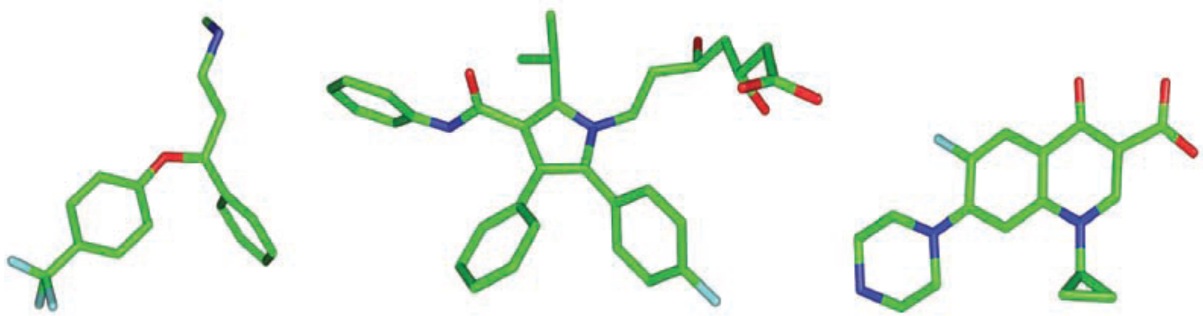
Recent Advances in Radical Mediated Csp^3–H Bond Fluorination

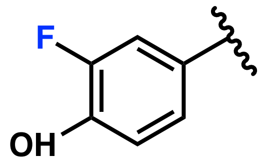


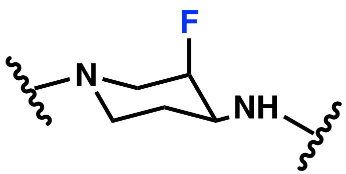
Stoltz/Reisman Literature Meeting
Zainab Al Saihati
November 17, 2017

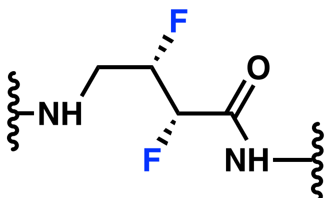
Outline

- *Properties & Importance of Fluorine Containing Compounds*
- *C–H Activation and Fluorination Challenges*
- *Overview of Organic Compounds Fluorination*
- *Recent Advances of Radical Mediated C–H Fluorination*
  - *Metal-Catalyzed C–H Fluorination*
  - *Metal-Free Catalyzed C–H Fluorination*

Properties & Importance of Fluorine Containing Compounds







9
F
fluorine
18.998

↑ potency

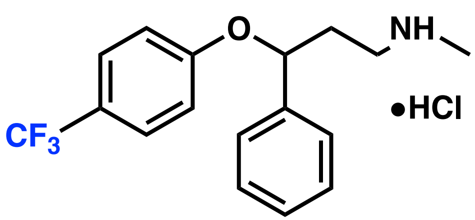
↓ pK_a

↑ permeability

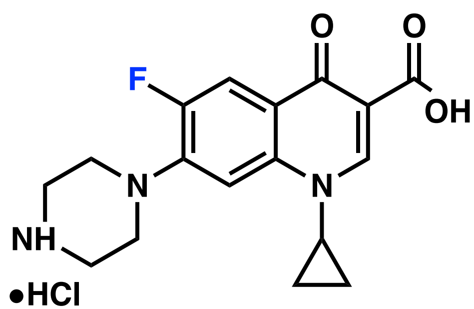
↓ clearance

conformational constraint

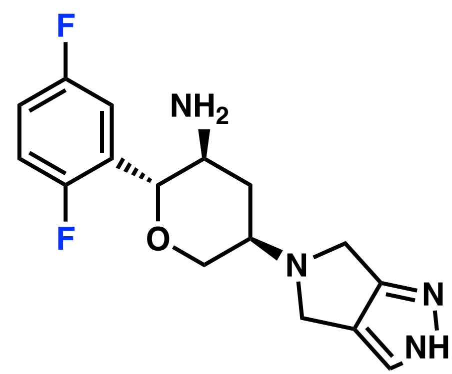
pharmacokinetic properties



Prozac



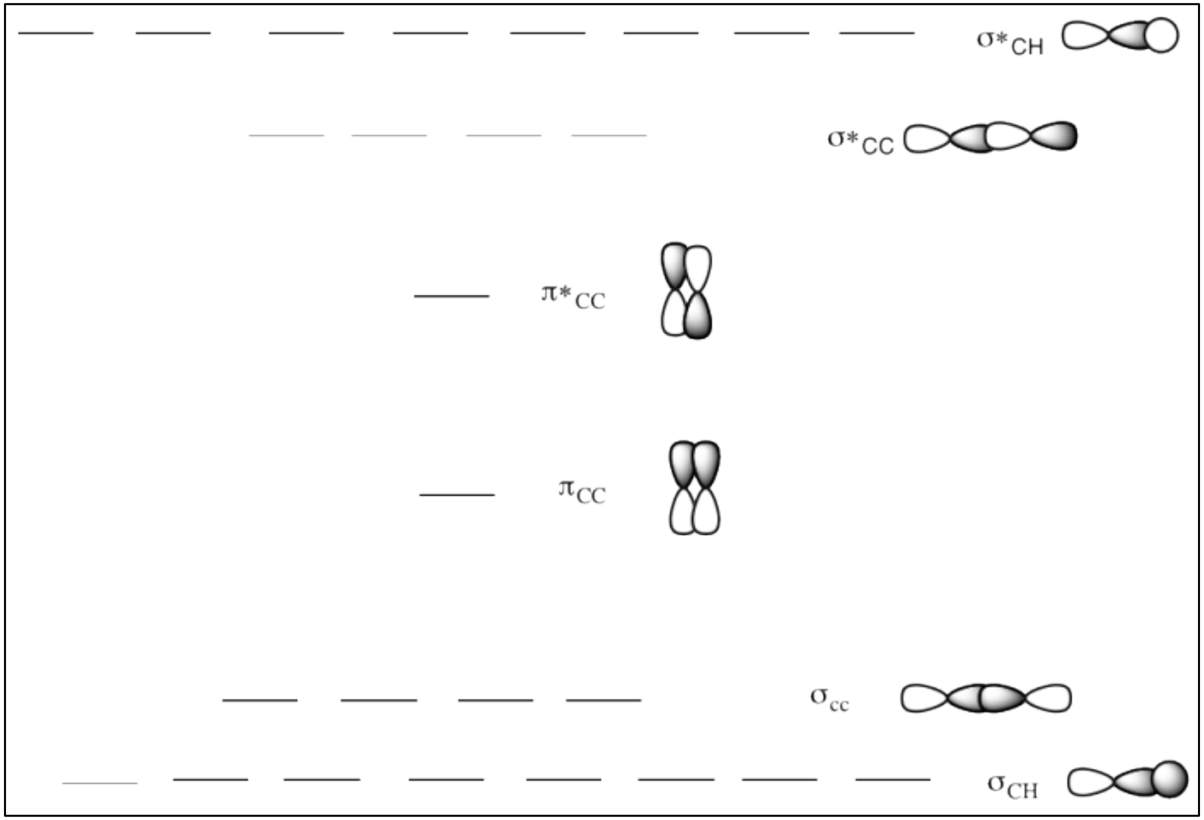
Ciprobay



DPP-4 inhibition activity

Diederich, *Science*, **2007**, 317, 1881.
Meanwell, *J. Med. Chem.*, **2015**, 58, 8315–8359.

Challenges of C–H Alkanes Activation

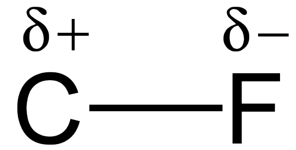


- *Alkanes are relatively inert*
- *C–H alkanes have high BDE ~ 90 – 100 kcal/mol.*

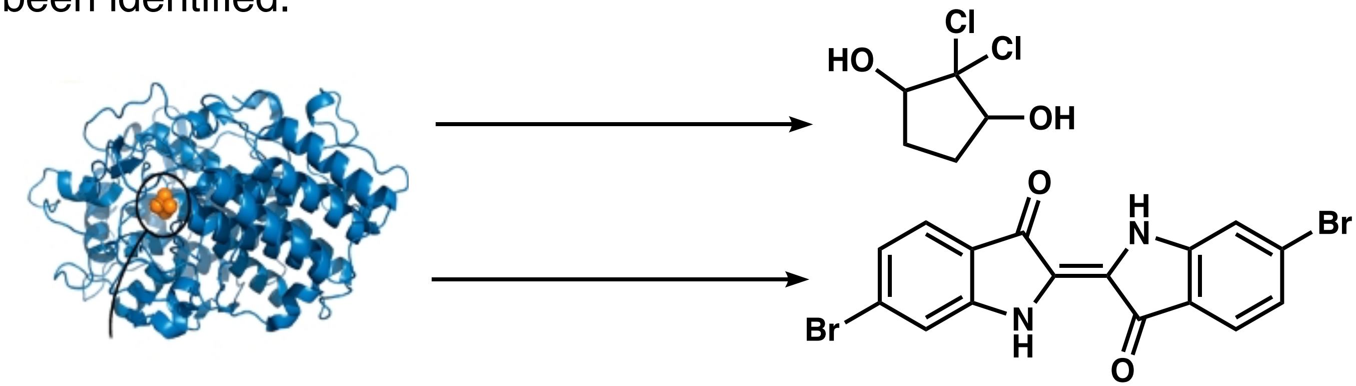
Perutz, *Chem Rev* **1996**, 96, 3125—3146.
Rayner, *JACS* **1990**, 112, 2530–2536.
Zhen, *JACS* **2000**, 122, 6783–6784.
Jones, *JACS* **2001**, 123, 7257–7270.
Luo Y–R. *Handbook of Bond Dissociation Energies in Organic Compounds*. CRC Press, Boca Raton.

Challenges of C–H Fluorination

- C–F bond formation is a challenging:
  - due to fluorine's high electronegativity
  - the high hydration energy of fluoride anion

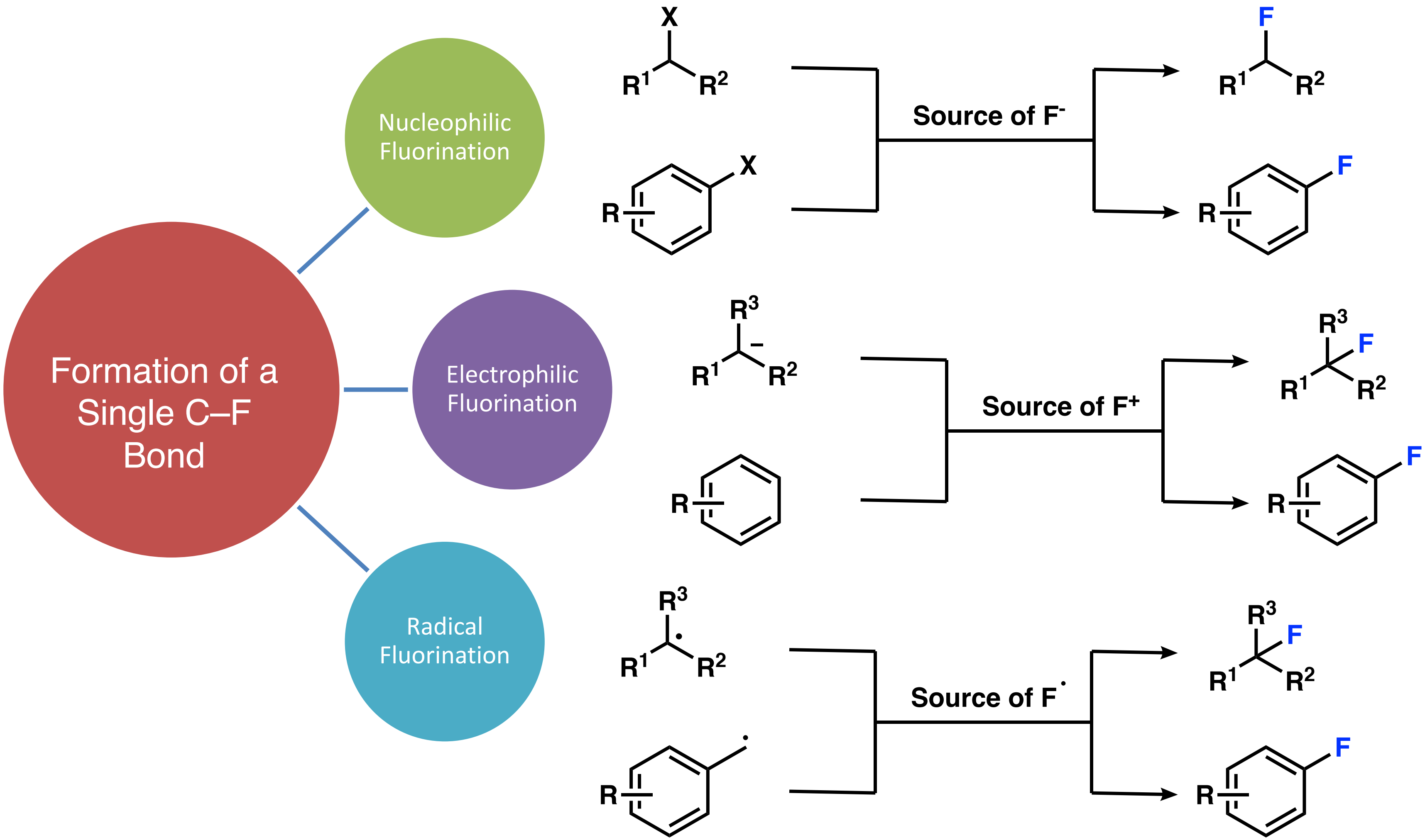


- In nature, haloperoxidase enzymes give rise to thousands of organochlorides and organobromides, but no fluoroperoxidase enzyme has been identified.



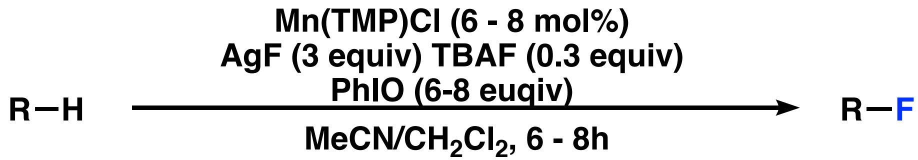
- Other Challenges Include:
  - Lack of solubility of alkali metal fluorides in organic solvents
  - Dearth of metal catalysts for selective C–F coupling reactions
  - Slow rate of most fluorination methods

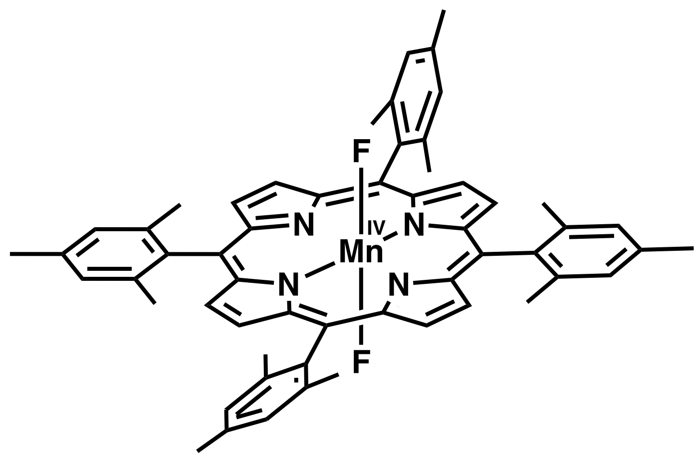
Overview of Modern Organic Compounds Fluorination



