

Outline:**I. Introduction and Background**

1. The importance of fluorinated compounds
2. The strategies to introduce the fluorine atom

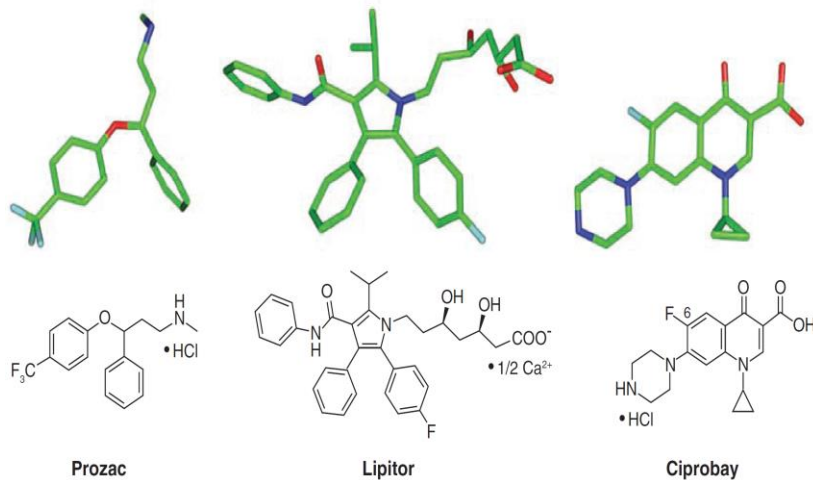
II. Methodologies for radical fluorination

1. Decarboxylative fluorination
2. Fluorination of alkenes
3. Fluorination of boronic acid derivatives
4. C_{sp3} C-H fluorination
5. C-C bond activation

III. Conclusions

For more information, please see these helpful reviews:

- 1) Sibi, M. P.; Landais, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 3570-3572.
- 2) Sammis, G. M.; et al. *Synthesis* **2015**, *47*, 2554-2569.

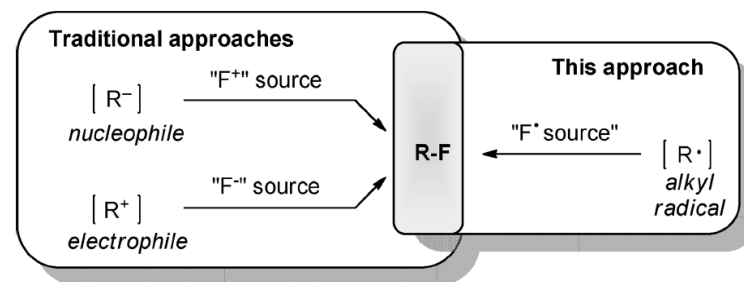
**I. Introduction and Background**

- One of the earliest synthetic fluorinated drugs, 5-fluorouracil, was first synthesized in 1957.
- Since then, over 150 fluorinated drugs have come to market and now make up ~20% of all pharmaceuticals, with even higher figures for agrochemicals (up to 30%).

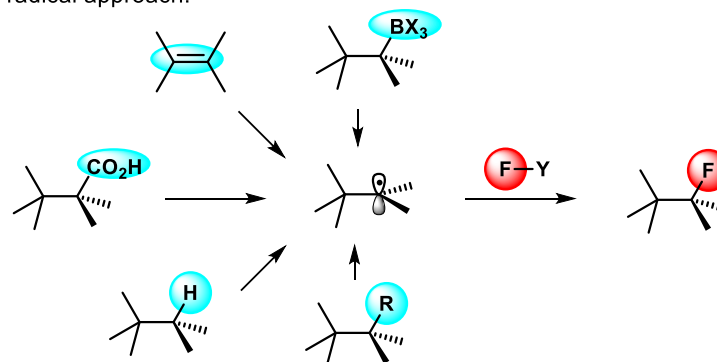
Gouverneur, V.; et al. *Chem. Soc. Rev.* **2008**, *37*, 320-330.

□ **The strategies to introduce the fluorine atom**

- For nucleophile approach:
Although it provides a **convenient entry** to **site-selective** monofluorination, this method is mainly **restricted** to the synthesis of **α -fluoro carbonyl** compounds.



- For electrophile approach:
The **weak nucleophilicity** of fluoride ions limits access to C-F bonds *via* direct nucleophilic substitution reactions
- For radical approach:



II. Methodologies for radical fluorination**Decarboxylative fluorination****Traditional source**

HF

molecular fluorine, HOF

or XeF₂

limitations to substrate stability and functional group tolerance under the relatively harsh reaction conditions

Drawbacks

uncontrollable reactivity and hazards

expensive noble gas, not adaptable to ¹⁸F labeling procedures**A remarkable breakthrough**

For electrophilic N-F reagents (NFSI, Selectfluor, NFPy), preliminary DFT calculations revealed that the N-F bond strength of those reagents was on the order of 60 kcal/mol, sufficiently low to allow homolytic cleavage.

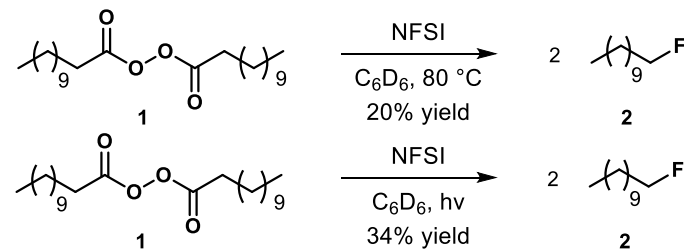
	<i>N</i> -fluorobenzenesulfonimide (NFSI) ^(a)				Selectfluor [®] (a,b)				<i>N</i> -fluoropyridinium salts (NFPY) ^(a,b)			
	r_{NF} (pm)	BO_{NF}	D_{NF} (kcal/mol)	q_{F}	r_{NF} (pm)	BO_{NF}	D_{NF} (kcal/mol)	q_{F}	r_{NF} (pm)	BO_{NF}	D_{NF} (kcal/mol)	q_{F}
hexane	143.8	0.839	63.4	-0.14	141.4	0.986	61.0	0.00	137.5	0.933	76.1	-0.02
THF	143.8	0.837	63.3	-0.14	141.9	0.966	61.7	-0.02	137.8	0.922	75.4	-0.05
MeCN	143.7	0.839	63.1	-0.14	142.1	0.956	60.9	-0.03	137.8	0.915	75.1	-0.06
H ₂ O	143.7	0.831	63.5	-0.14	142.2	0.956	62.2	-0.03	137.9	0.914	75.3	-0.06

N-F bond distance (r_{NF} in pm), Mayer bond order (BO_{NF}), and bond dissociation energy (D_{NF} in kcal/mol), Loewdin charge on the fluorine atom (q_{F})

- Sammis, Paquin, Kennepohl et al. hypothesized that such reagents might be amenable to act as atomic fluorine sources for the fluorination of alkyl radicals.

stable, easy to handle

excellent selectivity, high yield

Decarboxylative radical fluorination of Lauroyl peroxide

entry	substrate	product	time	yield (%)
1			16 h	24 ^{a,c}
2			12 h	24 ^{a,c}
3			19 min	98 ^{a,c} (54) ^{b,d,e}
4			15 min	98 ^{a,f}
5			6 min	45 ^{b,f}
6			4 min	44 ^{a,f} (C ₆ D ₆)
7			6 min	57 ^{b,f} (CD ₃ CN) (42) ^d
8			10 min	57 ^{a,f} (45) ^d

Sammis, G. M.; et al. *J. Am. Chem. Soc.* **2012**, *134*, 4026-4029.

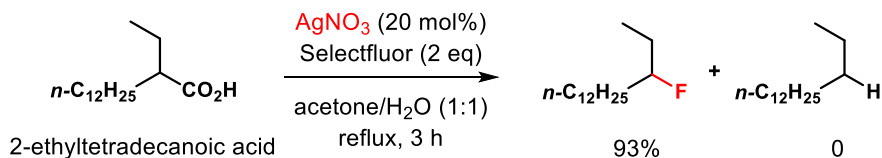
- Advantages**

- 1) First example of fluorine transfer from an organic reagent to an alkyl radical.
- 2) A broad range of alkyl radicals including tertiary, benzylic, and heteroatom-stabilized radicals were suitable.

