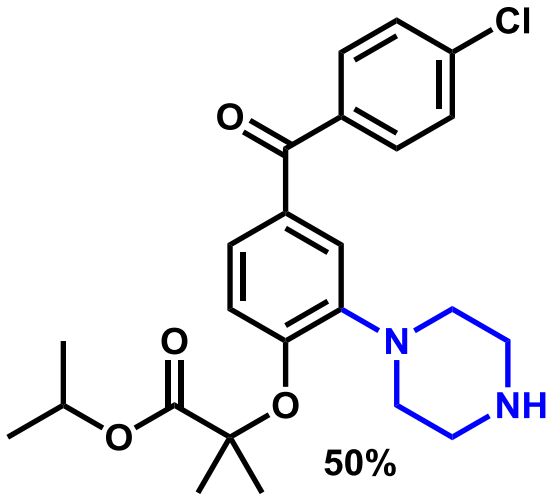
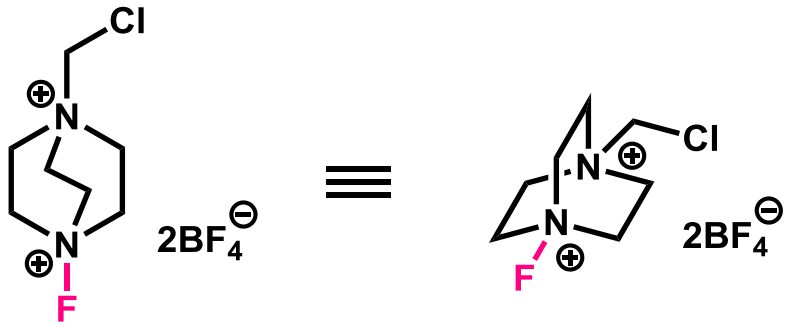



50%

fenofibrate derivative

# Summary




Selectfluor, F-TEDA-$BF_4$

- powerful fluorinating reagent
- powerful oxidant

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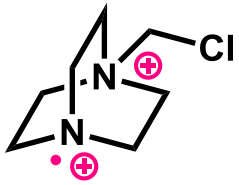
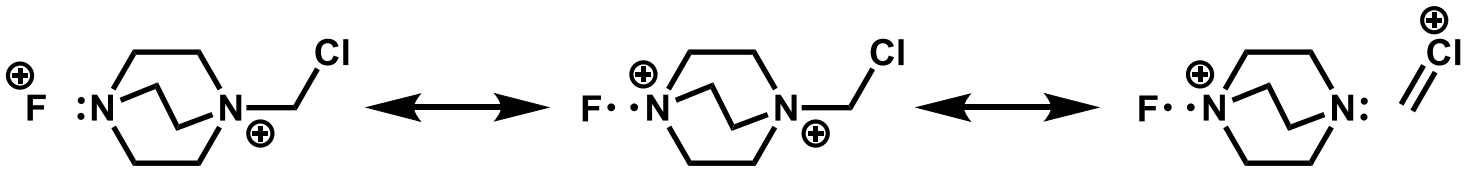