Recent Advances in Metal-Catalyzed Radical Mediated C–H Fluorination

Manganese Catalyzed Aliphatic C–H Fluorination

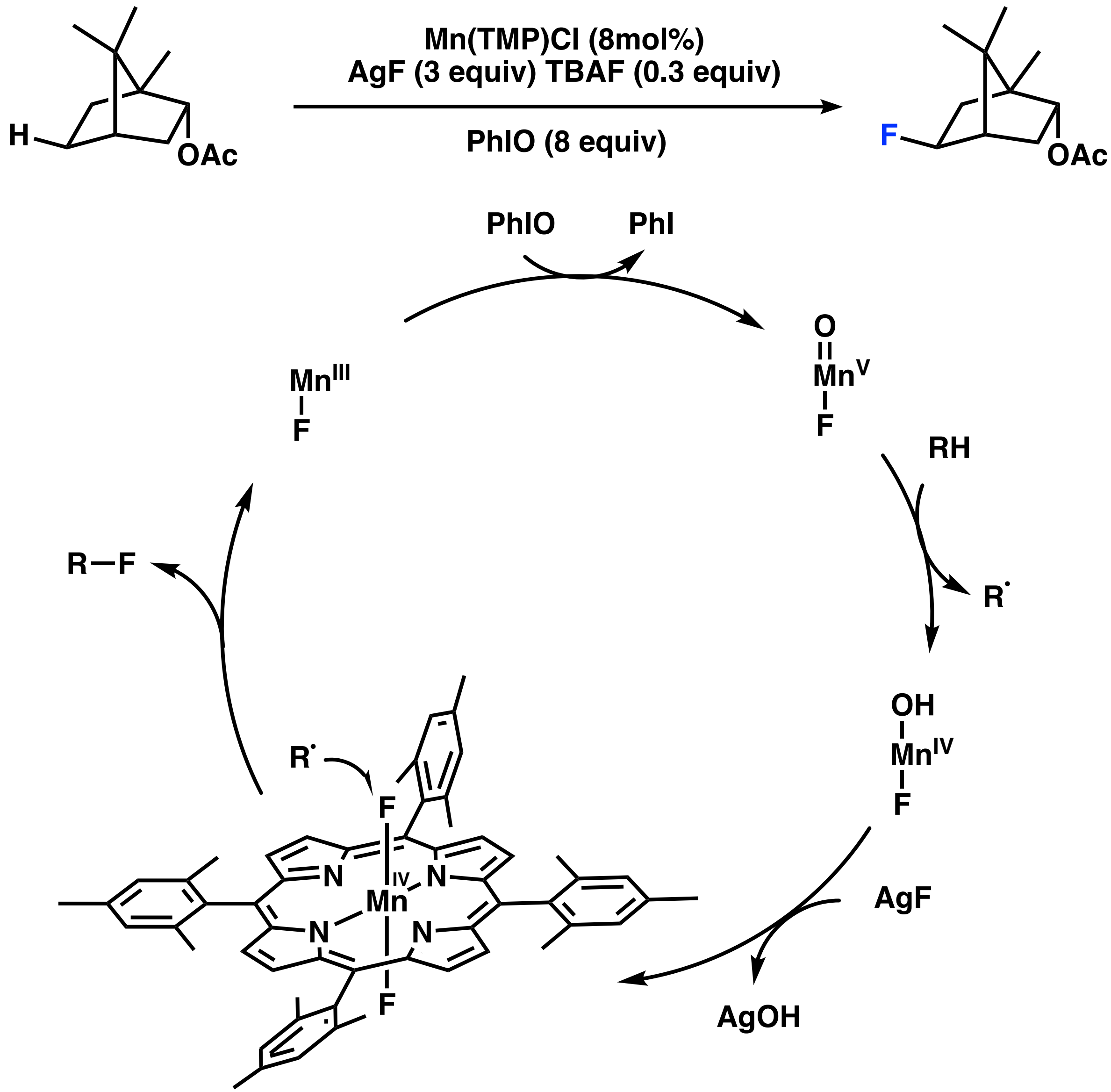




simple alkankes, amides,
ester, teriary alkohol,
terpenoids,
ketones,sterioids

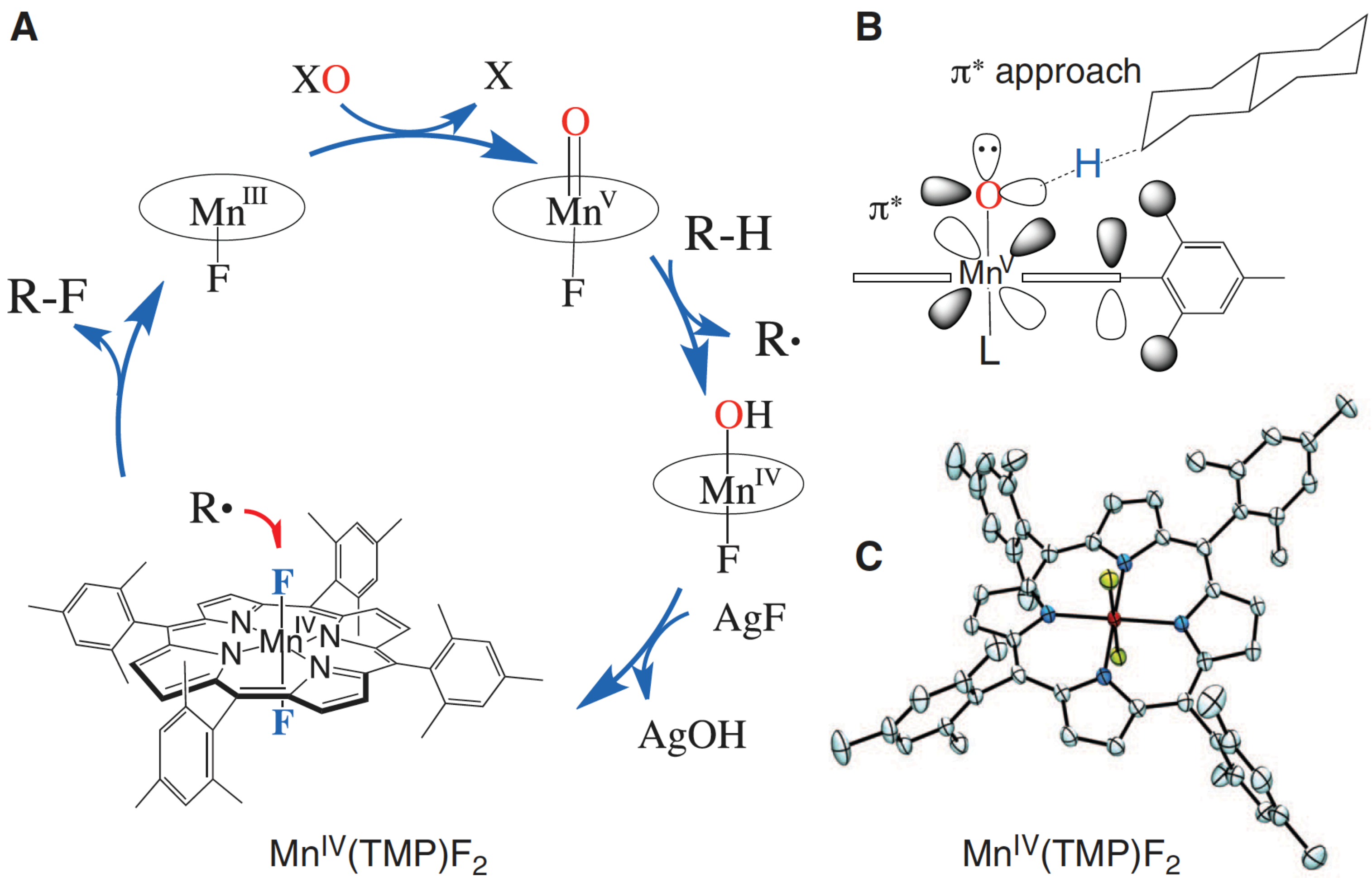
Groves, *Science* **2012**, 337, 1322–1325.

Manganese Catalyzed Aliphatic C–H Fluorination

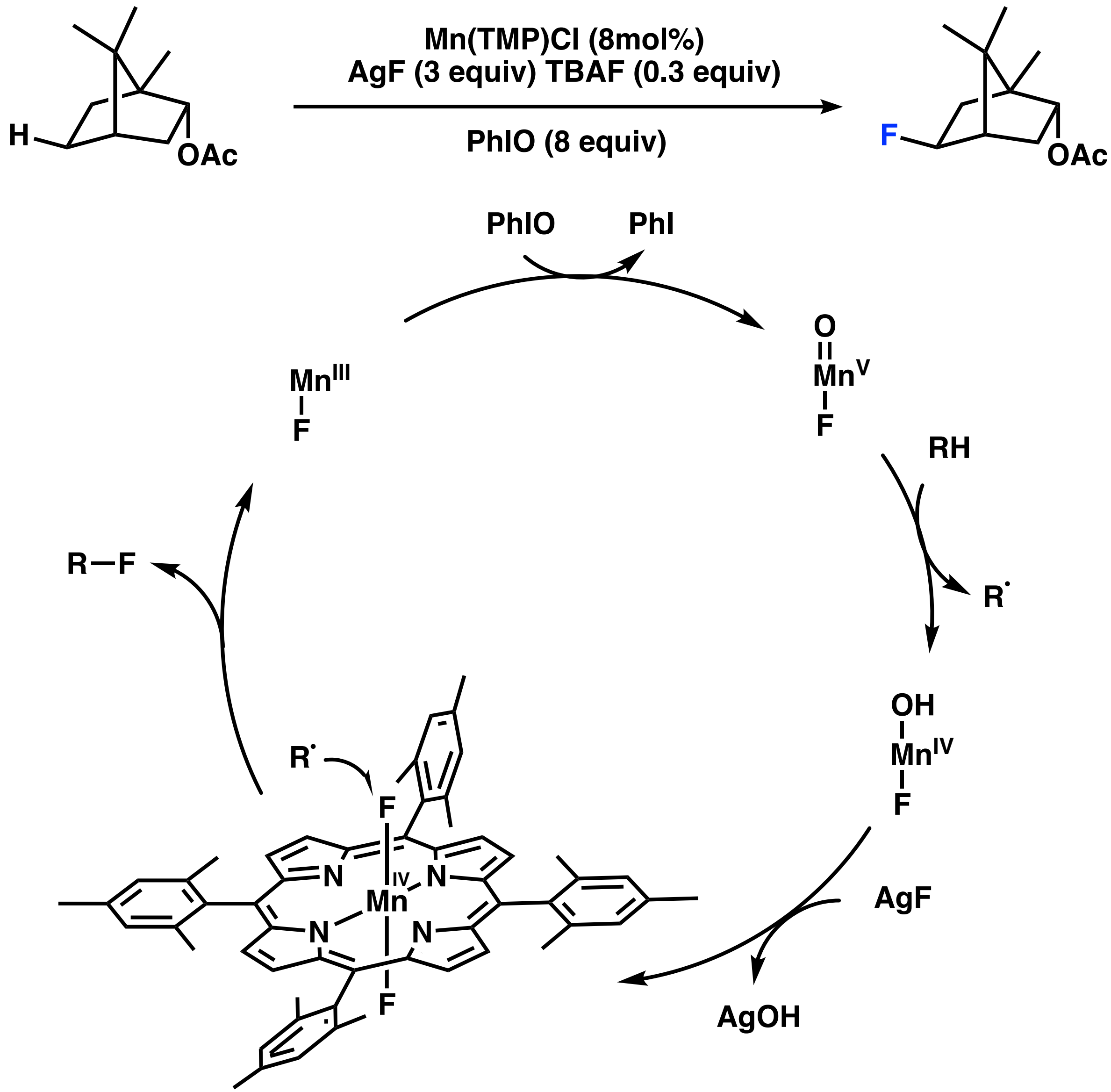


Groves, *Science* **2012**, 337, 1322–1325.

Manganese Catalyzed Aliphatic C–H Fluorination

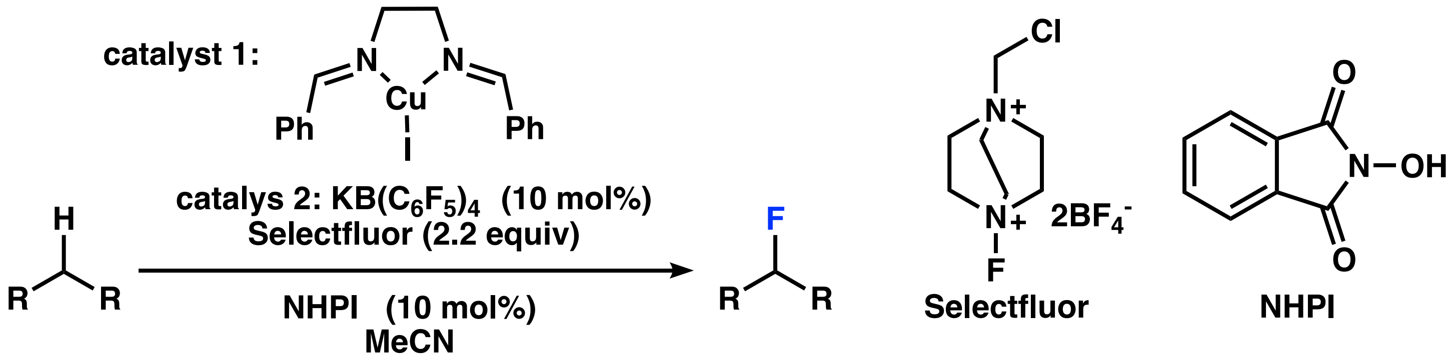


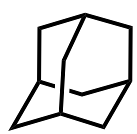
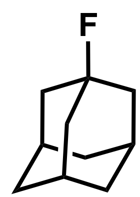
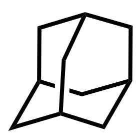
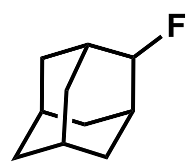
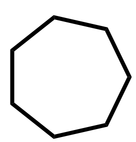
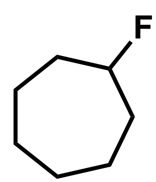
Manganese Catalyzed Aliphatic C–H Fluorination



Groves, *Science* **2012**, 337, 1322–1325.

Copper Promoted C–H Bond Fluorination via Radical Chain Propagation

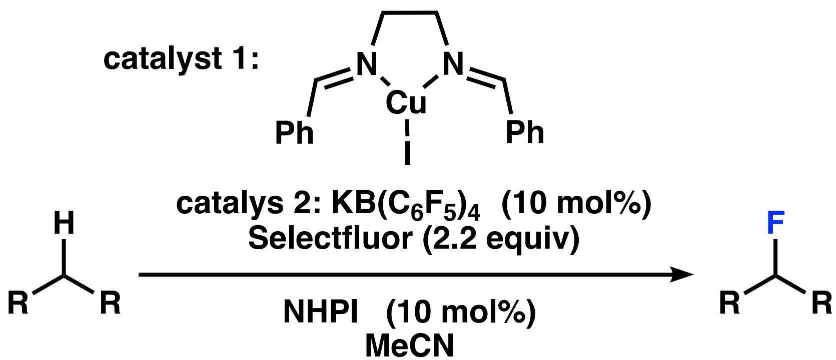


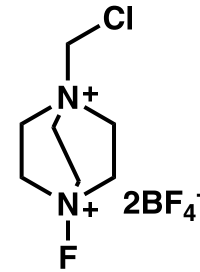
Entry	Substrate	Product	Yield [%]	*t* [h]	T [°C]
1			75[c]	3	25
2			40[c]	3	0
3			66[b]	1	81

[a] 10 mol% KI. [b] 1.2 equiv KI. [c] No KI.

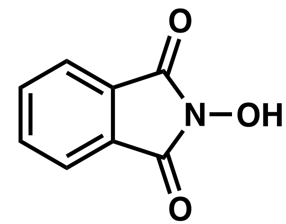
Lectka, *ACIE* **2012**, 51, 10580—10583.
Lectka, *JACS* **2014**, 136, 9780–9791.

Copper Promoted C–H Bond Fluorination via Radical Chain Propagation

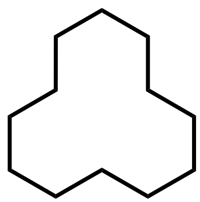
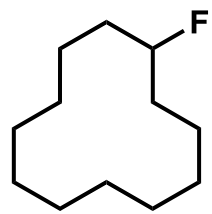
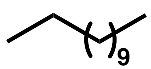
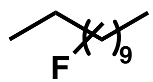
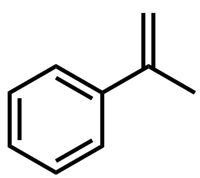
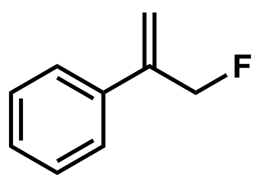




Selectfluor



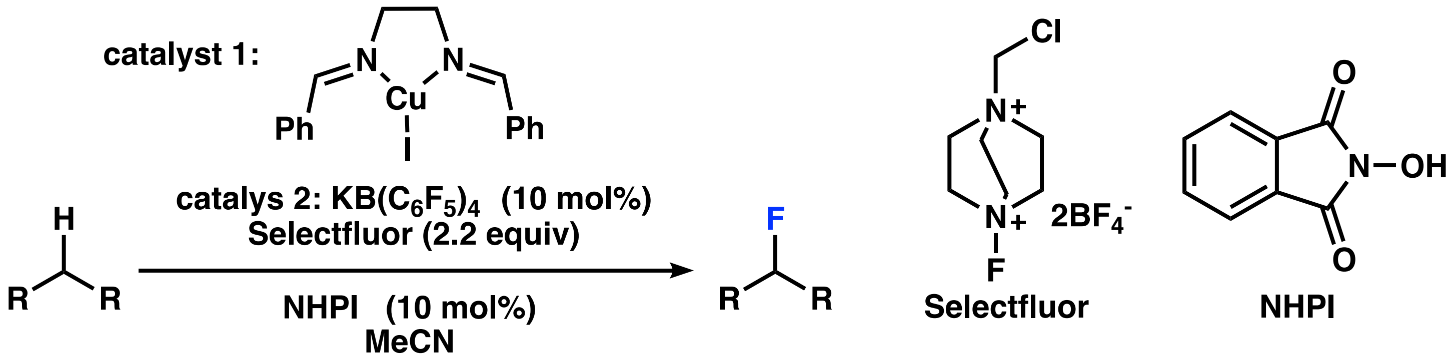
NHPI

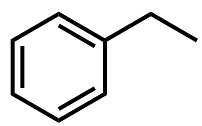
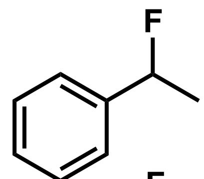
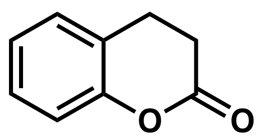
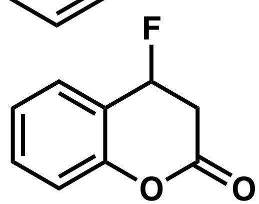
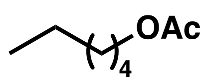
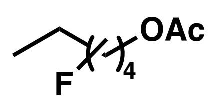
Entry	Substrate	Product	Yield [%]	*t* [h]	T [°C]
4			72[a]	2	81
5			63[b]	2	81
6			53[c]	24	25

[a] 10 mol% KI. [b] 1.2 equiv KI. [c] No KI.

Lectka, *ACIE* **2012**, 51, 10580—10583.
Lectka, *JACS* **2014**, 136, 9780–9791.