- Disadvantages**

- 1) Requiring the prior conversion of carboxylic acids to peresters
- 2) Efficiency for the fluorination of primary alkyl radicals is low
- 3) Highly reactive tert-butoxyl radicals in this system is undesirable

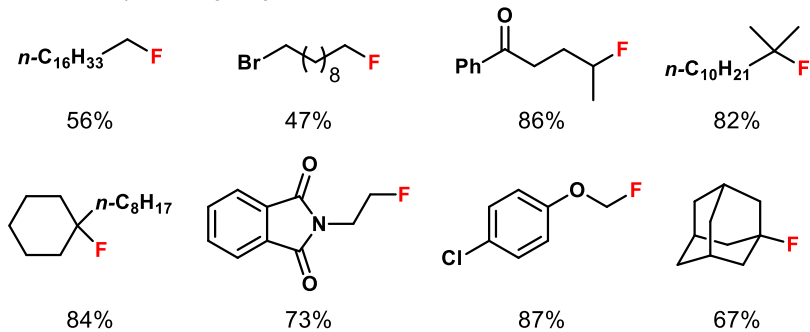
- Silver-Catalyzed Decarboxylative Fluorination**



* **Other Ag(I) salts**, such as AgBF_4 , AgOAc , and AgOTf , exhibited almost the **same catalytic behavior** as AgNO_3 , while **no** reaction occurred **without** the presence of a Ag(I) salt.

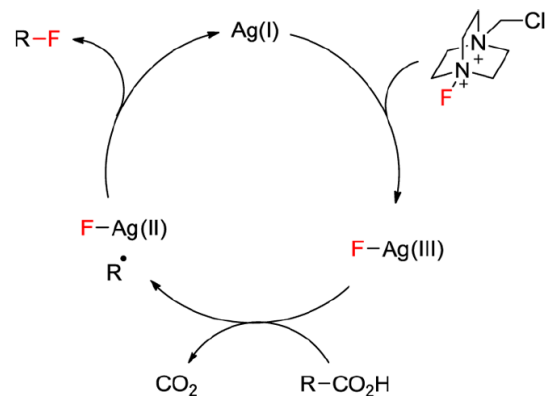
* Switching the fluorine source from **Selectfluor** to **NFSI** led to **no reaction** at all.

* **Water** proved to be **essential**. No decarboxylation occurred in any of the anhydrous organic solvents screened, even with the catalysis of AgBF_4 , which has better solubility than AgNO_3 in these solvents.



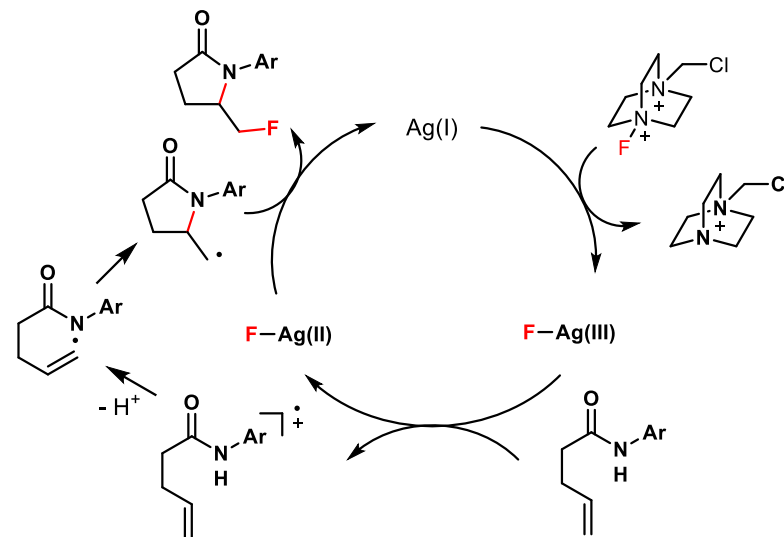
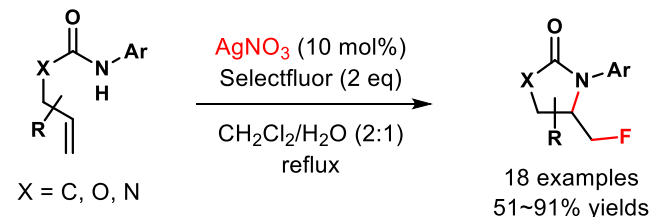
tertiary > secondary > primary >> aromatic

Li, C.; et al. *J. Am. Chem. Soc.* **2012**, *134*, 10401-10404.

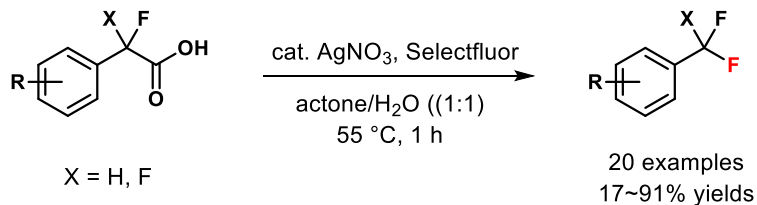


An alternative explanation for the fluorine transfer would be a SET mechanism involving oxidation of the alkyl radical to a carbocation by Ag(II) with subsequent capture of the carbocation by a fluoride anion. However, this is unlikely because solvated F^- is much less nucleophilic than H_2O .

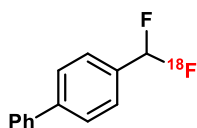
- Aminofluorination of unactivated alkenes**



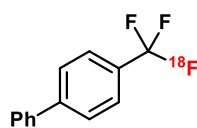
Li, C.; et al. *J. Am. Chem. Soc.* **2013**, *135*, 4640-4643.

• **Synthesis of tri- and difluoromethyl arenes**

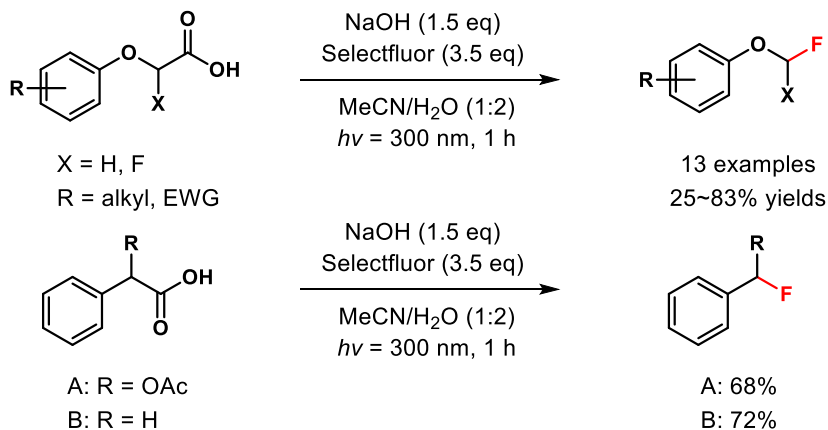
radiolabelled examples



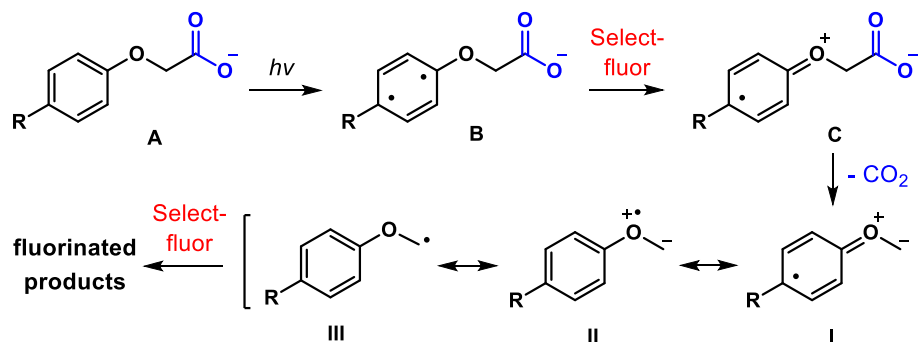
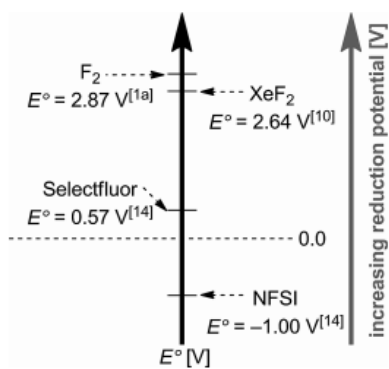
radiochemical yield (RCY): 8.6% ± 2.6%
specific activity (SA): 2.5 ± 0.2 GBq/μmol



RCY: 9.1% ± 2.4%
SA: 3.3 ± 0.2 GBq/μmol

Gouverneur, V.; et al. *Org. Lett.* **2013**, *15*, 2648-2651.• **Photo-fluorodecarboxylation**

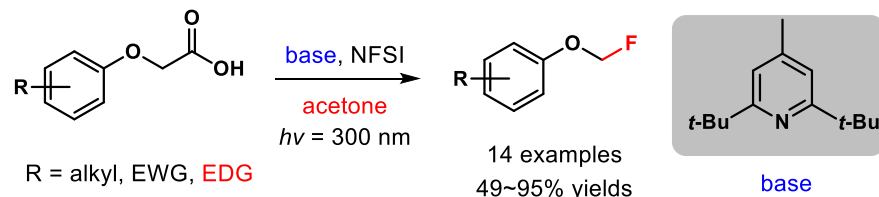
** all substrates lacking either the 2-aryloxy or the 2-aryl substituent were not successfully fluorinated.