$TEDA^{2+\cdot}$

- powerful electrophilic radical to develop new radical C-H functionalization

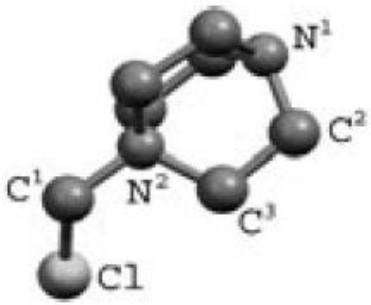
# Appendix

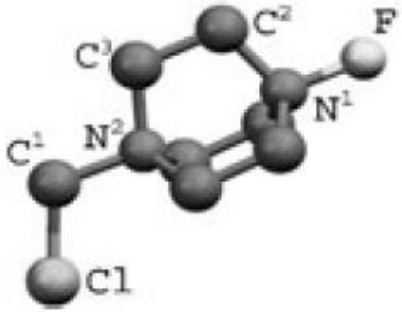
# Possible Resonance Structure



**X-ray structure of F-TEDA-$BF_4$ and precursor[1)]**

Structure



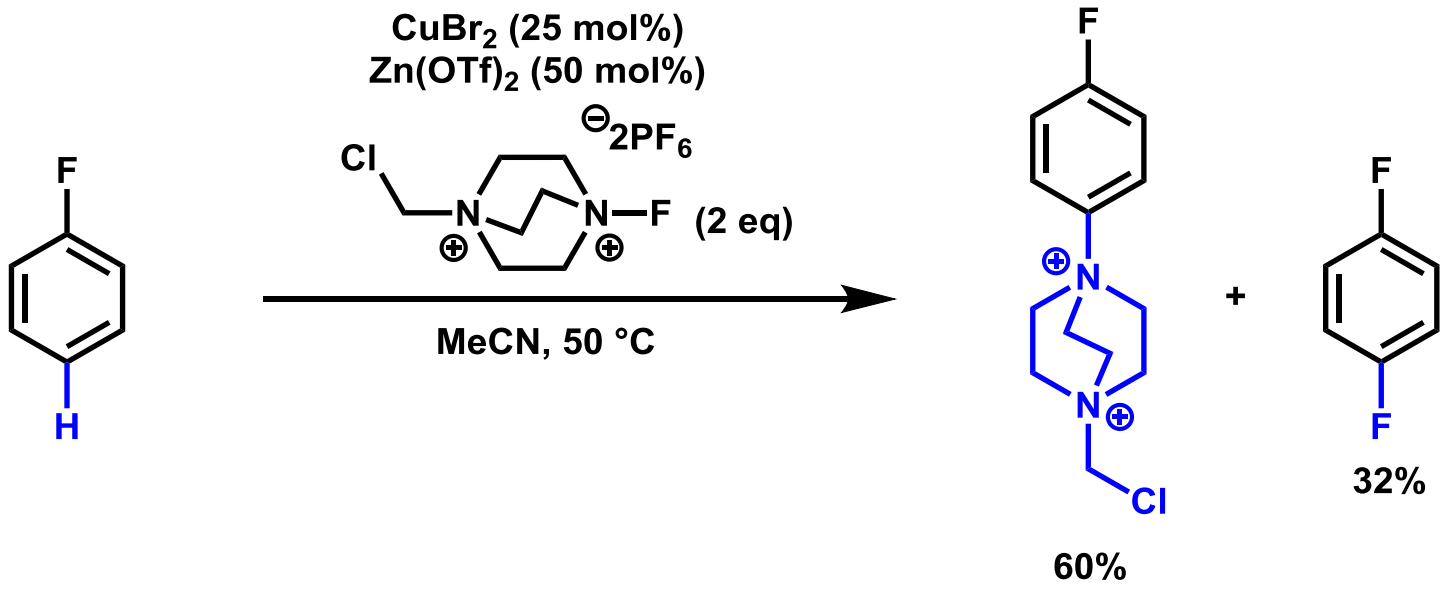




| | | | |
|---|---|---|---|
| Bond lengths/ interatomic distances [Å] | | | |
| $N^1$—$N^2$ | 2.559 | | 2.477 |
| $N^2$—$C^1$ | 1.491 | shorten → | 1.525 |
| $C^1$—Cl | 1.760 | | 1.715 |
| Bond angles [°] | | | |
| $N^1$-$C^2$-$C^3$ | 108.61 | | 107.79 |
| $N^2$-$C^3$-$C^2$ | 108.65 | | 110.59 |