Copper Promoted C–H Bond Fluorination via Radical Chain Propagation

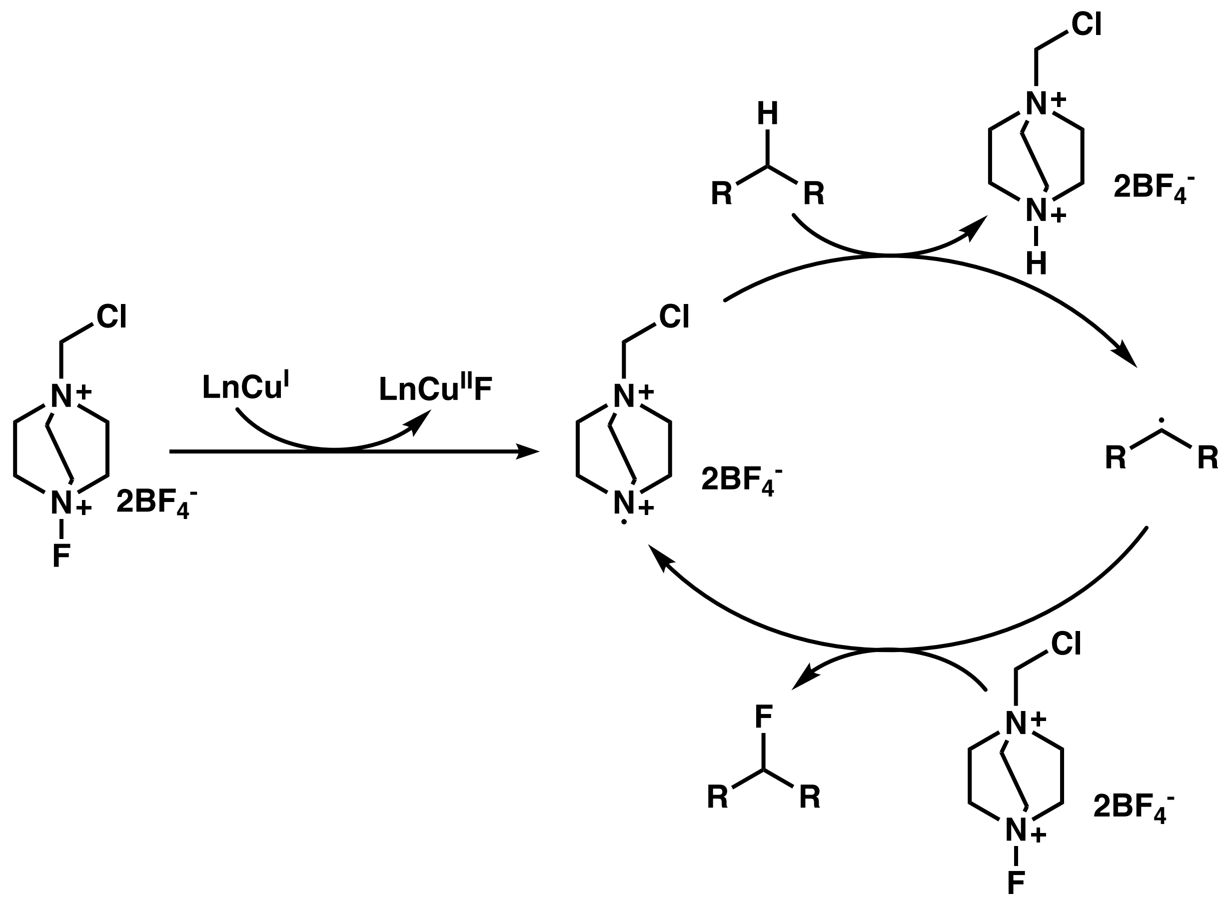


Entry	Substrate	Product	Yield [%]	*t* [h]	T [°C]
7			28[c]	24	25
8			47[b]	3	25
9			56[b]	1.5	81

[a] 10 mol% KI. [b] 1.2 equiv KI. [c] No KI.

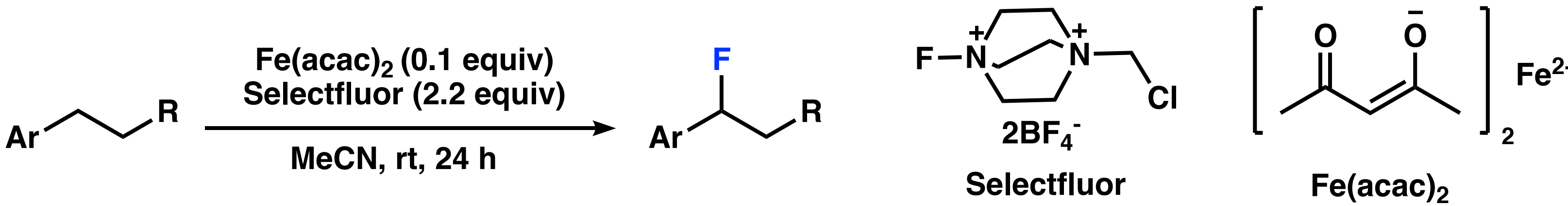
Lectka, *ACIE* **2012**, 51, 10580—10583.
Lectka, *JACS* **2014**, 136, 9780–9791.

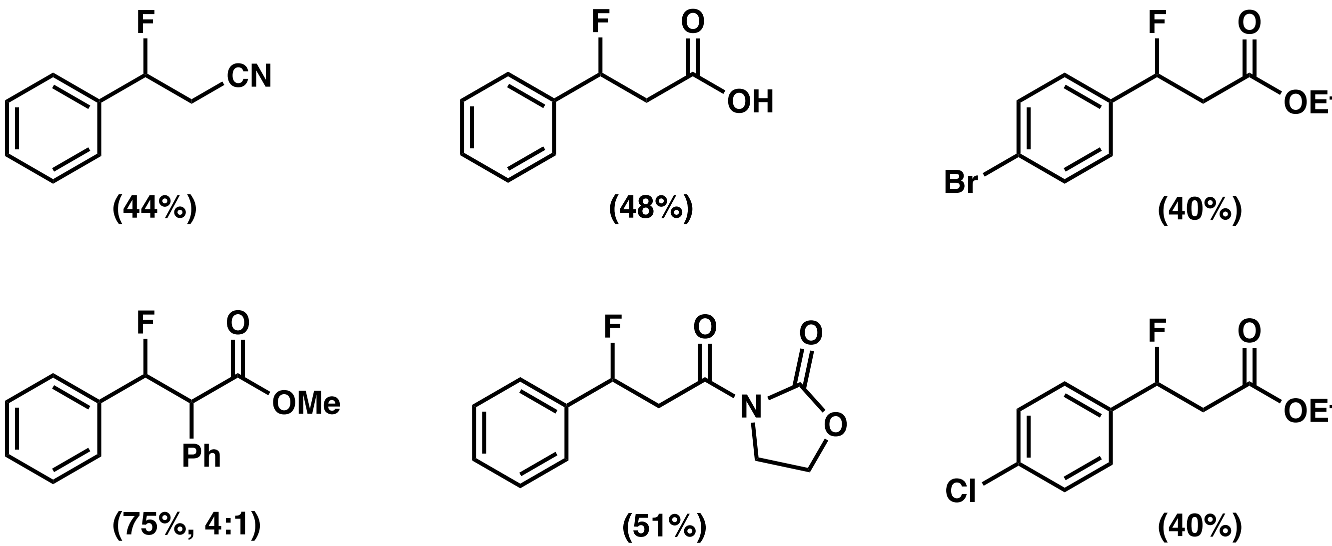
Copper Promoted C–H Bond Fluorination via Radical Chain Propagation



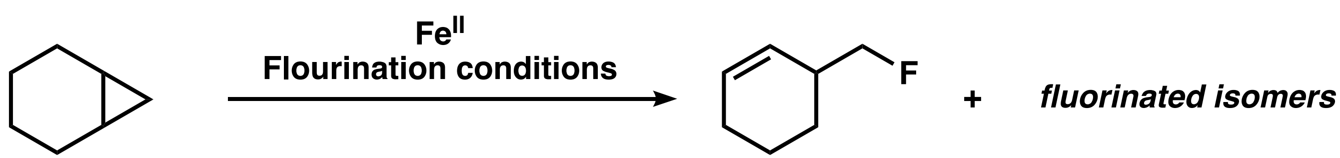
Lectka, *ACIE* **2012**, 51, 10580–10583.
Lectka, *JACS* **2014**, 136, 9780–9791.

Iron Catalyzed Benzylic C–H Fluorination



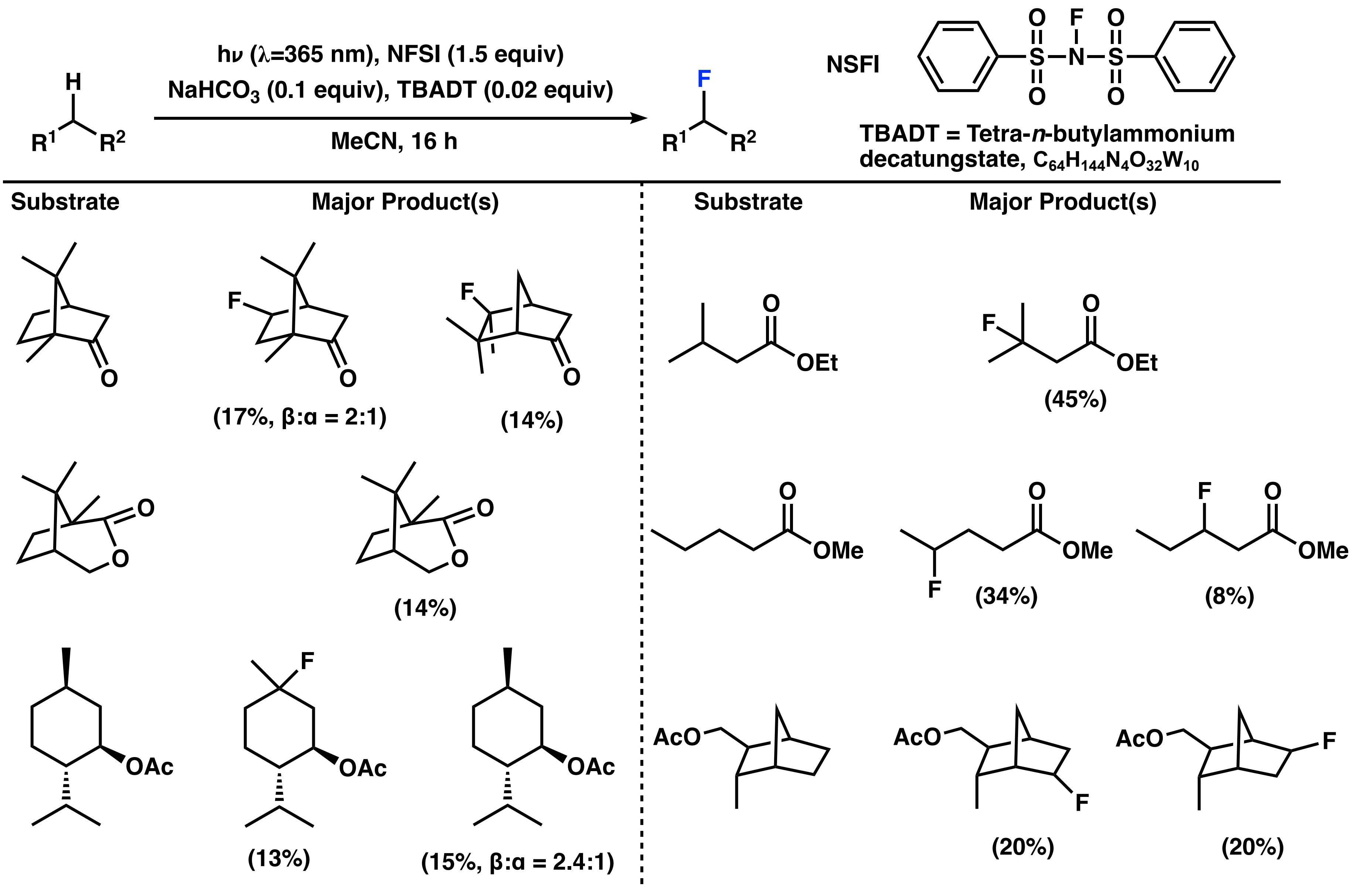


Premilinary Evidence of Radical Involved Fluorination



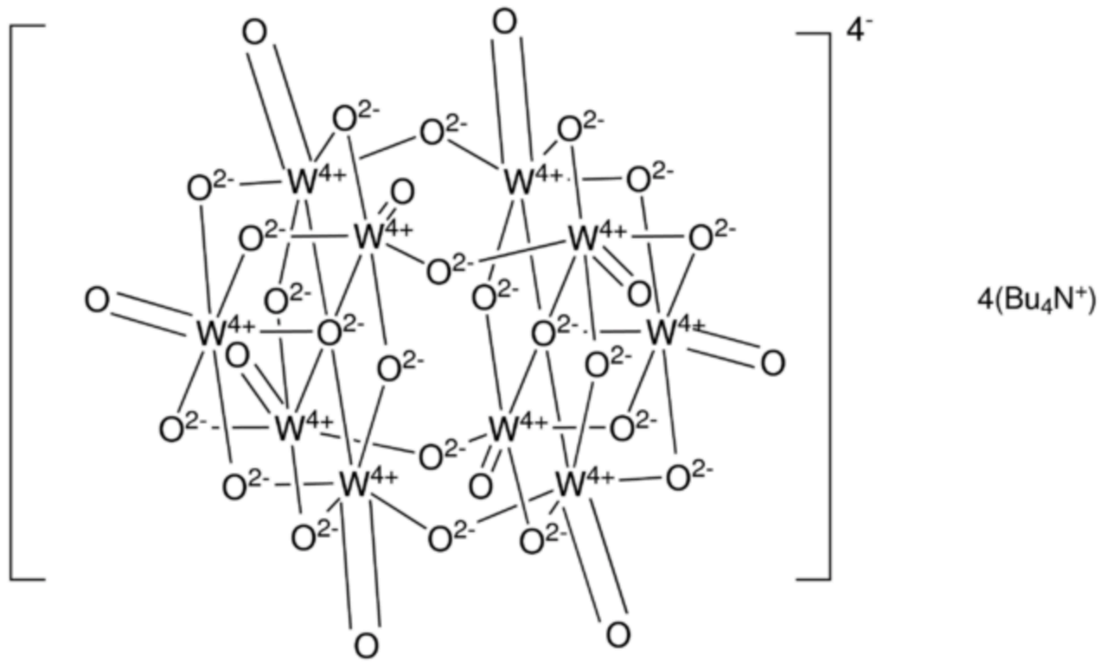
Lectka, *J. Org. Chem.* **2013**, 78, 11082–11086.

Decatungstate Anion Catalyzed C–H Fluorination under Photo–irradiation

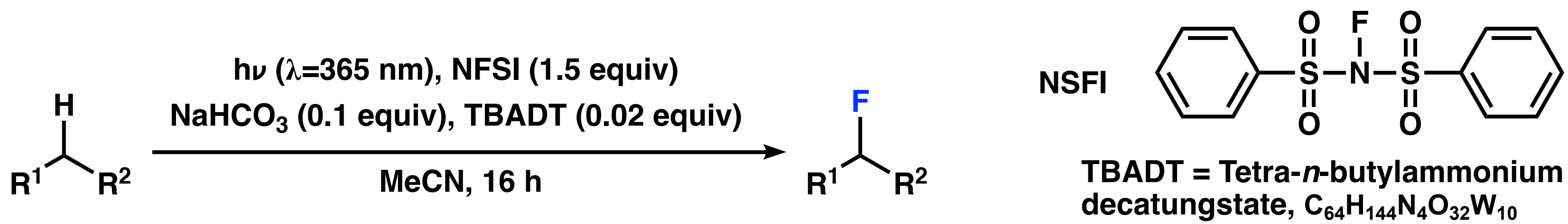


Britton, *ACIE* **2014**, 53, 4690–4693.

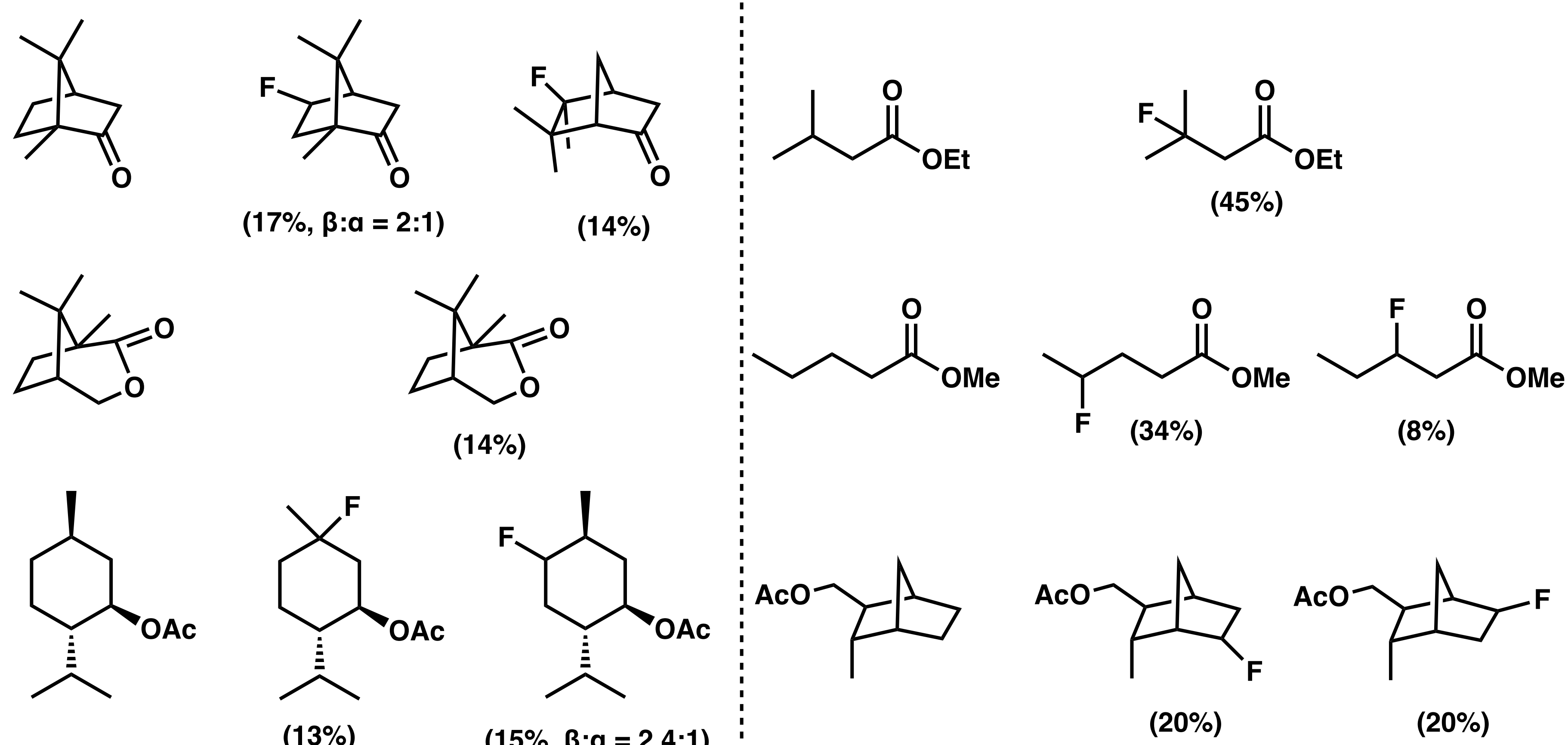
Decatungstate Anion Catalyzed C–H Fluorination under Photo–irradiation



Decatungstate Anion Catalyzed C–H Fluorination under Photo–irradiation



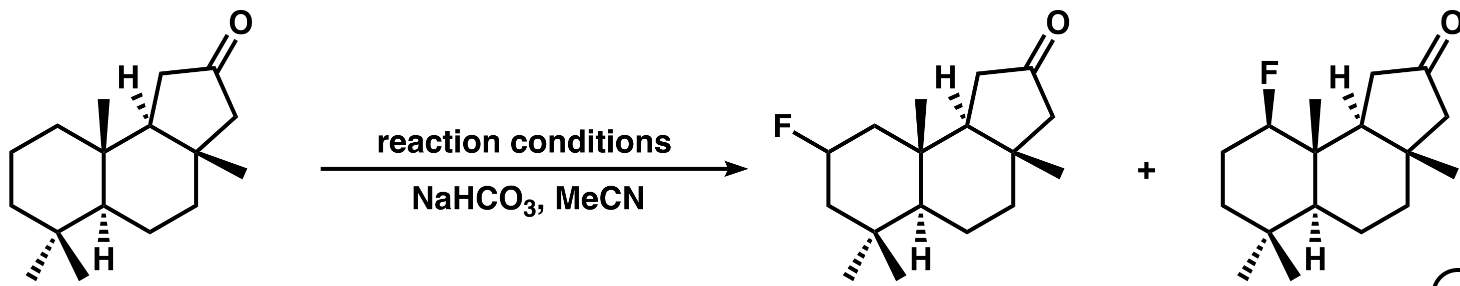
Substrate | **Major Product(s)** | **Substrate** | **Major Product(s)**



Britton, *ACIE* **2014**, 53, 4690–4693.