Sammis, G. M.; et al. *Angew. Chem. Int. Ed.* **2012**, *51*, 10804-10807.• **Photo-fluorodecarboxylation using NFSI**

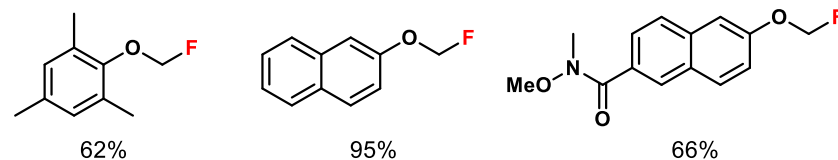
* Comparison of fluorodecarboxylation reagents by reduction potential with the standard hydrogen electrode (SHE).

* Selectfluor can directly fluorinate electron-rich aryl rings

* NFSI has been demonstrated to be a weaker electrophilic source of atomic fluorine and a weaker oxidant.



Selected examples:

Sammis, G. M.; et al. *Eur. J. Org. Chem.* **2015**, 2197-2204.

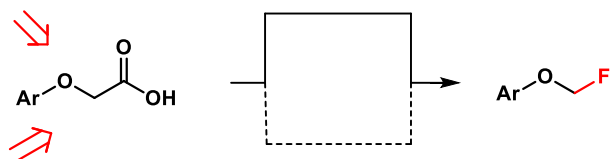
* **Disadvantages:** Need near-UV light

Direct excitation of the substrate, and any significant structural change necessitates changing the light source.

• **C-F bond formation using photoredox catalysis**

Note: Selectfluor may complicate photocatalytic transformations because it is an oxidant and has the potential to interfere with the redox catalytic cycle.

Cannot be directly oxidized by Selectfluor but can be oxidized with the assistance of a photocatalyst.

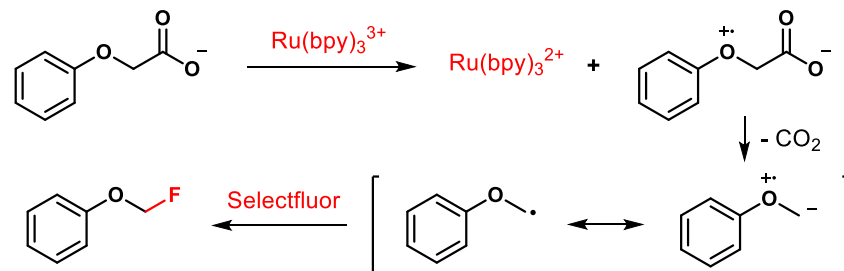
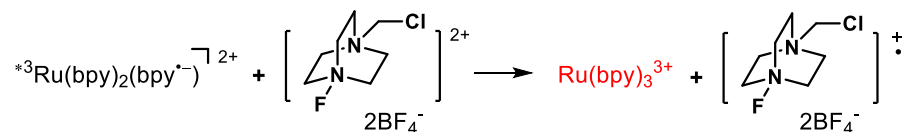
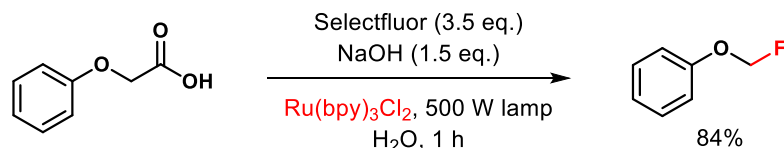
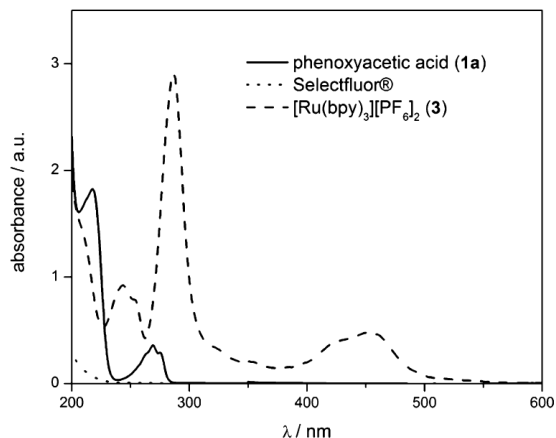


In the visible region needed to access the photoexcited catalyst (400-500 nm), substrate should not absorb light

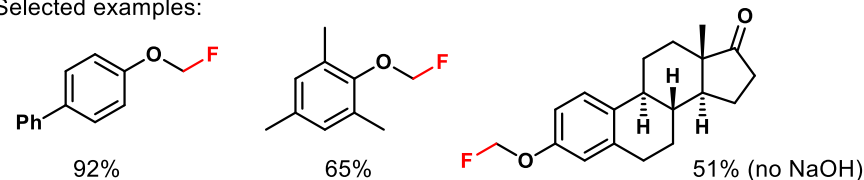
Selectfluor
photocatalyst
 $h\nu = 450 \text{ nm}$

* **Absorption spectra**

neither the aryloxyacetic derivatives nor Selectfluor absorbs light in the visible region

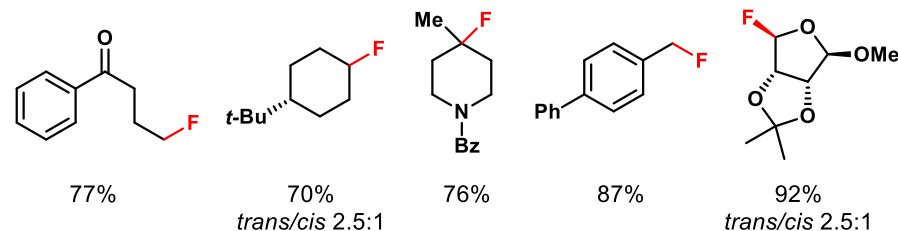
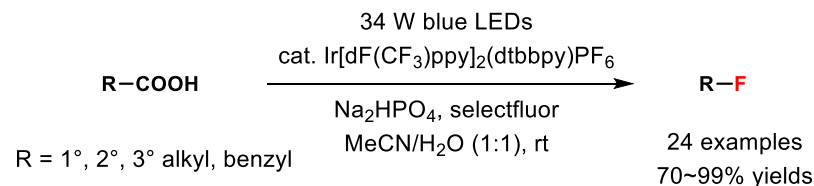


Selected examples:

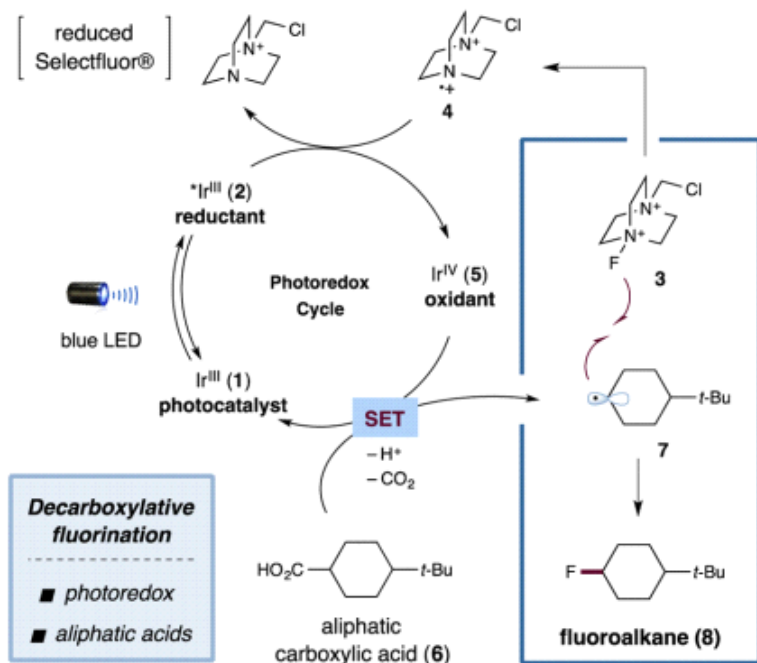


Sammis, G. M.; et al. *J. Am. Chem. Soc.* **2014**, *136*, 2637-2641.