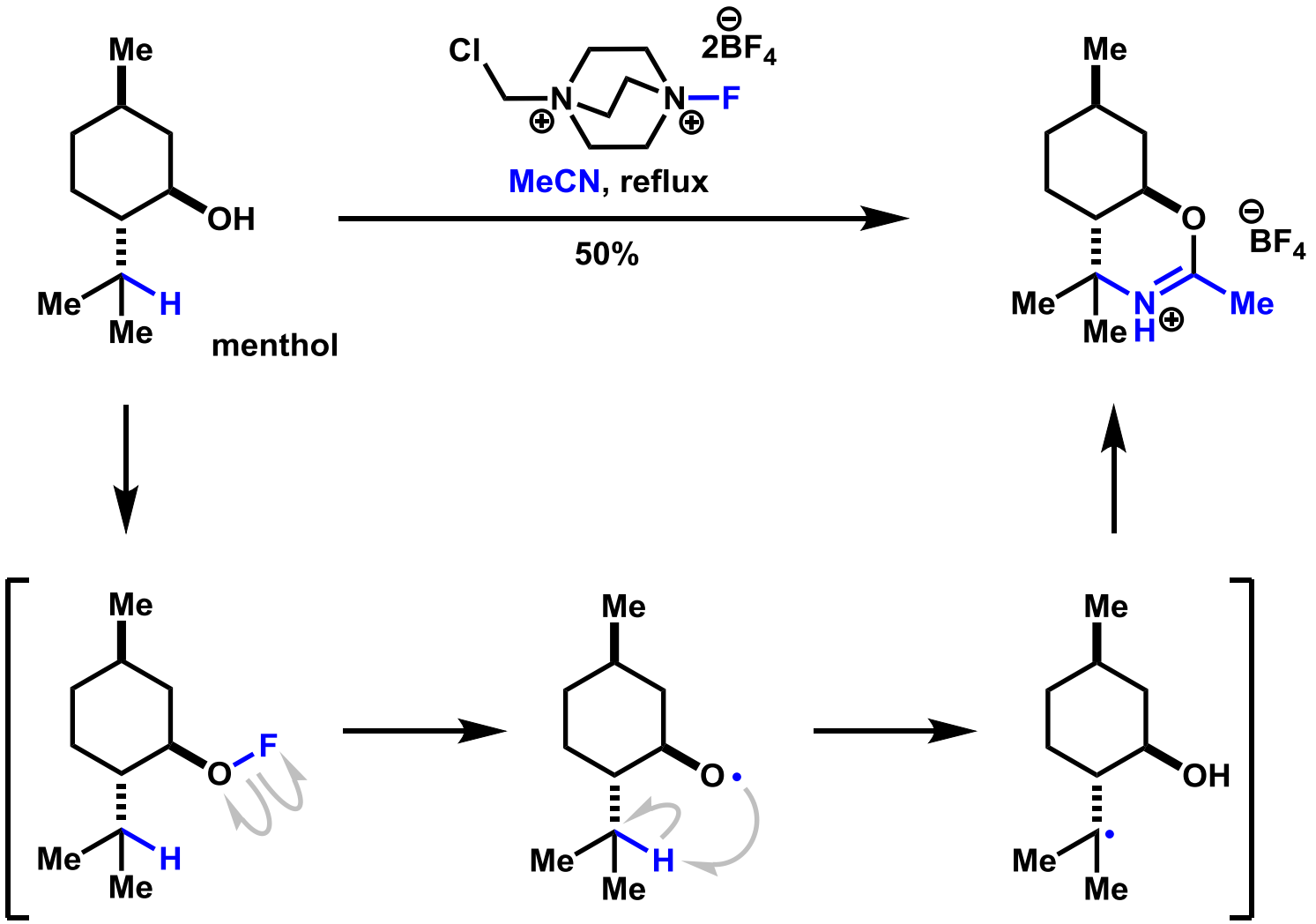


Banks, R. E.; Sharif, I.; Pritchard, R. G.. *Acta. Crystallogr. Sect. C* **1993**, 49, 492.

# Ar-TEDA Synthesis by Baran's Conditions



# Unexpected C-H Functionalization of Menthol






Banks, R. E.; Lawrence, N. J.; Besheesh, M. K.; Popplewell, A. L.; Pritchard, R. G. *Chem. Commun*. **1996**, 1629.

# Conversion of TEDA into Piperizine