Decatungstate Anion Catalyzed C–H Fluorination under Photo–irradiation

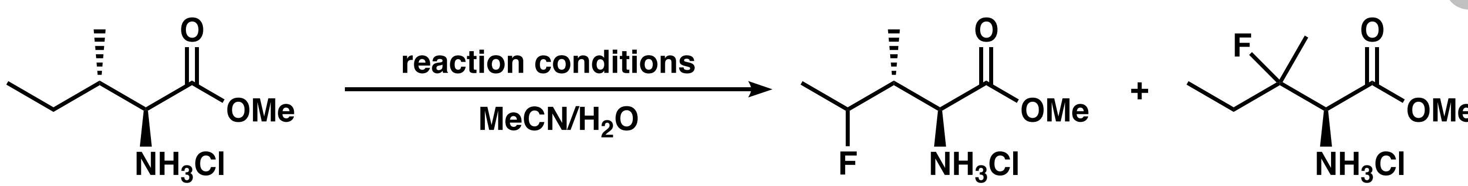
Fluorination of Natural Product Sclareolide



(58%, α:β = 4:1)   (10%)

Reaction Conditions:
NSFI (1.5 Equiv)
TBADT (0.02 equiv)
hν (λ=365 nm)

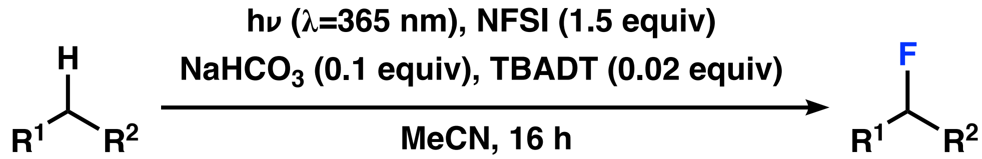
Fluorination of Amino Acid Derrivatives

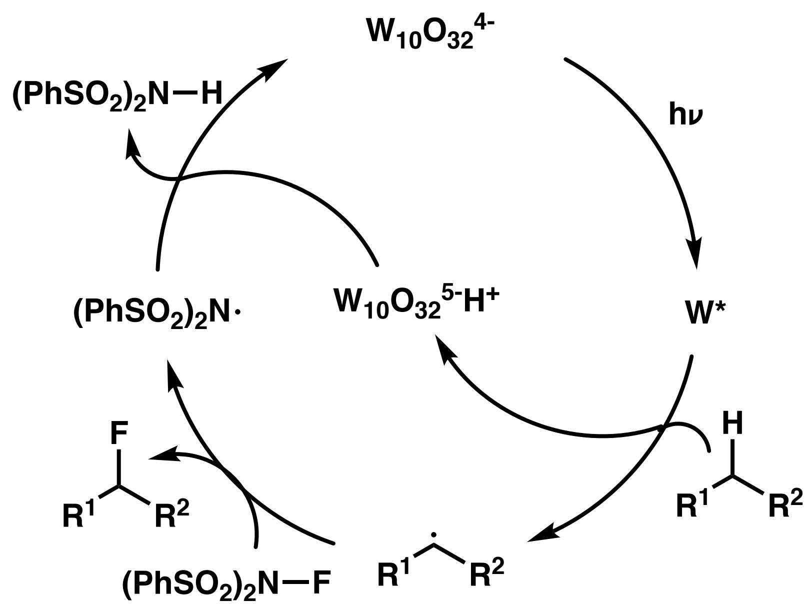


(40%, α:β = 1:1)   (19%, α:β = 1:1)

Britton, *ACIE* **2014**, 53, 4690–4693.

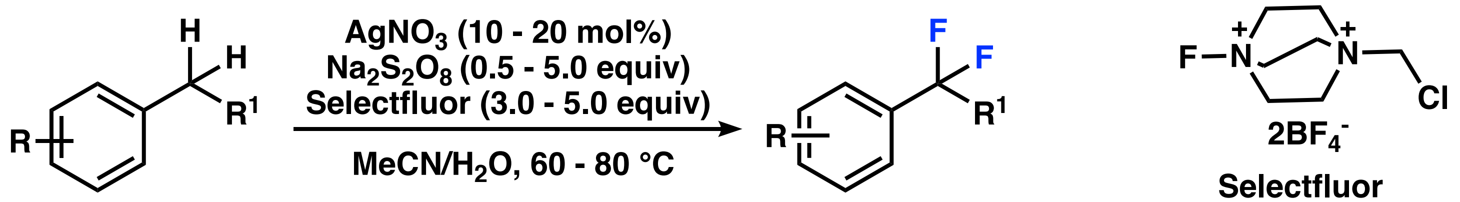
Decatungstate Anion Catalyzed C–H Fluorination under Photo–irradiation
Proposed Mechanism

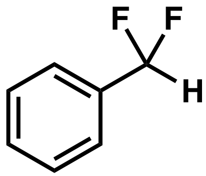




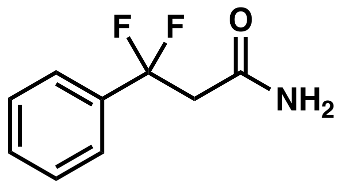
Britton, *ACIE* **2014**, 53, 4690–4693.

Silver–Catalyzed Oxidative Benzylic C–H Bonds Difluorination of Arenes

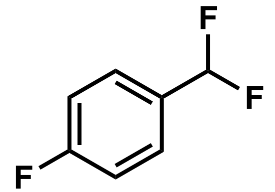




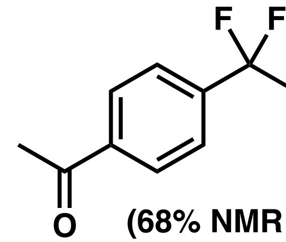
(85% NMR yield, 5H h)



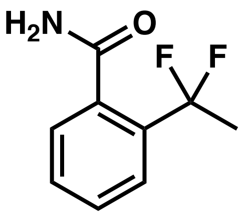
(42%, 3 h)



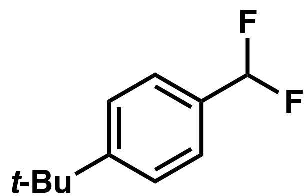
(65% NMR yield, 5 h)



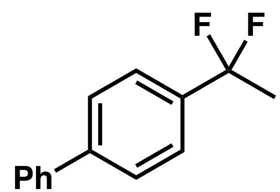
(68% NMR yield, 5 h)



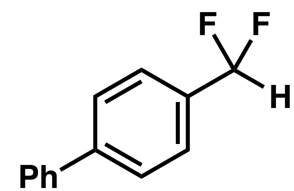
(84%, 3 h)



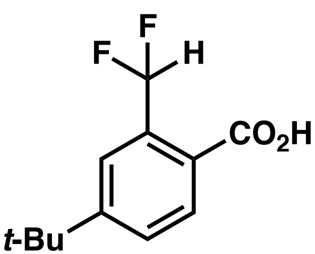
(75% NMR yield, 5 h)



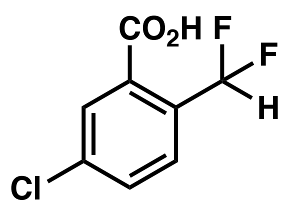
(74%, 3 h)



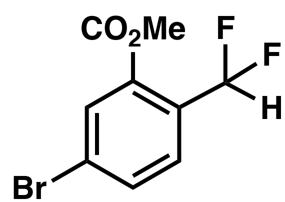
(93%, 3 h)



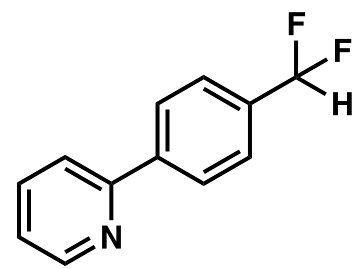
(53%, 3 h)



(88%, 3 h)



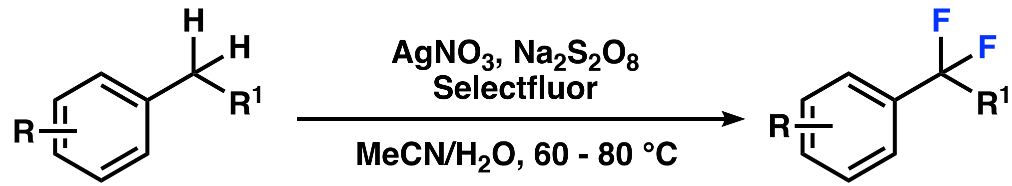
(88%, 3 h)



(82%, 3 h)

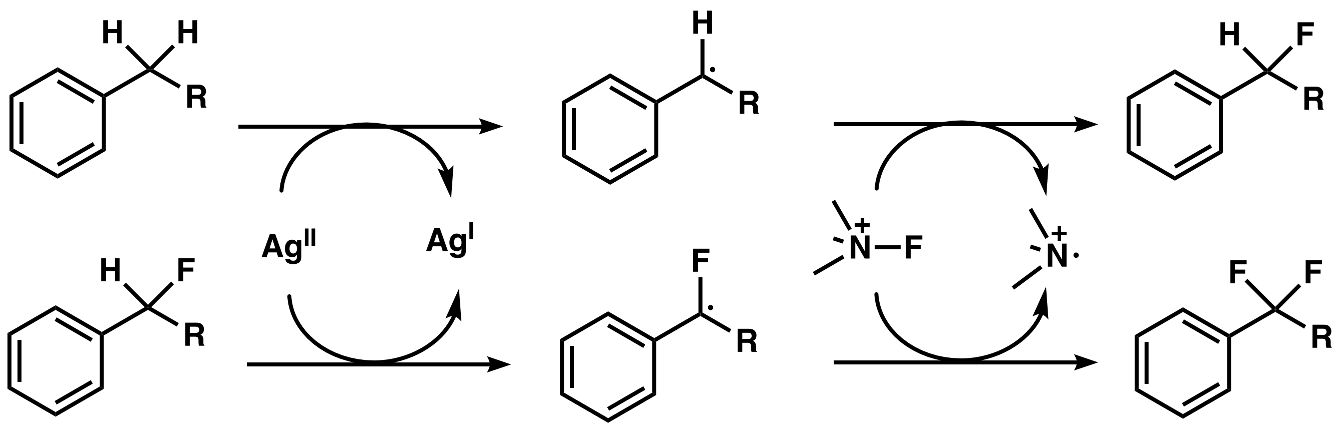
Tang, *ACIE* **2014**, 53, 5955–5958.

Silver–Catalyzed Benzylic C–H Bonds Difluorination of Arenes Proposed Mechanism



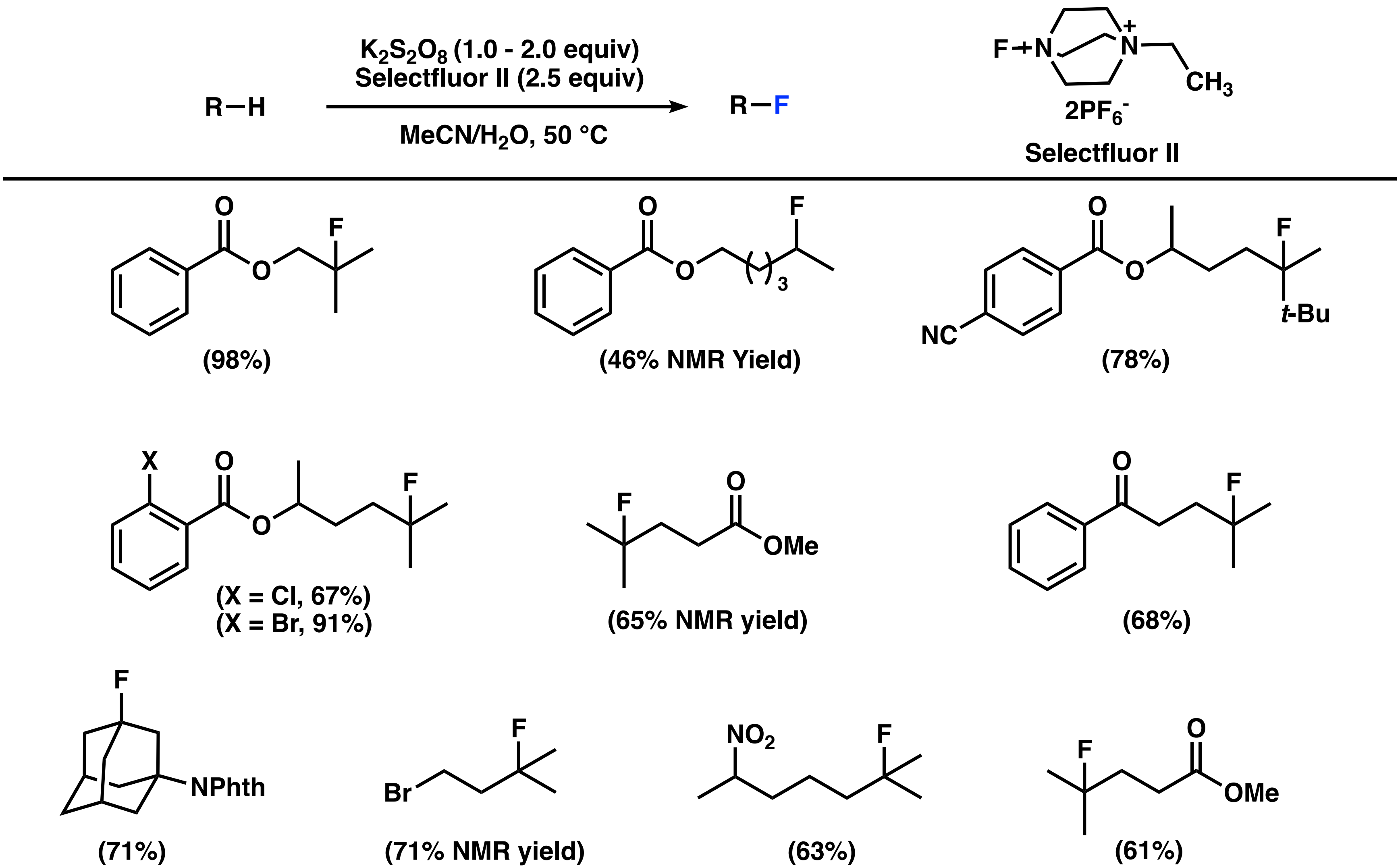
$Ag^{I} + S_2O_8^{2-} \longrightarrow Ag^{I} + SO_4^{2-} + SO_4^{-\bullet}$

$Ag^{I} + SO_4^{-\bullet} \longrightarrow Ag^{II} + SO_4^{2-}$



Tang, *ACIE* **2014**, 53, 5955–5958.