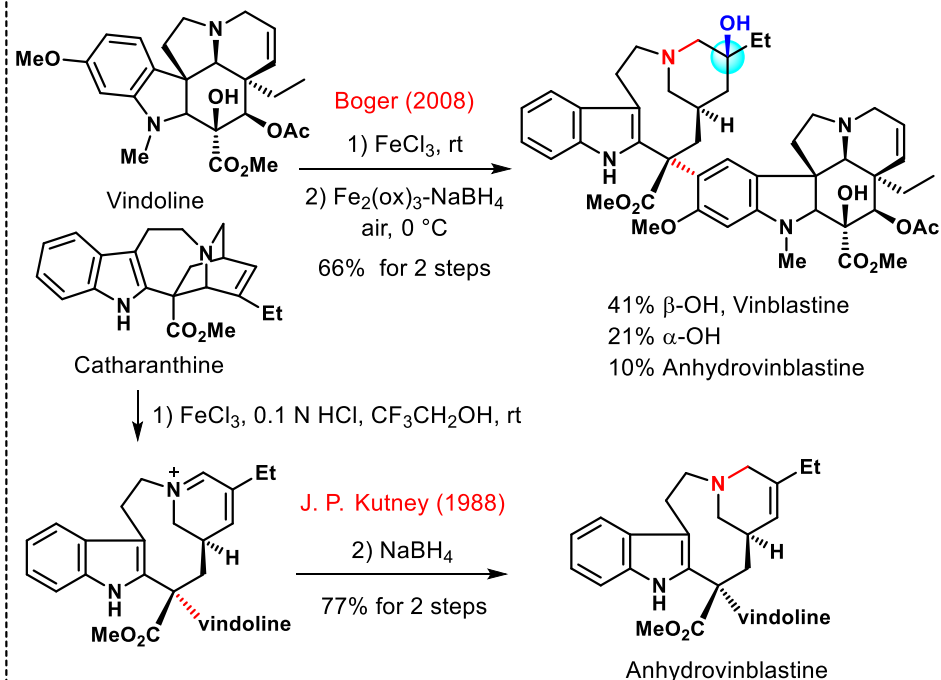
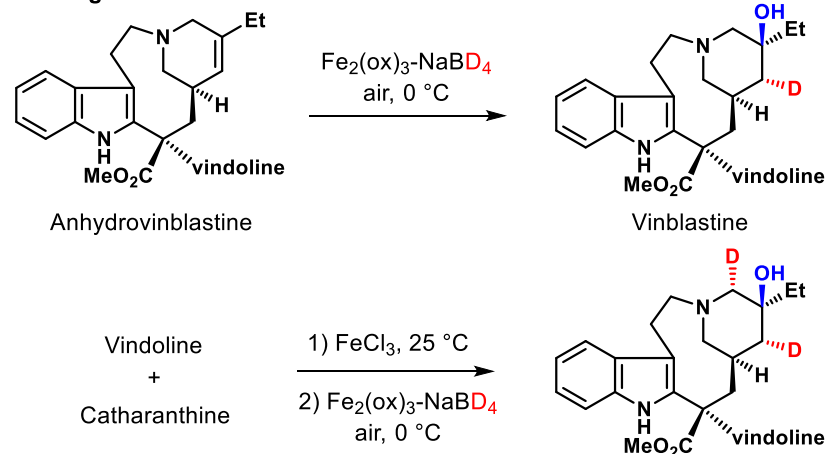
• **Decarboxylative fluorination of aliphatic carboxylic acids**

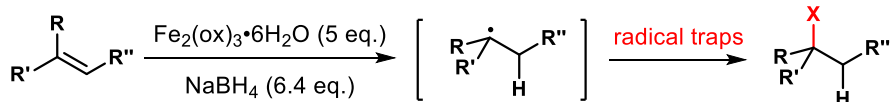


Macmillan, D. W. C.; et al. *J. Am. Chem. Soc.* **2015**, *137*, 5654-5657.

Mechanism for decarboxylative fluorination

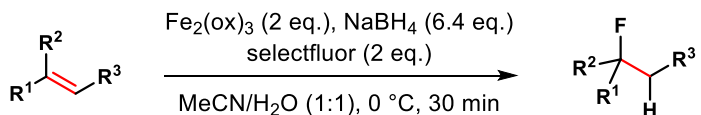
- * A wide range of carboxylic acids, does not require activated substrates
- * Operational simplicity and mild reaction conditions.

□ **Fluorination of alkenes*** **labeling studies**Boger, D. L.; et al. *J. Am. Chem. Soc.* **2009**, *131*, 4904-4916.



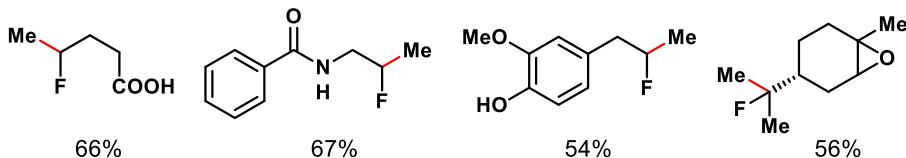
radical trappers X = N₃, SCN, Cl, CN, TEMPO, NO

Boger, D. L.; et al. *Org. Lett.* **2012**, *14*, 1428-1431.



R¹ = alkyl; R² = H, alkyl
R³ = alkyl, amine, amide, aryl

22 examples
52~79% yield

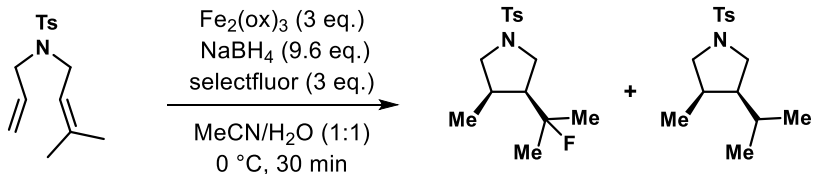


66%

67%

54%

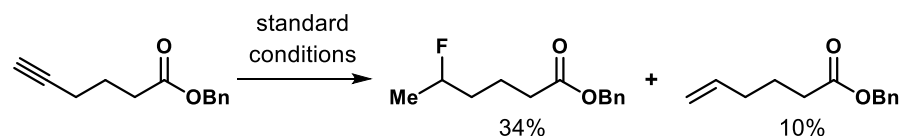
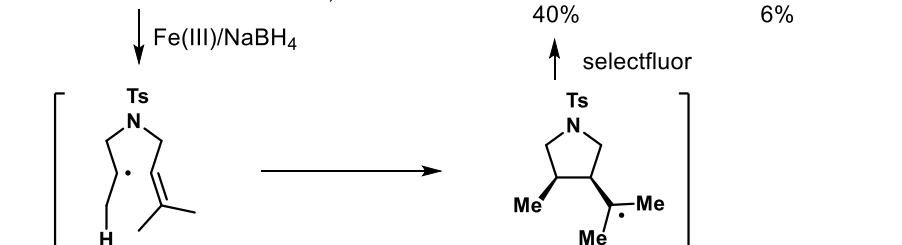
56%



40%

6%

selectfluor



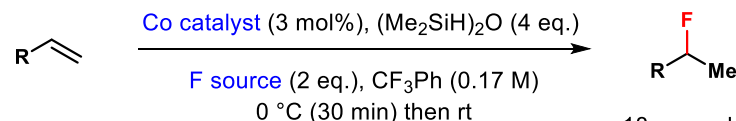
34%

10%

Boger, D. L.; et al. *J. Am. Chem. Soc.* **2012**, *134*, 13588-13591.