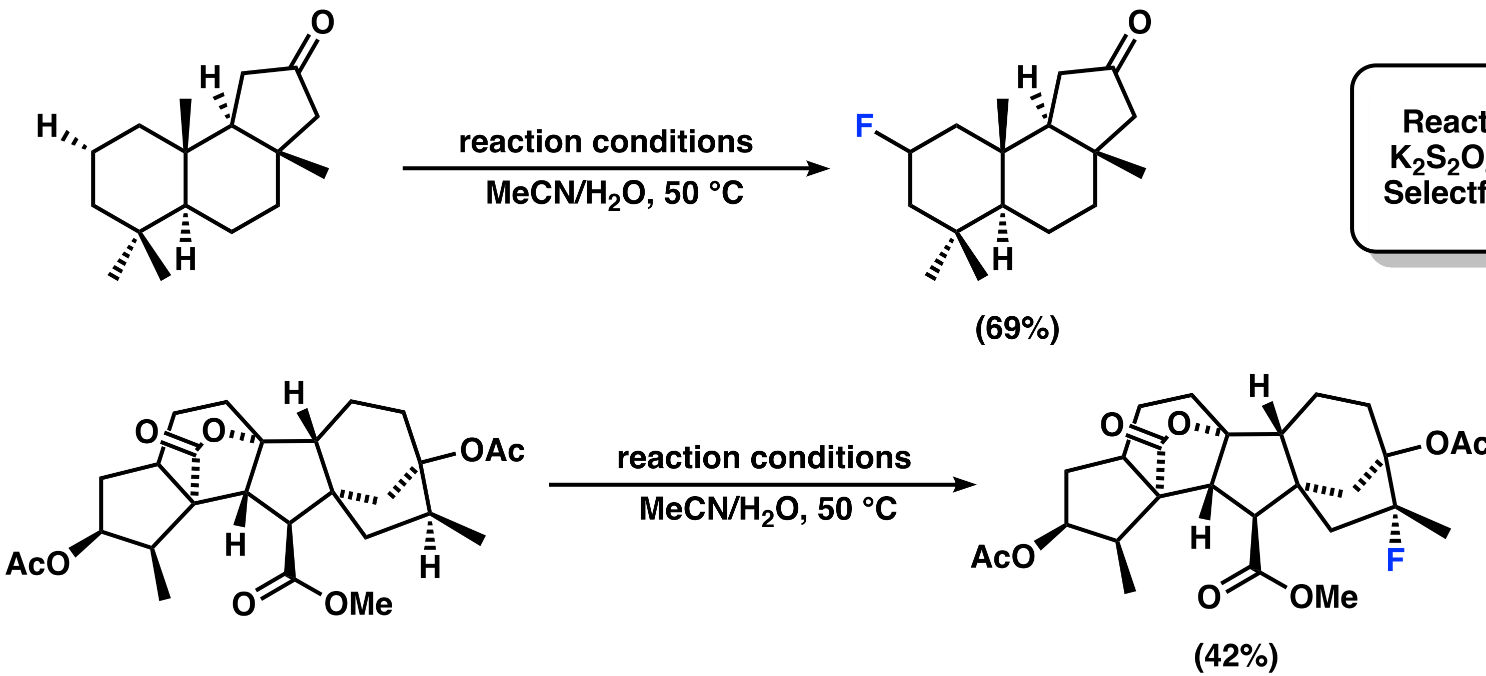
Transition–Metal Free Oxidative Aliphatic C–H Fluorination



Tang, *Org Chem Front* **2015**, 2, 806–810.

Transition–Metal Free Oxidative Aliphatic C–H Fluorination

Late Stage Fluorination of Complex Molecules

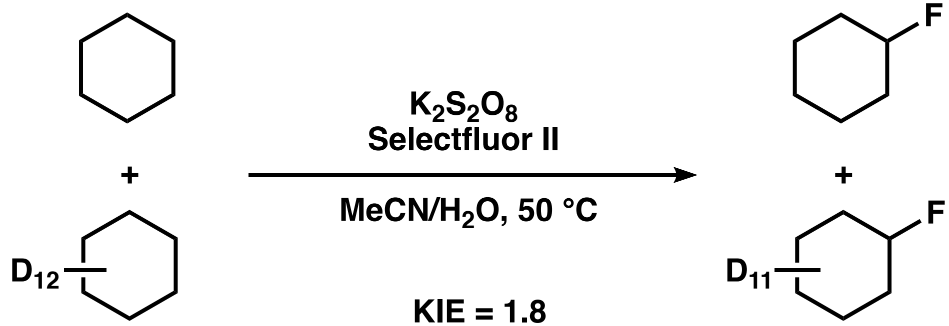


Reaction Conditions:
$K_2S_2O_8$ (1.0 - 4.0 equiv)
Selectfluor II (2.5 equiv)

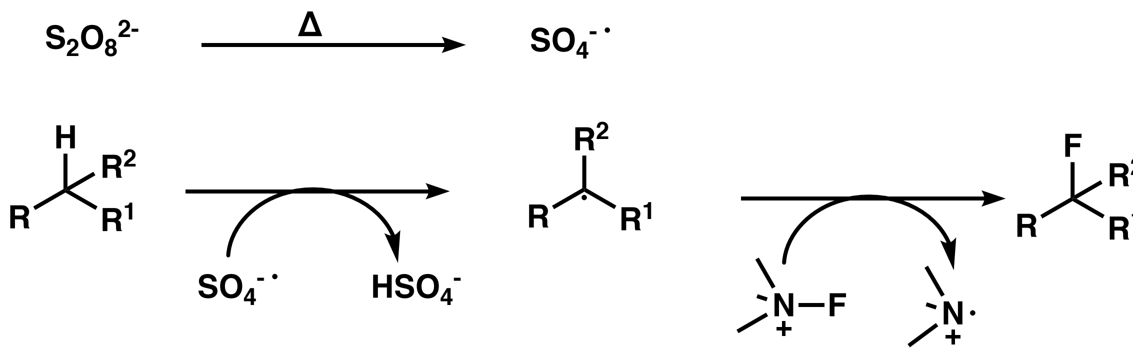
Tang, *Org Chem Front* **2015**, 2, 806–810.

Transition–Metal Free Oxidative Aliphatic C–H Fluorination

Kinetic Deuterium Isotope Effect

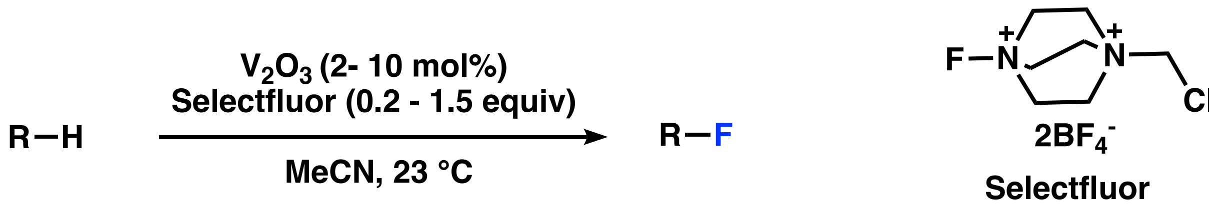


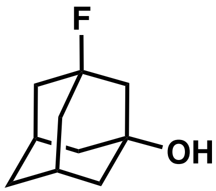
Proposed Mechanism



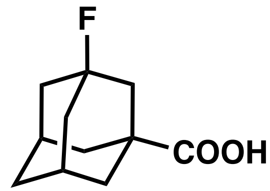
Tang, *Org Chem Front* **2015**, 2, 806–810.

Vanadium–Catalyzed Fluorination of C–H Bonds

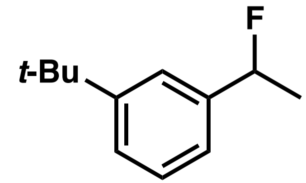




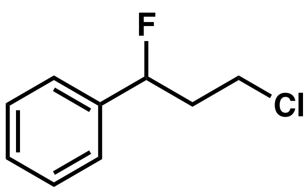
(74%, 20 h)



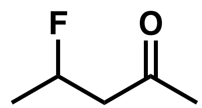
(70%, 20 h)



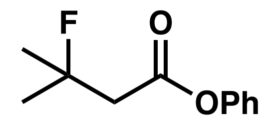
(47%, 48 h)



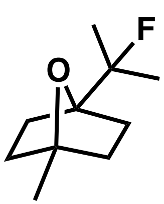
(35%, 24 h)



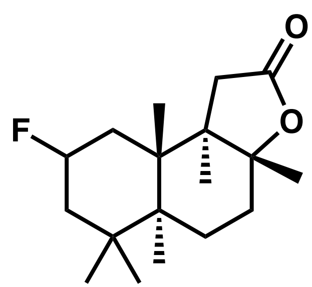
(47% NMR yield)



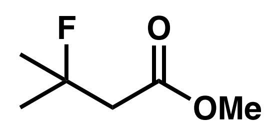
(12% NMR yield)



(53%, 24 h)



(61%, 48 h, α:β= 9:1)

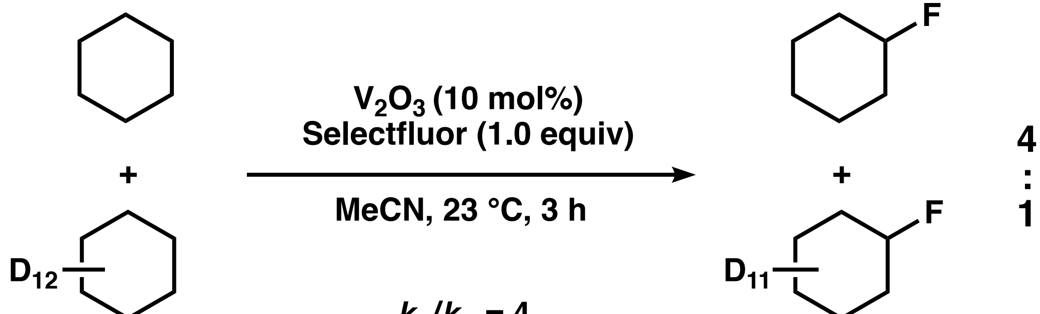


(85% NMR yield)

Chen, *Org Chem Front* **2014**, 1, 468–472.

KIE Study of Vanadium–Catalyzed Fluorination of Aliphatic C–H Bonds

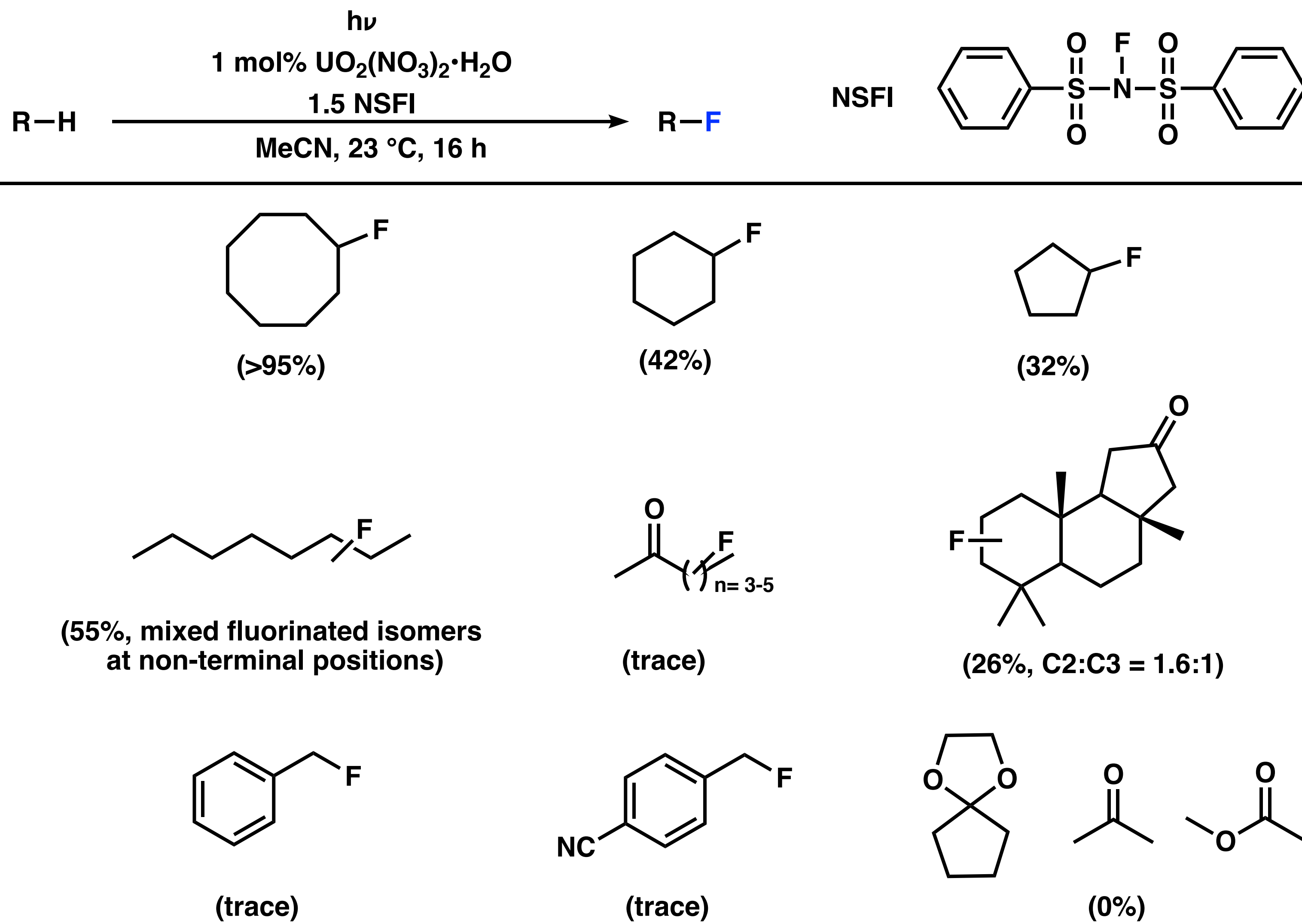
Kinetic Deuterium Isotope Effect



$k_H/k_D = 4$

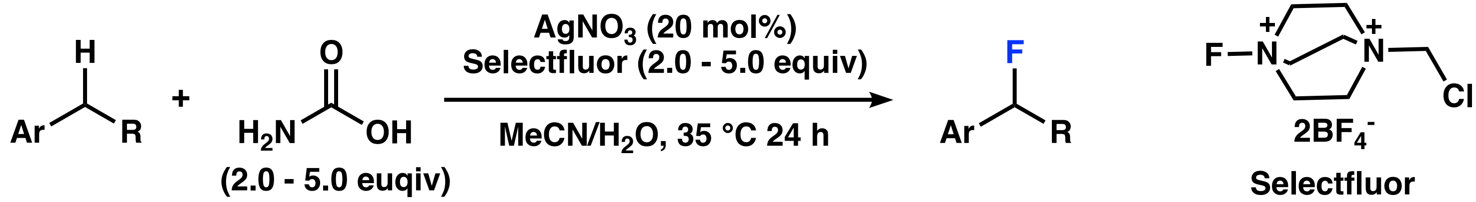
Chen, *Org Chem Front* **2014**, 1, 468–472.

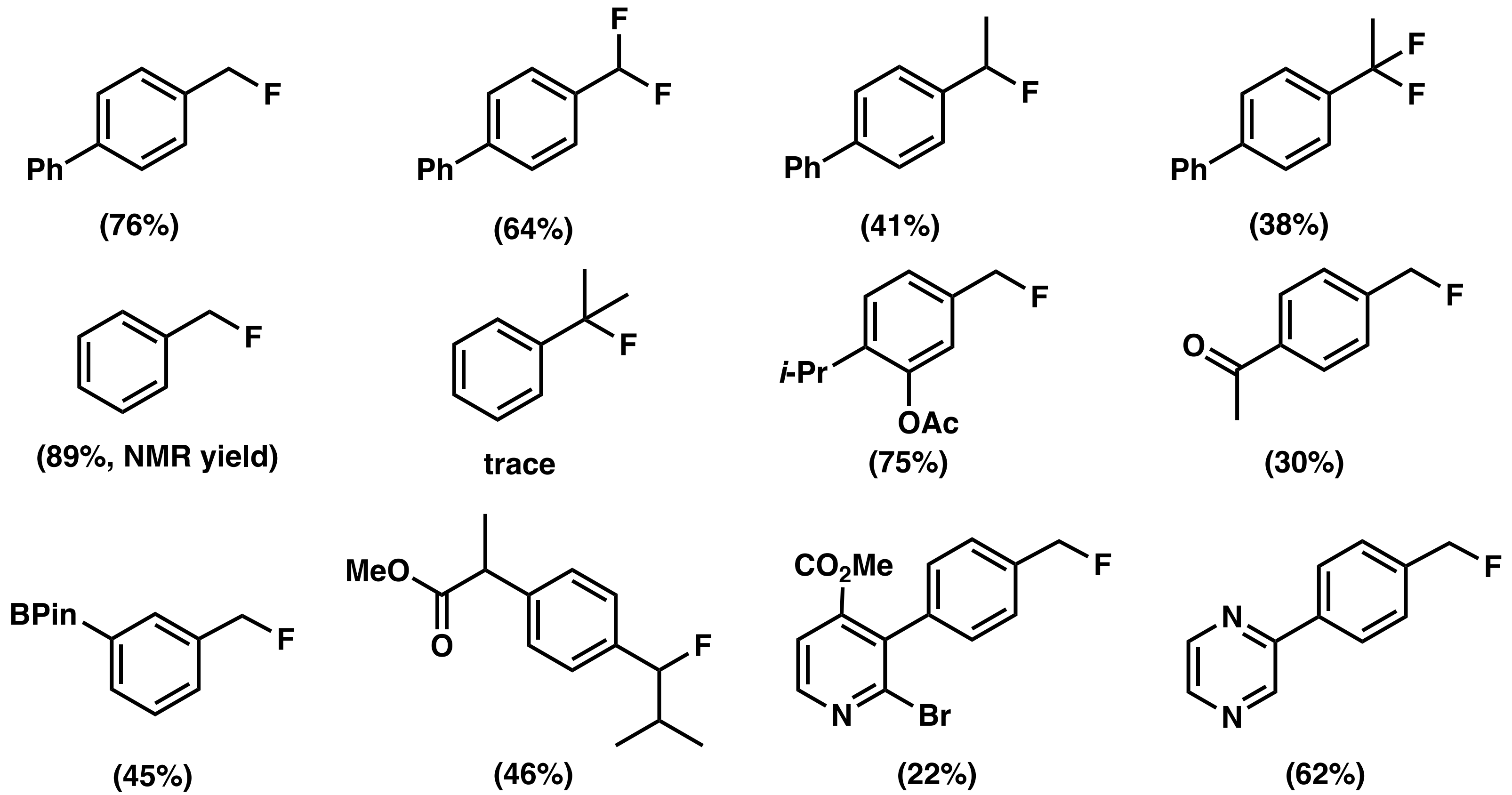
Uranyl Nitrate Catalyzed C–H Fluorination Under Visible Light Irradiation



Sorensen, *ACIE* **2016**, 55, 8923–8927.