* Disadvantage: Stoichiometric metal catalyst

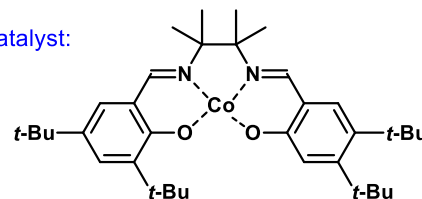
• Hydrofluorination of unactivated alkenes by catalytic cobalt



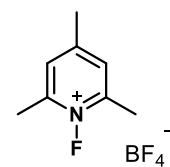
R = alkyl, aryl, ester, amide

18 examples
41~82% yields

Co catalyst:



F source:

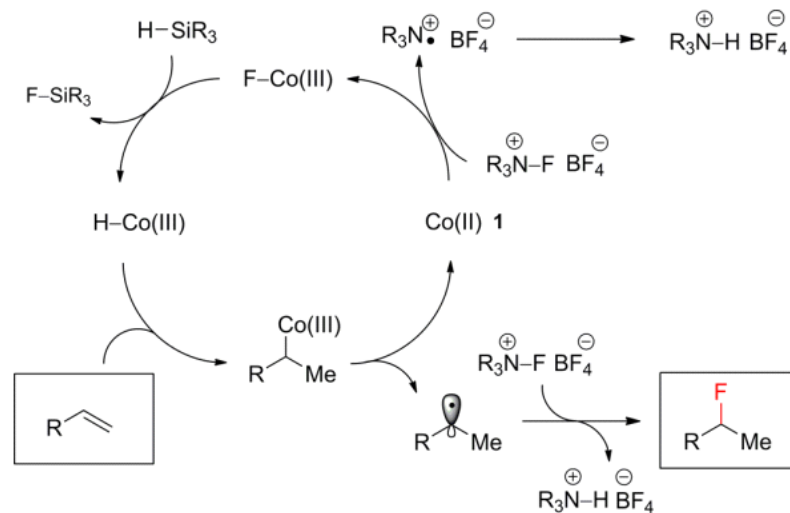


* Catalytic, mild reaction conditions, gram scale (Boger's method, 0.0125 M);

* Not very good yields for di- and trisubstituted olefins;

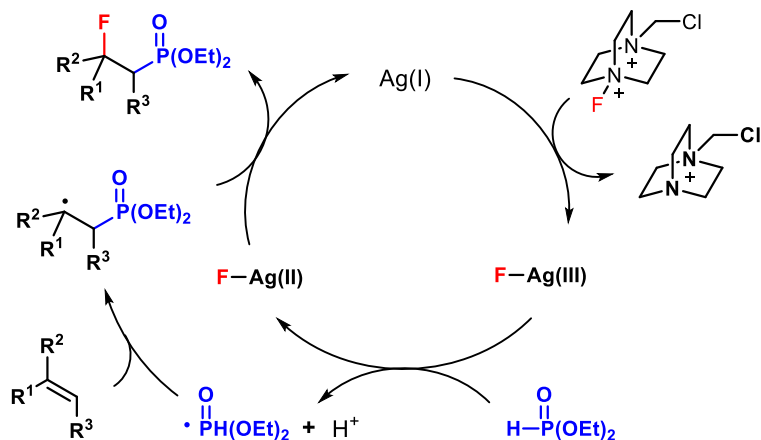
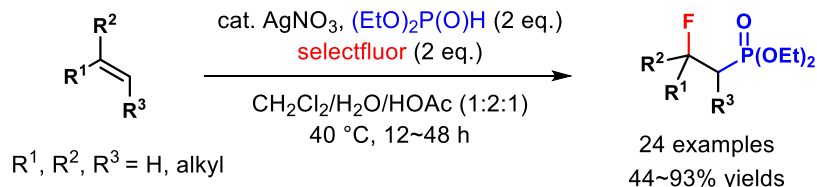
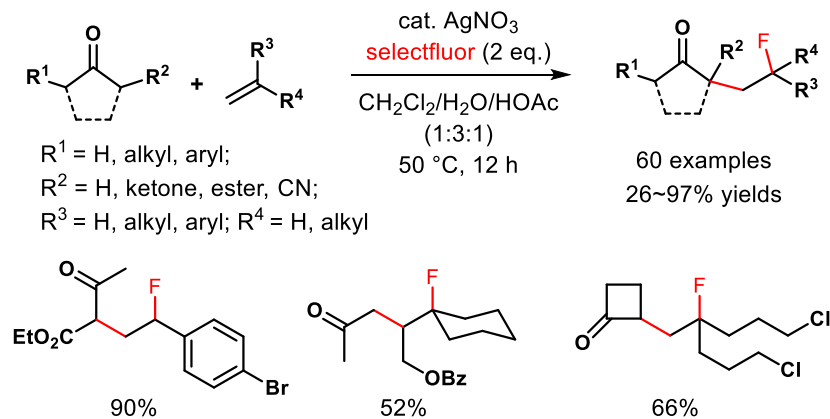
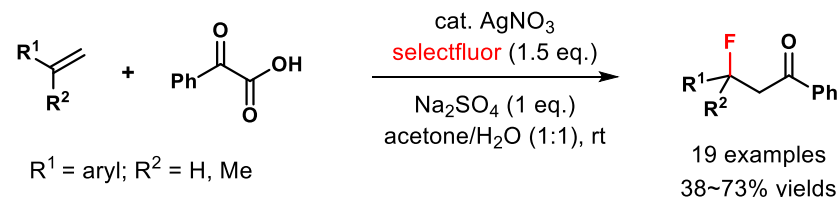
* The method was found to be ineffective for compounds including amino, carboxylic acid, phenol, or alkyne moieties.

Proposed mechanism

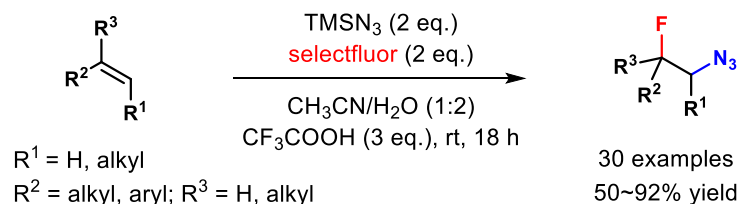


Driving force for the transformation of Co-F to Co-H is the strong F-Si bonding energy.

Hiroya, K.; et al. *Org. Lett.* **2013**, *15*, 5158-5161.

• Intermolecular phosphonofluorinationLi, C.; et al. *J. Am. Chem. Soc.* **2013**, *135*, 14082-14085.**• Silver-catalyzed carbofluorination**Li, C.; et al. *Org. Chem. Front.* **2014**, *1*, 1299-1305.**• Acylfluorination of unactivated alkenes**

* Aliphatic terminal alkenes were not compatible with the reaction conditions.

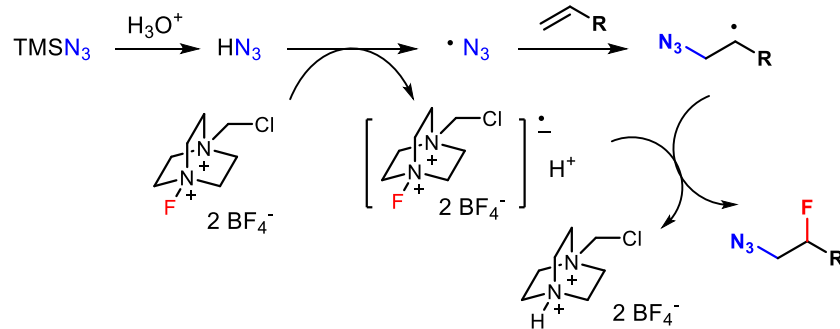
Duan, X.-H.; et al. *Chem. Commun.* **2014**, *50*, 7382-7384.**• Azidofluorination of unactivated alkenes**

* Transition metal-free

* The versatility of alkyl azides means that β-fluoroalkyl azides can be elaborated into a variety of fluorinated molecules

* Electron deficient alkenes such as methyl acrylate failed

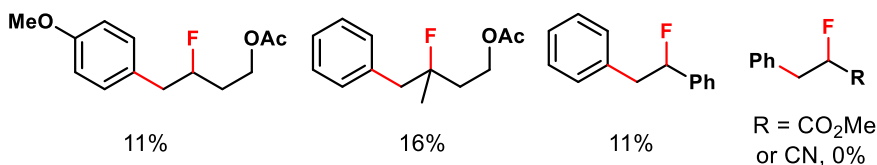
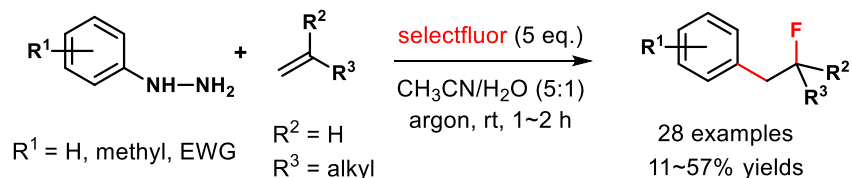
* A wide range of functional groups were well tolerated, including unprotected and protected alcohol, protected amine, alkyl chloride, ether, ketone, ester, sulfonate, amide, sulfonamide, nitrile and N-protected indole.



TFA slows down the SET process, thus lowering concentration of azidyl radical

Li, C.; et al. *Org. Chem. Front.* **2014**, *1*, 100-104.