Silver Catalyzed Fluorination of C–H Bonds Using Unprotected Amino Acids



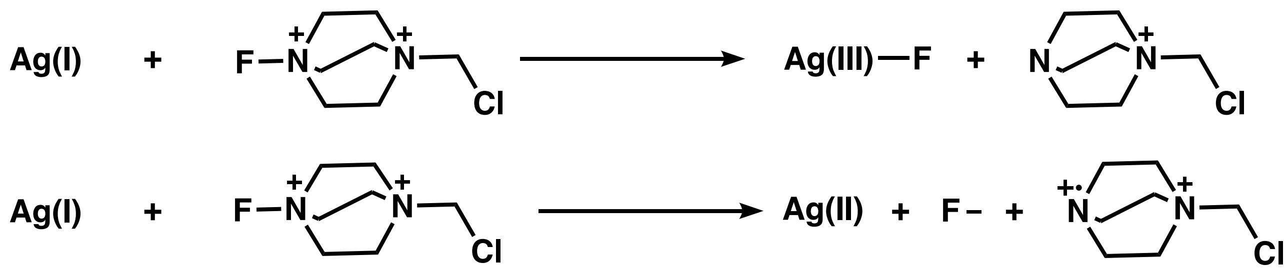


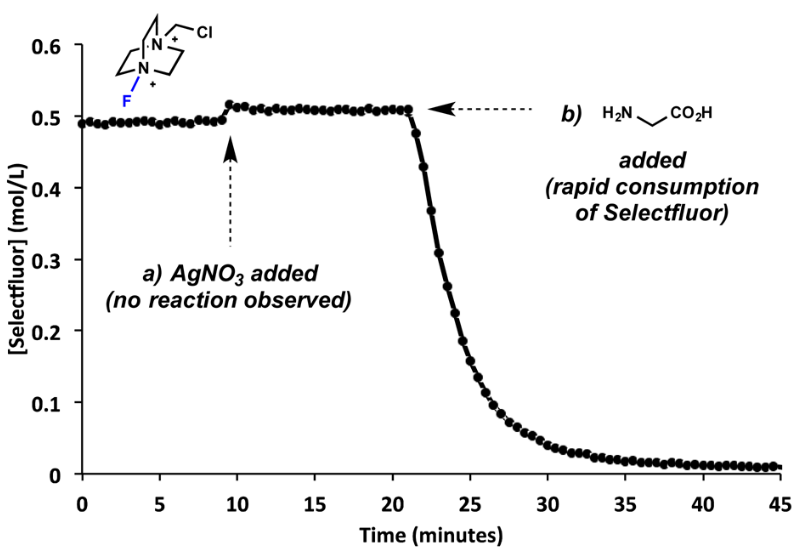
Baxter, *Org Lett* **2017**, 19, 2949–2952.

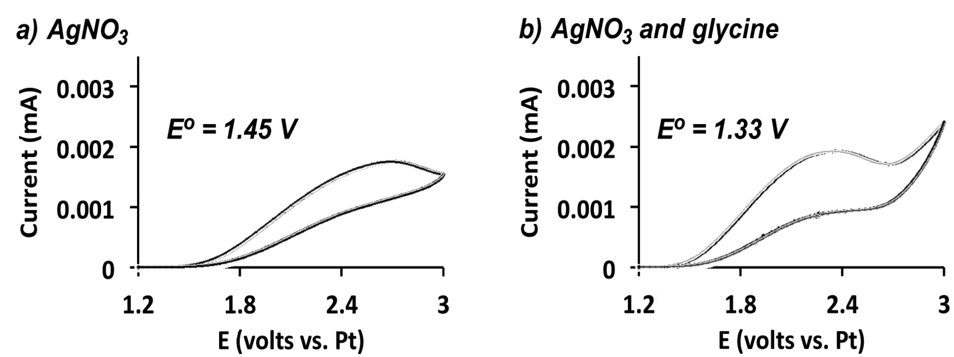
Silver Catalyzed Fluorination of C–H Bonds Using Unprotected Amino Acids

Mechanistic Studies

Two Mechanistic Scenarios for Ag(I) Oxidation

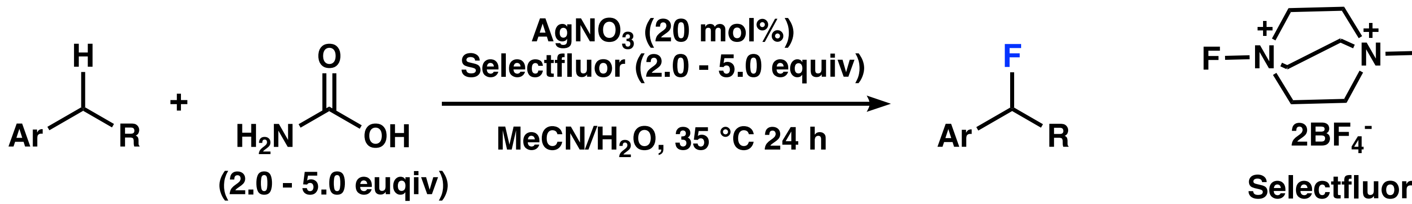


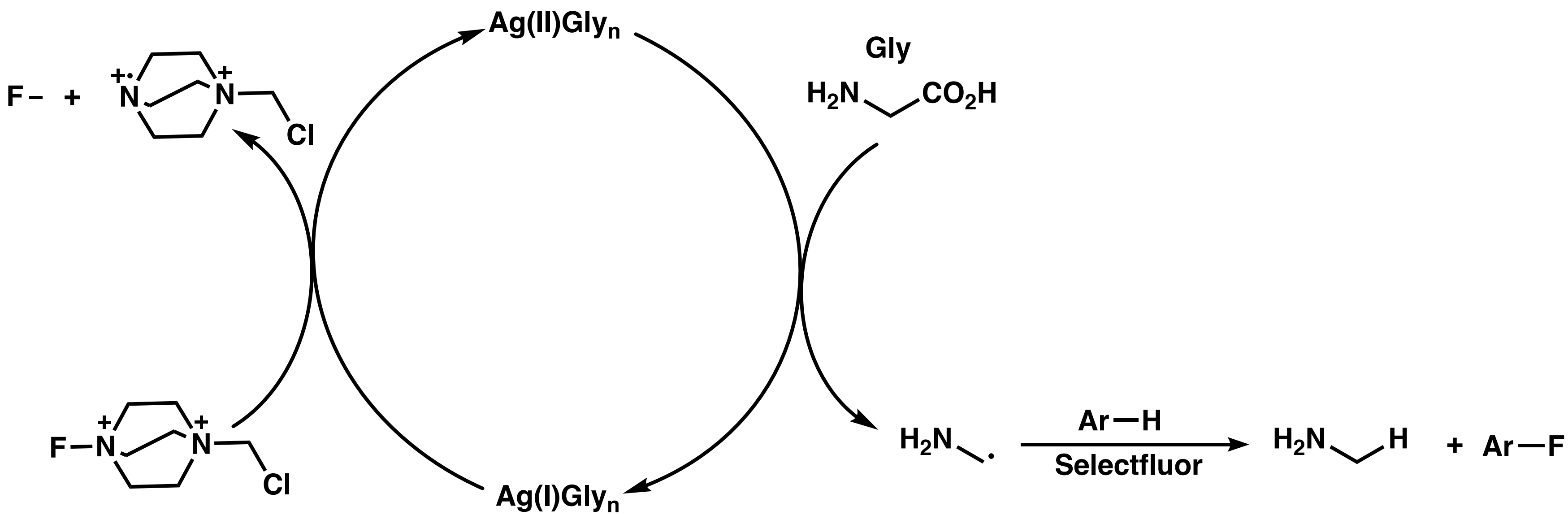




Baxter, *Org Lett* **2017**, 19, 2949–2952.

Silver Catalyzed Fluorination of C–H Bonds Using Unprotected Amino Acids

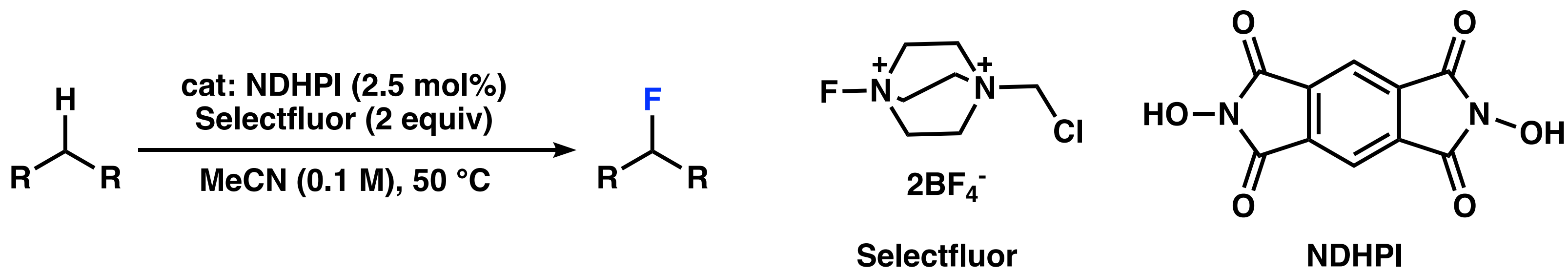


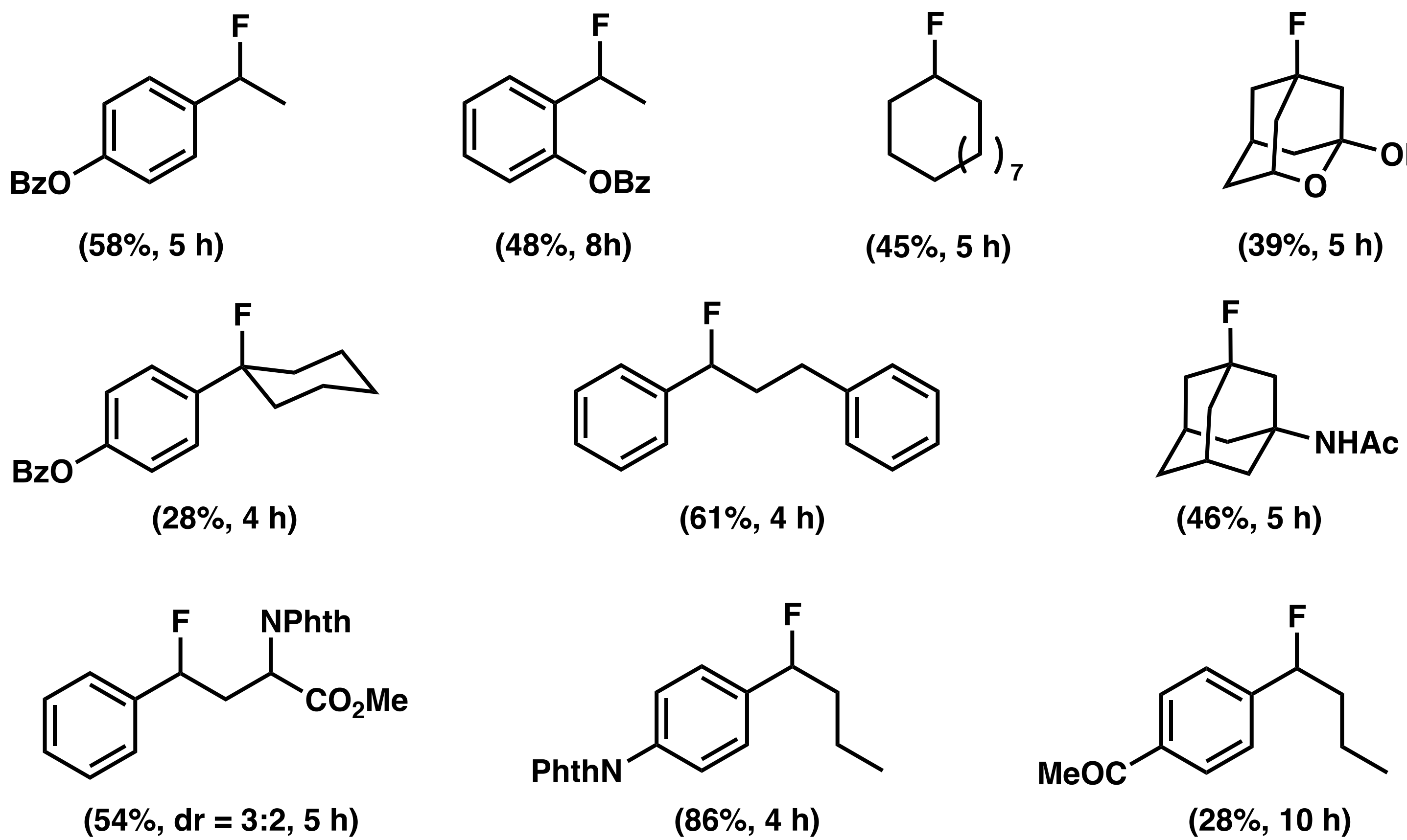


Baxter, *Org Lett* **2017**, 19, 2949–2952.

Recent Advances in Non-Metal Catalyzed Radical Mediated C–H Fluorination

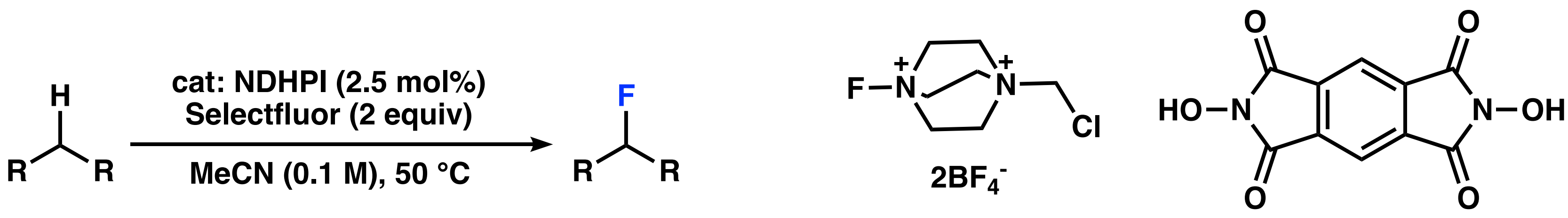
Metal–Free C–H Fluorination Using N–Oxyl Radical



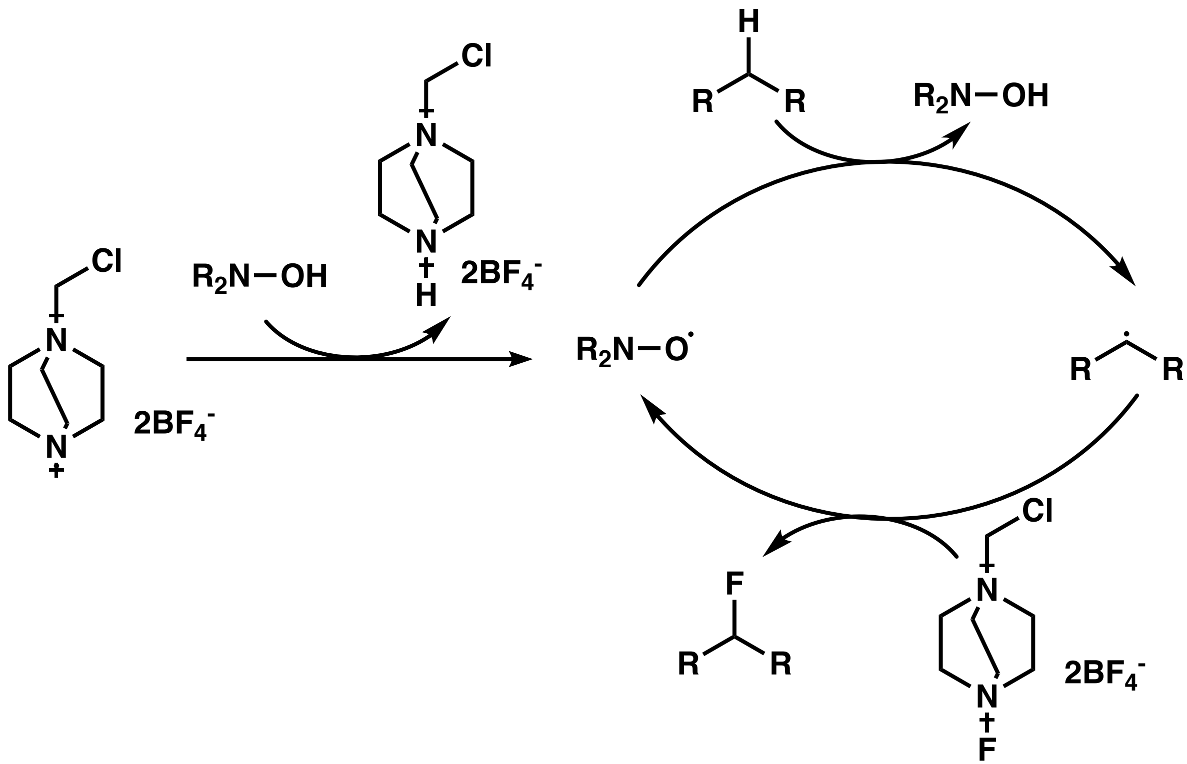


Inoue, *Org Lett.* **2013**, 15, 2160–2163.

Metal–Free C–H Fluorination Using N–Oxyl Radical

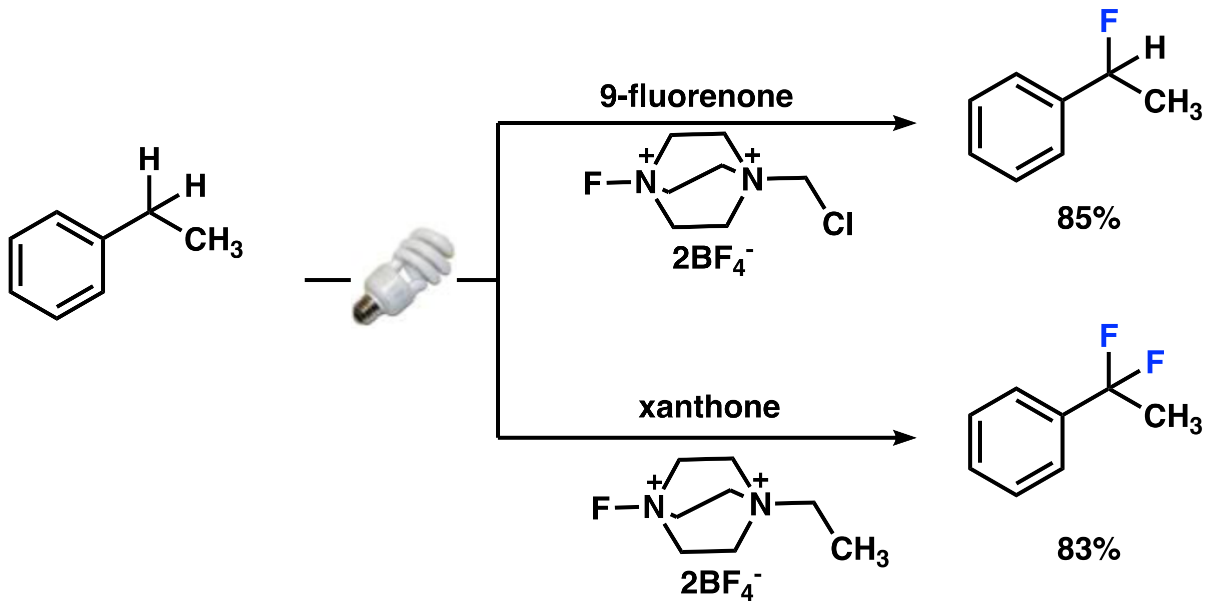


Selectfluor NDHPI



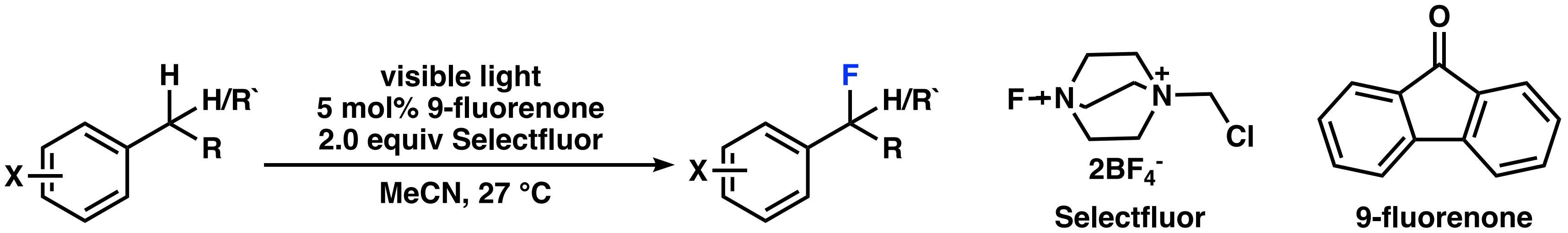
Inoue, *Org Lett.* **2013**, 15, 2160–2163.

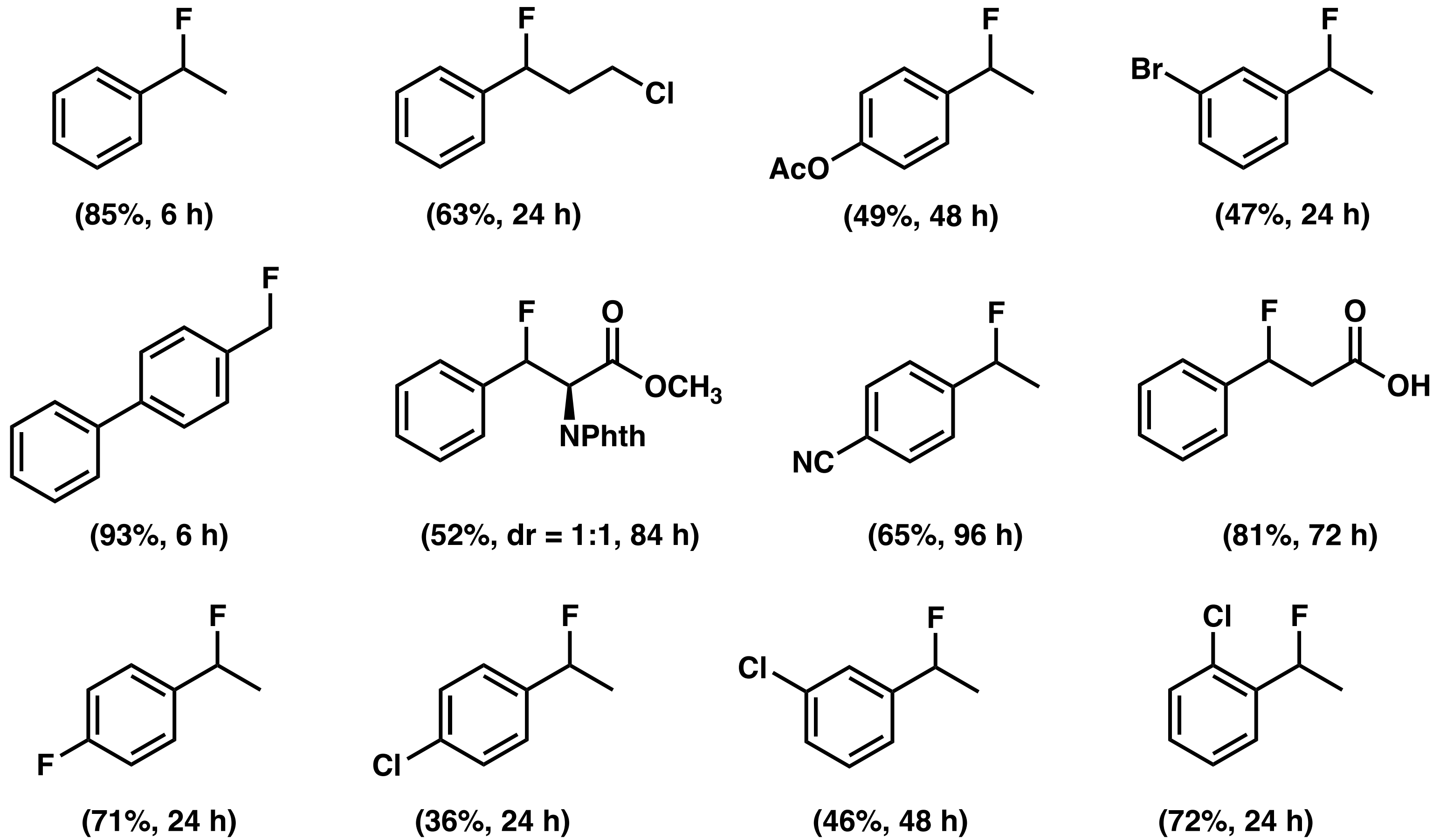
Photocatalyzed Metal–Free Benzylic C–H Fluorination



Chen, *JACS* **2013**, 135, 17494–17500.

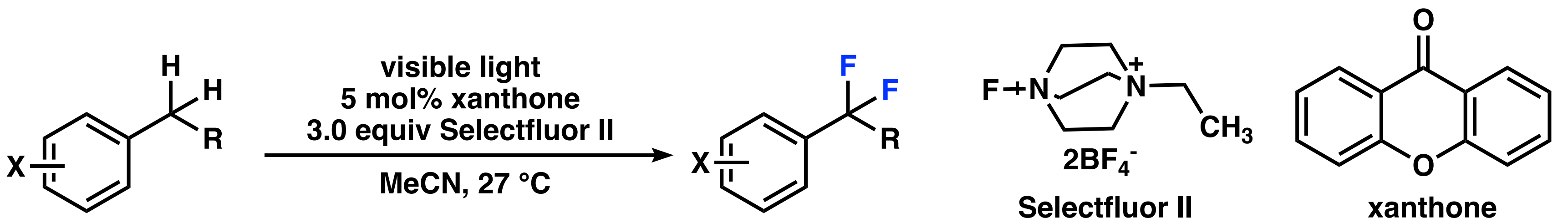
Photocatalyzed Metal–Free Benzylic C–H Monofluorination

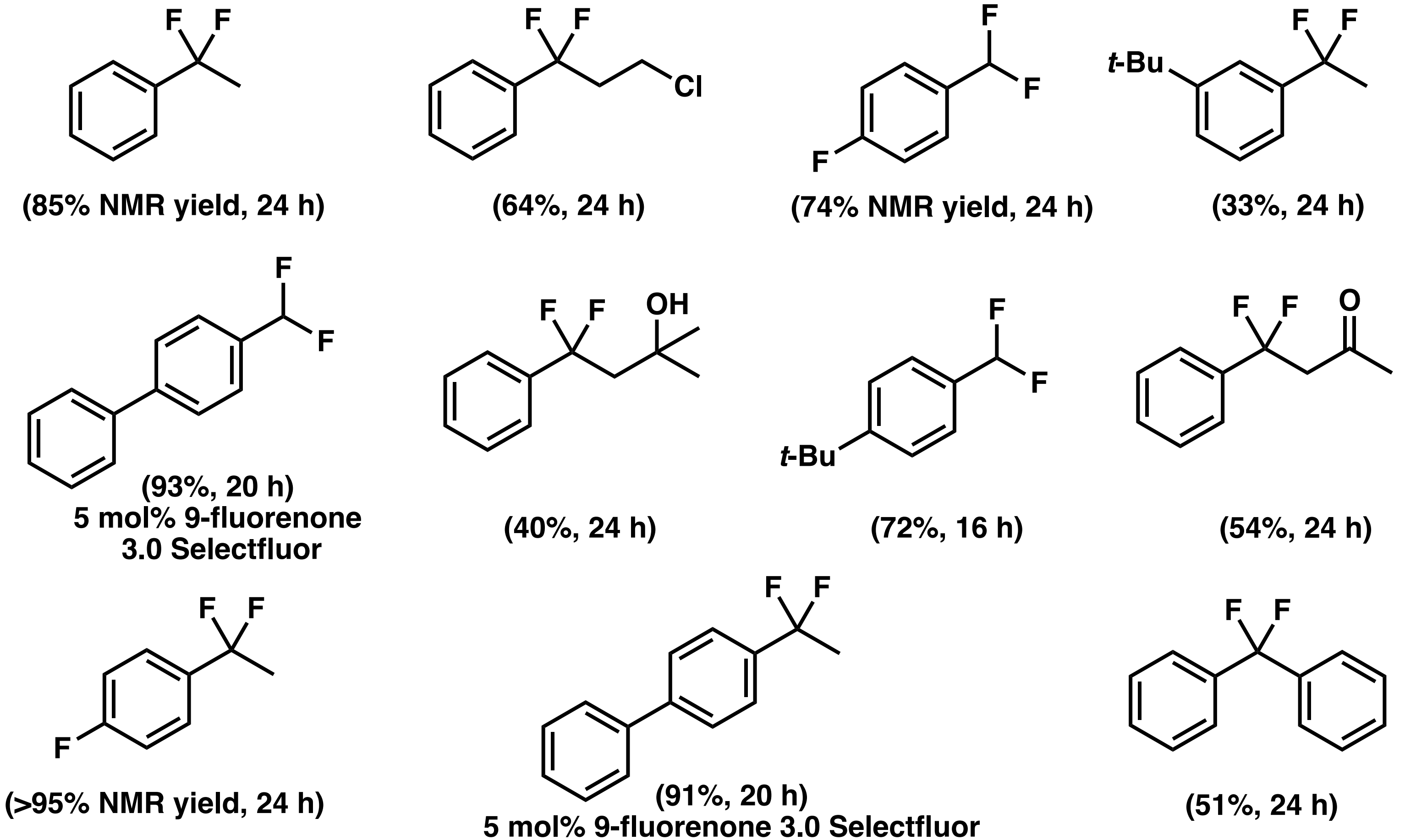




Chen, *JACS* **2013**, 135, 17494–17500.

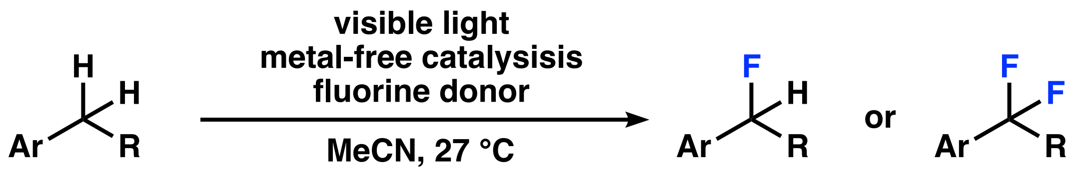
Photocatalyzed Metal–Free Bencylic C–H gem–Difluorination

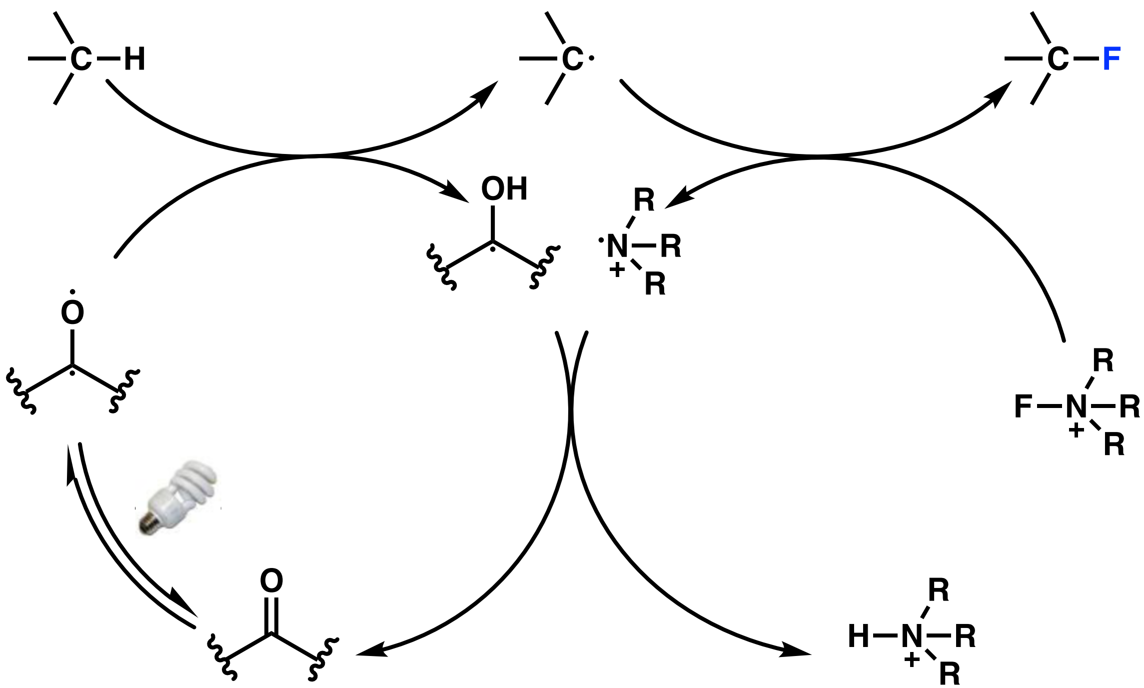




Chen, *JACS* **2013**, 135, 17494–17500.

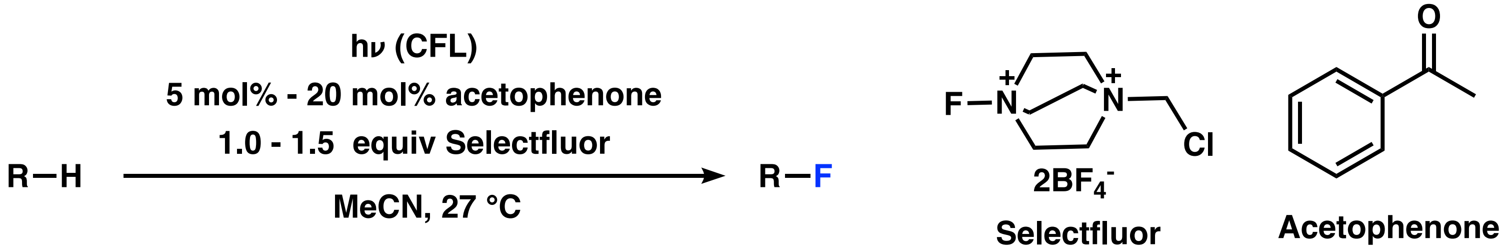
Photocatalyzed Metal–Free Benzylic C–H Fluorination Proposed Mechanism

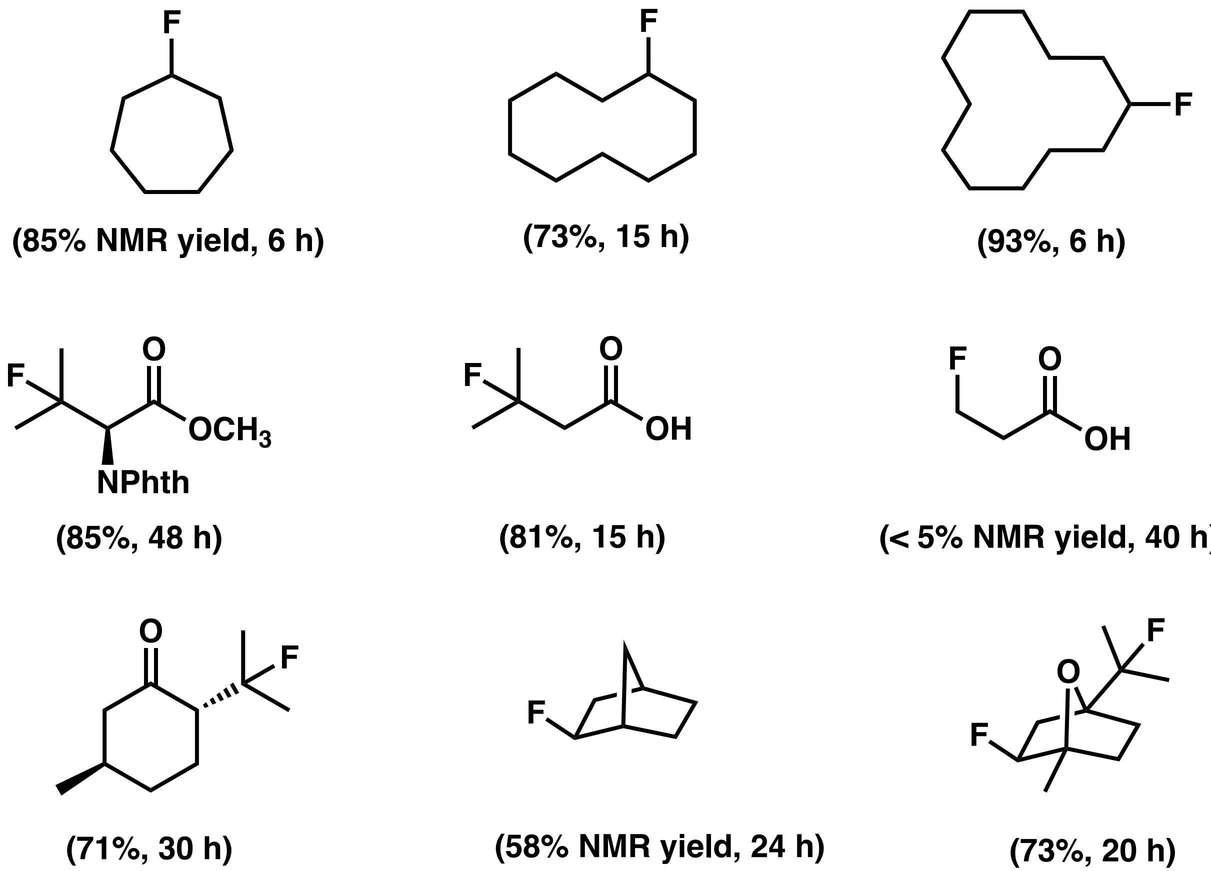




Chen, *JACS* **2013**, 135, 17494–17500.