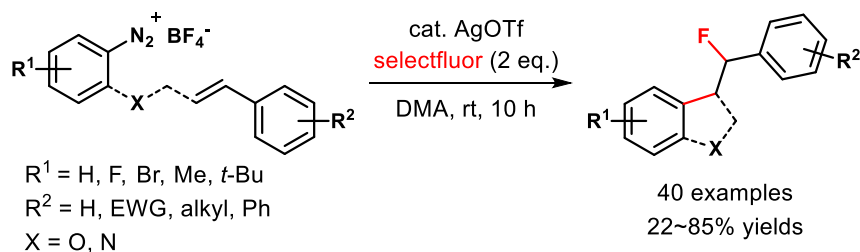
- **Meerwein-type carbofluorination of alkenes**



* The study deepens the impression that the preference of radical fluorine transfer to different types of alkyl radicals largely depends on the actual process involved.

Heinrich, M. R.; et al. *Chem. Eur. J.* **2014**, *20*, 15344-15348.

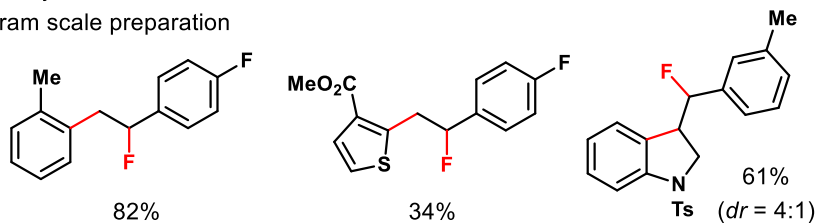
- **Silver-catalyzed intermolecular or intramolecular fluoroarylation of styrenes**



* Several functional groups including ester, carboxylic acid, ketone, halogens and alkyl groups are tolerated.

* Less than 10% desired product yield was observed with unactivated alkenes and heterocyclic alkenes.

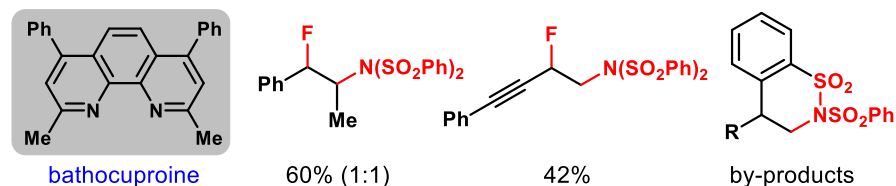
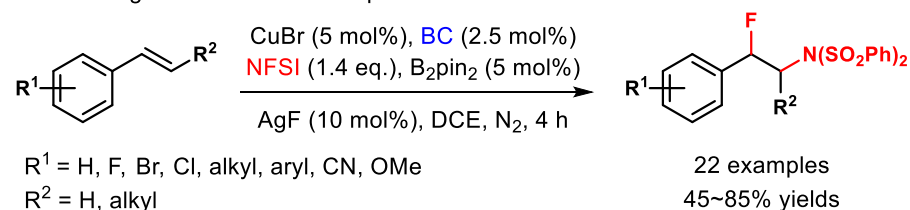
* Gram scale preparation



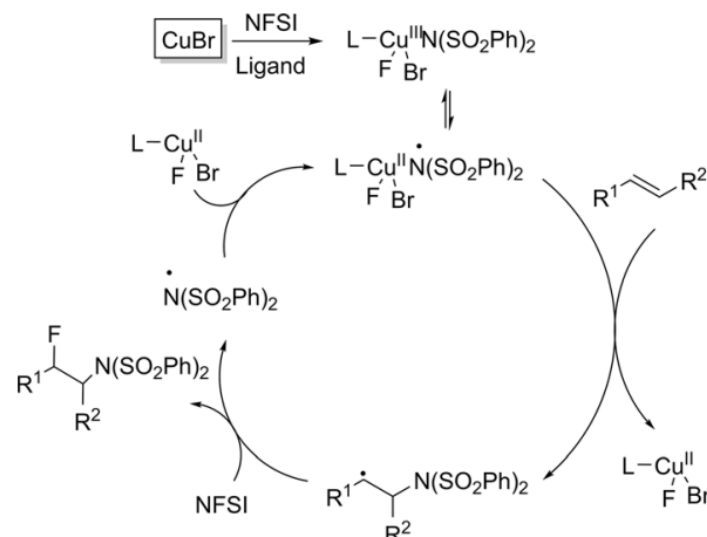
Tang, P.; et al. *Chem. Commun.* **2015**, *51*, 8829-8832.

- **Regioselective radical aminofluorination of styrenes**

Intermolecular radical aminofluorination of alkenes has not been documented, which might be attributed to the lack of a convenient route for the generation of relatively stable nitrogen-centered radical species.



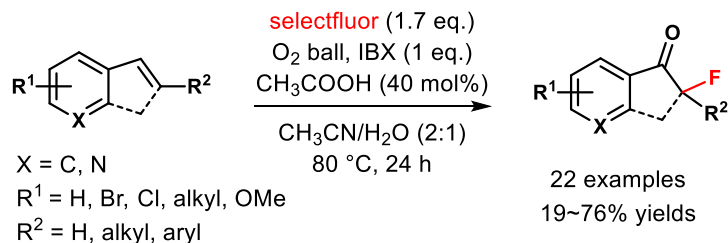
* For unactivated olefins, such as 1-octene and allylbenzene, the desired products were not formed, as the six-membered-ring sultam products were predominant.



first example of NFSI as both a radical nitrogen source and radical fluorine source

Zhang, Q.; et al. *Angew. Chem. Int. Ed.* **2014**, *53*, 11079-11083.

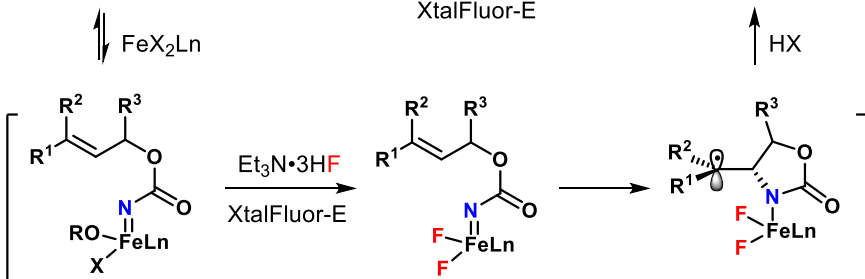
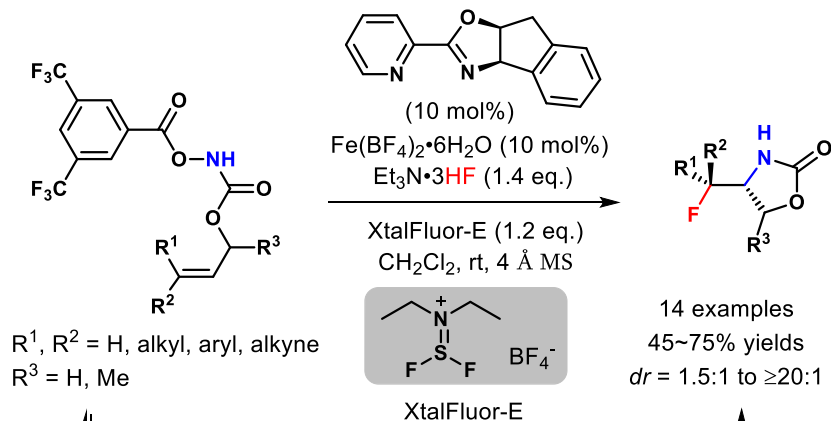
- Metal-Free oxyfluorination of Olefins**



* While the role of acetic acid remains unclear, it might adjust the pH of the reaction system and promote the production of fluorine free radicals.

Yang, S.-D.; et al. *Org. Lett.* **2014**, *16*, 3460-3463.

- Iron(II)-catalyzed intramolecular olefin aminofluorination**

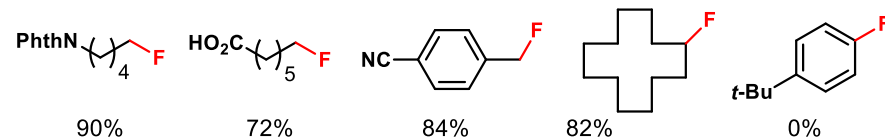
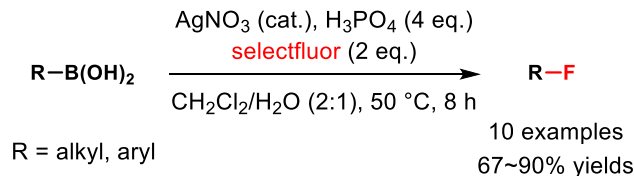


XtalFluor-E acted as carboxylate trapping reagent to accelerate exchange of OR and F a detectable ee (23%) when the optically pure ligand

Xu, H.; et al. *Org. Lett.* **2014**, *16*, 2912-2915.