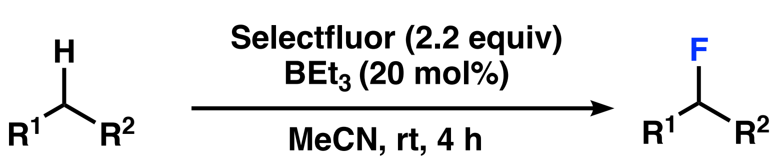
Photocatalyzed Metal–Free Aliphatic C–H Fluorination



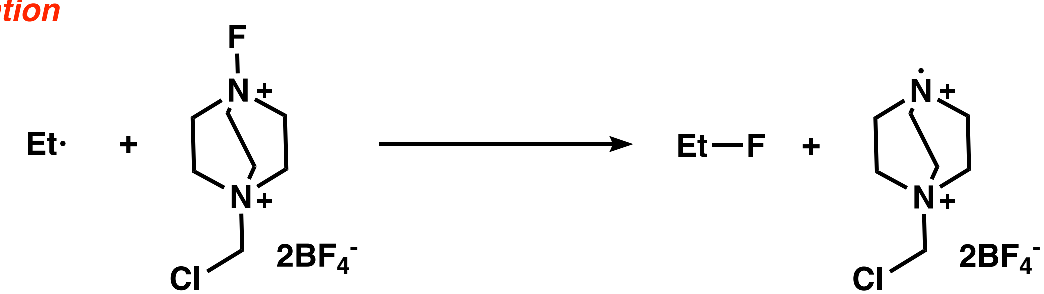


Chen, *Chem Commun* **2014**, 50, 11701–11704.

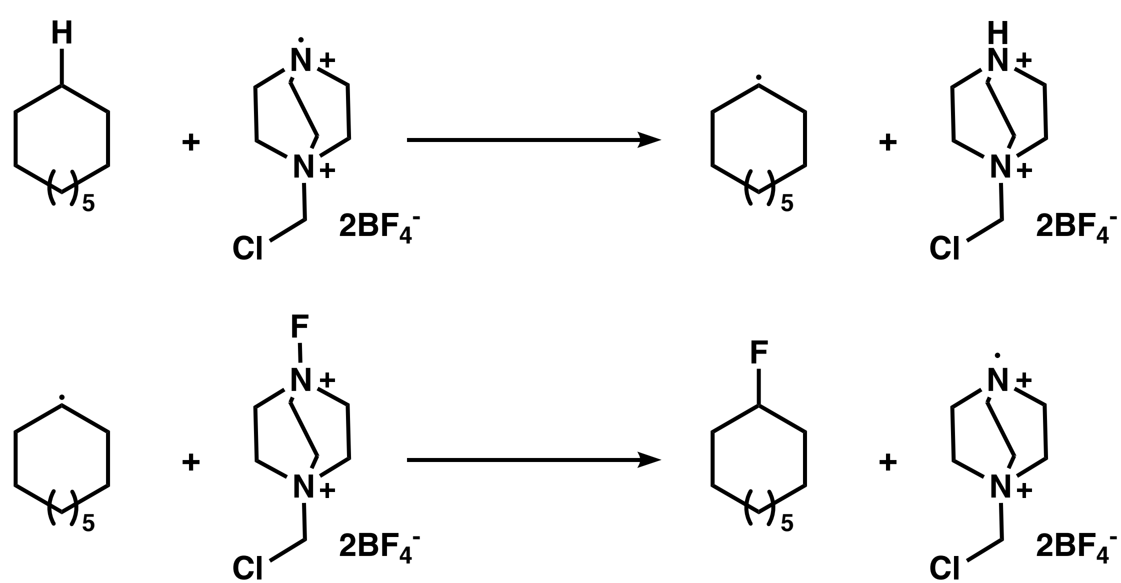
Triethylborane–Initiated Radical C–H Fluorination Proposed Mechanism

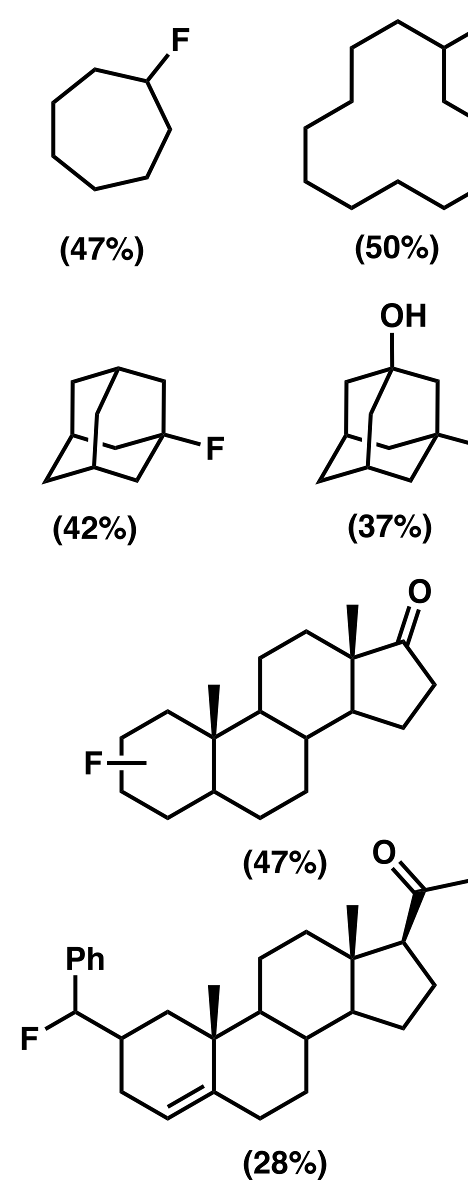


Initiation



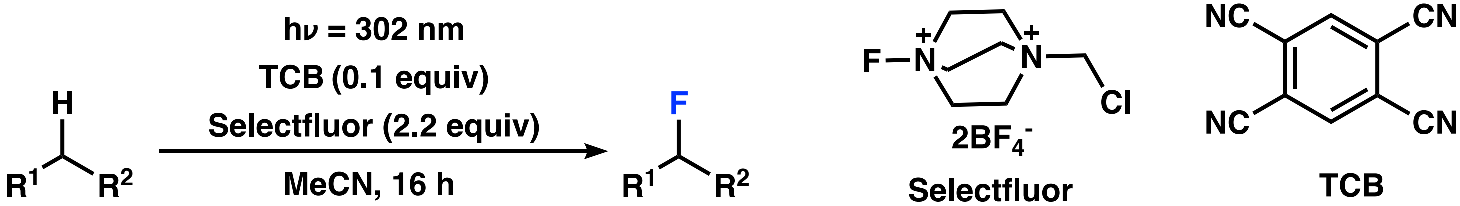
Propagation

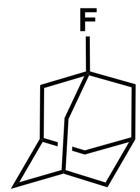




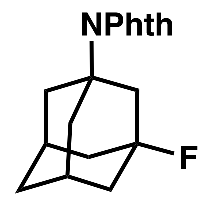
Lectka, *J. Org. Chem.* **2014**, 79, 8895–8899.

Tetracyanibenzene Catalyzed Fluorination of Aliphatic C–H Bonds

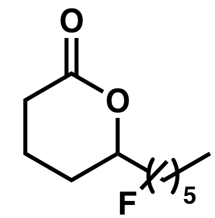




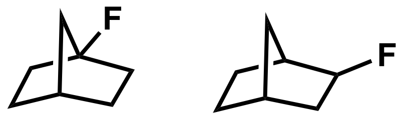
(58%)



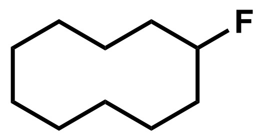
(61%)



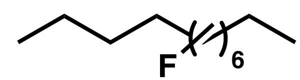
(46%, C5)



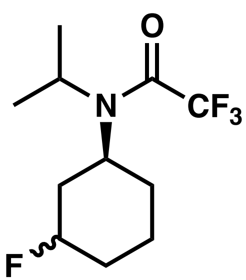
(54% NMR yield, 1:3)

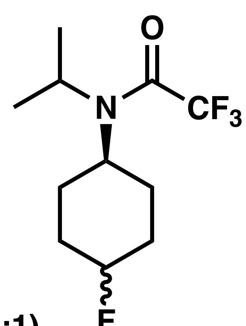


(62% NMR yield)

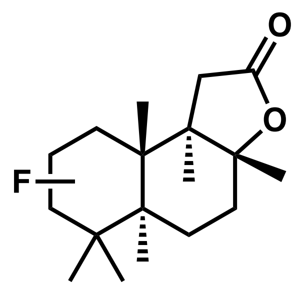


(59% NMR yield
2:2:1:1:,C2:C3:C4:C5)

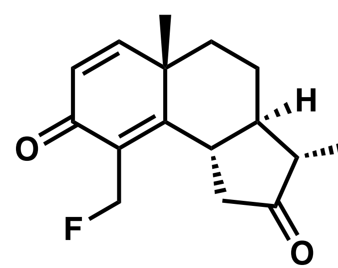




(73%, 1:1)



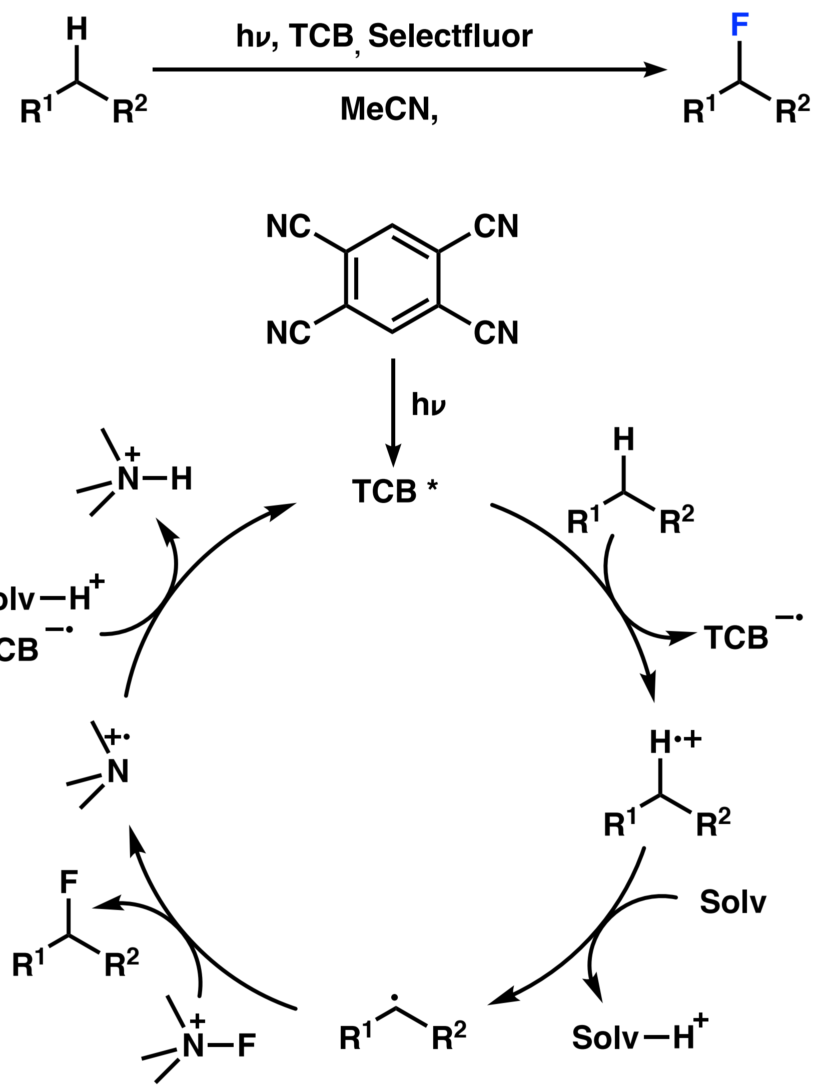
(41% 2α : 10% 2α)



(57%)

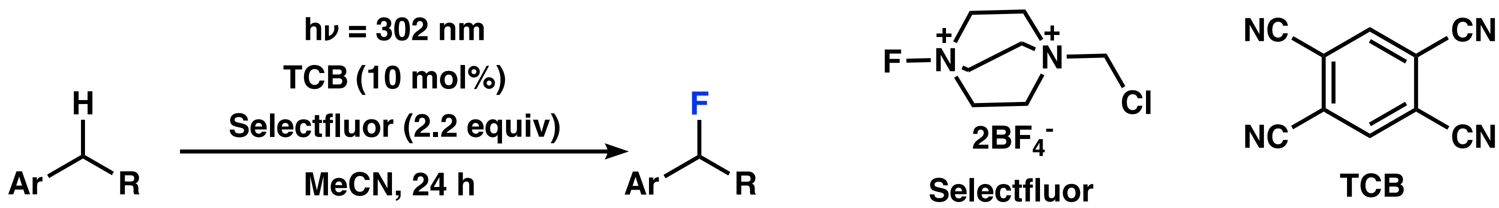
Lecktka, *Chem Sci* **2014**, 5, 1175–1178.

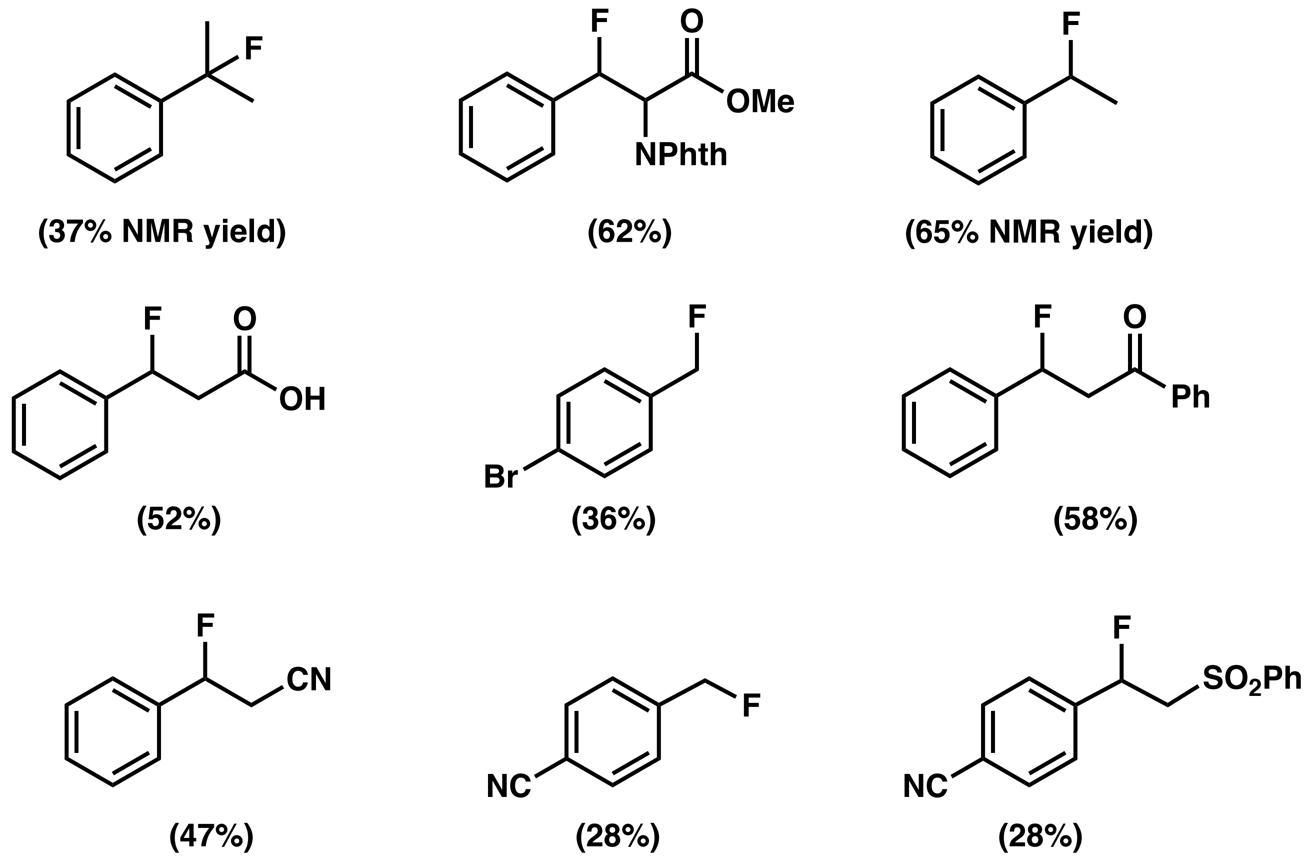
Hypothesized Mechanism of Tetracyanibenzene Catalyzed Fluorination of Aliphatic C–H Bonds



Lecktka, *Chem Sci* **2014**, 5, 1175–1178.

Tetracyanibenzene Catalyzed Fluorination of Benzylic C–H Bonds





Lectka, *Org Lett* **2014**, 216, 6339–6341.

Summary

- *Presented the different systems and associated mechanisms of C–H Fluorination*
- *Monofluorination vs. Difluorination*
- *Compatibility with various functional groups:*
  - *Aldehydes*
  - *Esters*
  - *Tertiary alcohols*
  - *Halogens*
  - *Amines*
  - *Carboxylic acids*