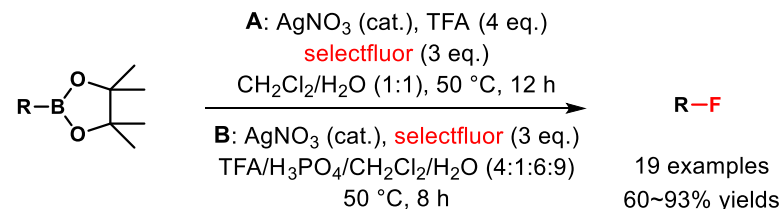
- Fluorination of boronic acid derivatives**

- Silver-catalyzed radical fluorination of alkylboronates**



* Functional groups such as nitrile, carbonyl, ether and ester were well tolerated.

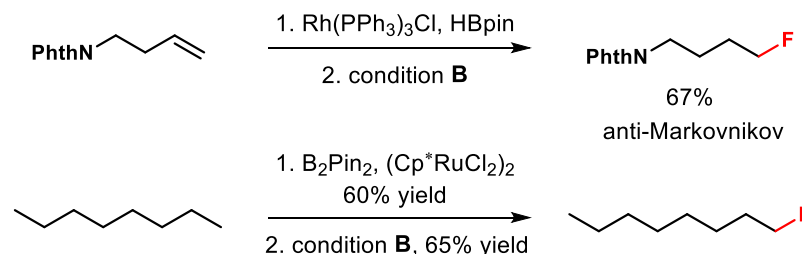
* Secondary or tertiary alkylboronic acids, especially functionalized ones, were hampered by their difficult purification due to instability.



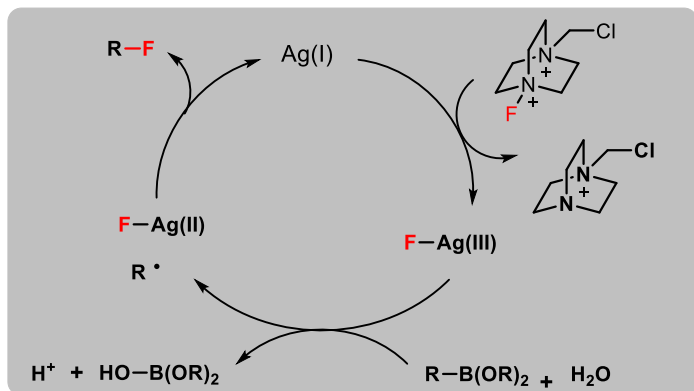
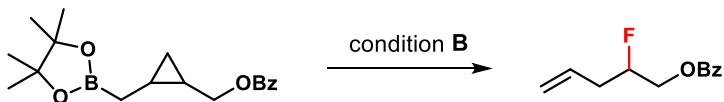
Condition A: secondary and tertiary alkylboronic esters;

Condition B: primary alkylboronic esters.

* While the role of TFA as a cosolvent is unclear, it might increase the solubility of substrate boronates in the aqueous phase.

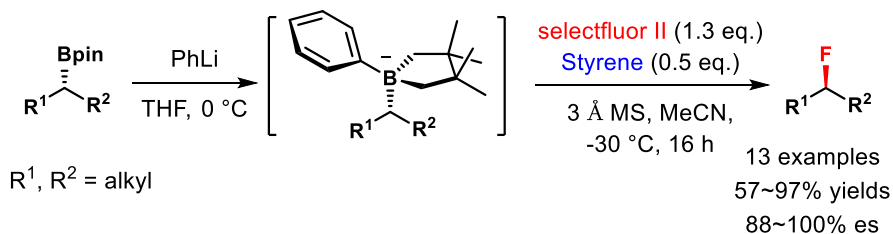


provides a nice complement for terminal C-H fluorination

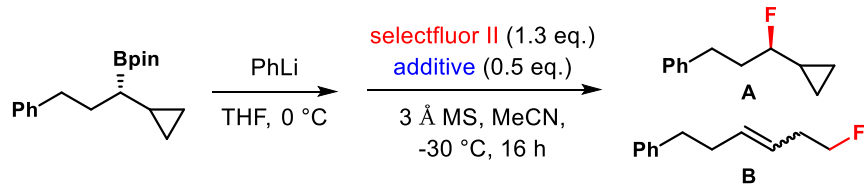


Li, C.; et al. *J. Am. Chem. Soc.* **2014**, *136*, 16439-16443.

• Enantioenriched alkylfluorination of boronate complexes

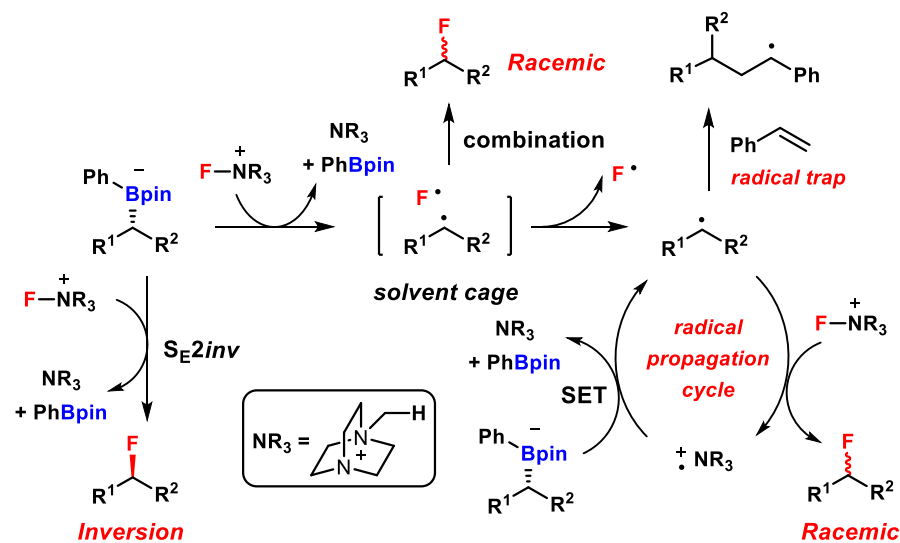


$R^1, R^2 = \text{alkyl}$



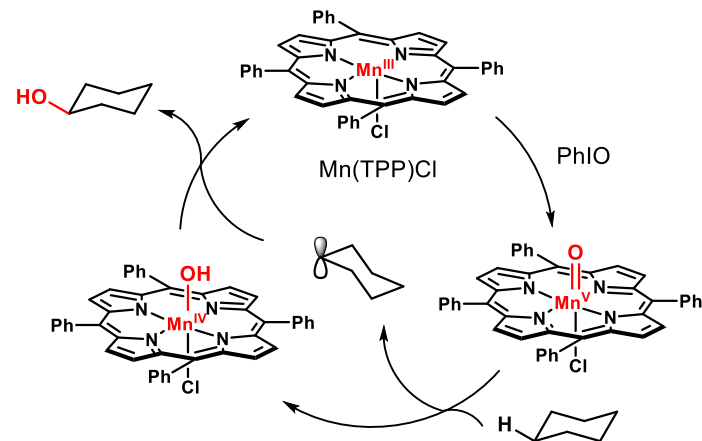
no additive	52% (A:B = 97:3)	es (A) = 56%
styrene	74% (A:B > 99:1)	es (A) = 64%

Low enantiospecificity implicated the existence of a second racemic pathway.
Styrene acts as a radical scavenger which trapping a radical propagating species.



Aggarwal, V. K.; et al. *J. Am. Chem. Soc.* **2015**, *137*, 10100-10103.

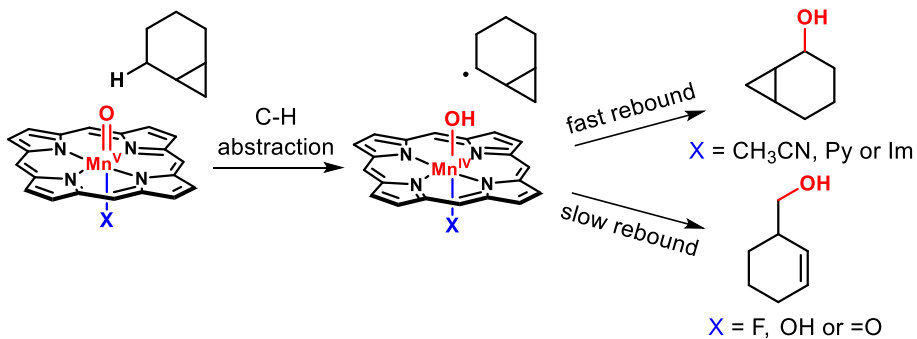
□ $C(sp^3)$ -H Fluorination



* The radical recombination step was very fast, up to 10^{10} s^{-1} .

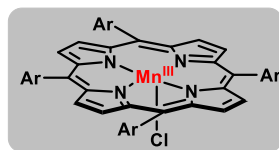
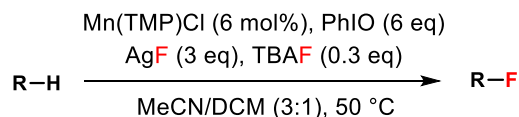
* Due to the fast radical recombination rate for $[R\bullet\text{HO-Mn}^{\text{IV}}(\text{por})]$, it was reasonable to believe that any transformations that involved $\text{O}=\text{Mn}^{\text{V}}(\text{por})$ intermediates would necessarily lead to the formation of oxygenated products.

Groves, J. T.; et al. *J. Am. Chem. Soc.* **1980**, *102*, 6375-6377.

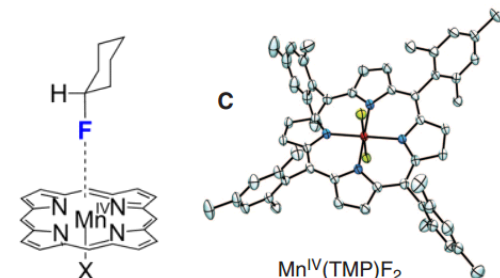
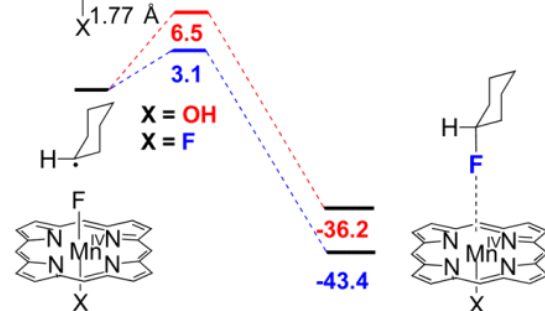
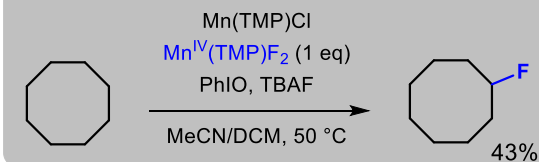
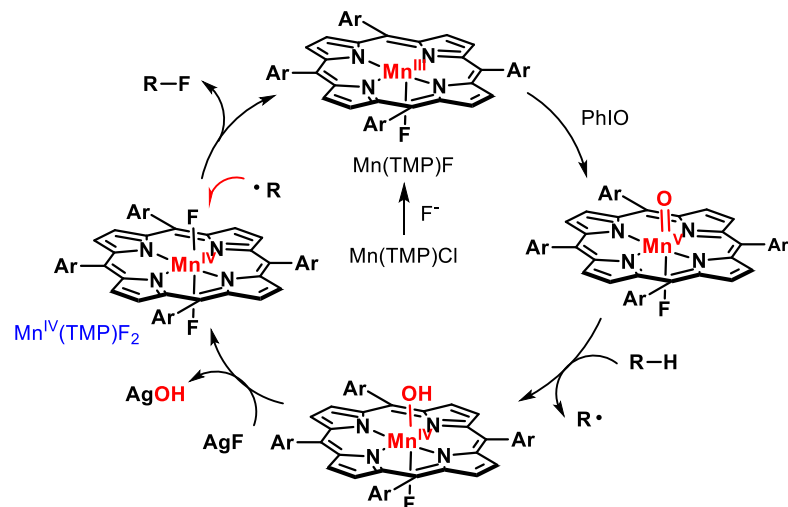
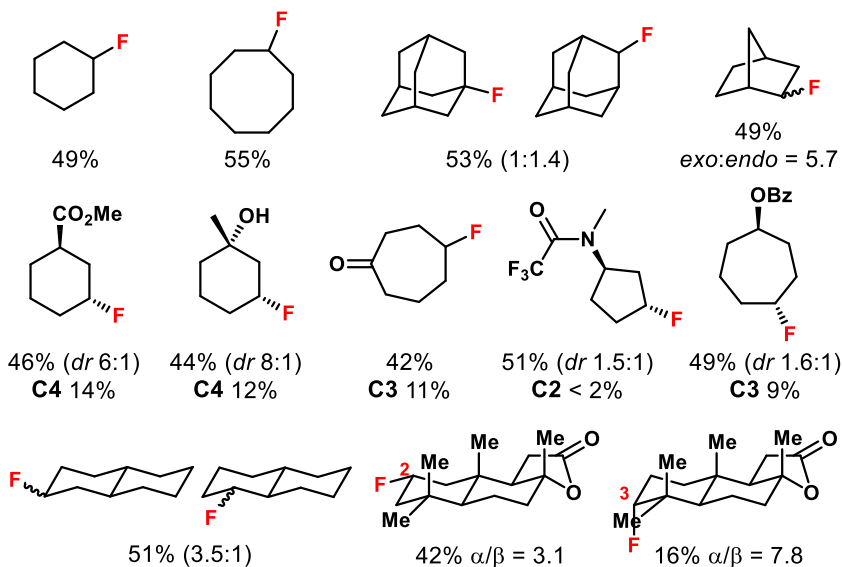


* The coordination of strong donor ligands, hydroxide and fluoride, might increase the energetic barrier of the oxygen rebound step, and oxygen rebound was apparently slower than cage escape.

Groves, J. T.; et al. *J. Am. Chem. Soc.* **2010**, *132*, 12847-12849.



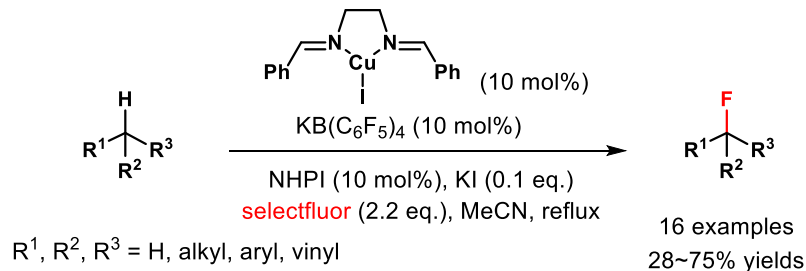
Ar = 2,4,6-methyl phenyl



Silver fluoride in this scenario first converts the $\text{Mn}(\text{TMP})\text{Cl}$ to the manganese(III) fluoride to form the catalyst, and then replenishes the inventory of manganese(IV) fluoride during turnover.

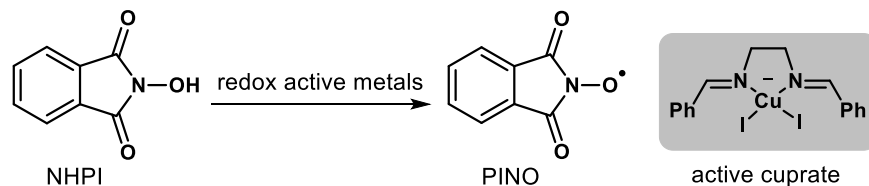
Groves, J. T.; et al. *Science* **2012**, *337*, 1322-1325.

- Copper-catalyzed C(sp³)-H fluorination**



* A rather complex reaction mixture, including N-hydroxyphthalimide as a cocatalyst, the phase-transfer catalyst $\text{KB}(\text{C}_6\text{F}_5)_4$ to solubilize Selectfluor, and KI to promote the formation of the active cuprate species

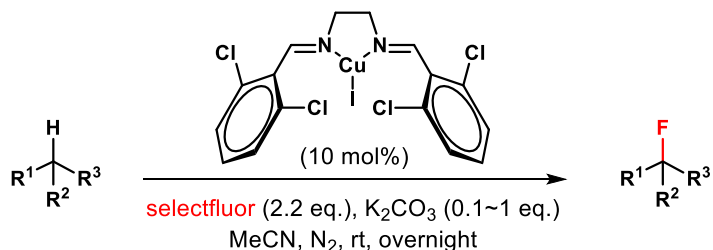
* Careful optimization of the reaction conditions was necessary



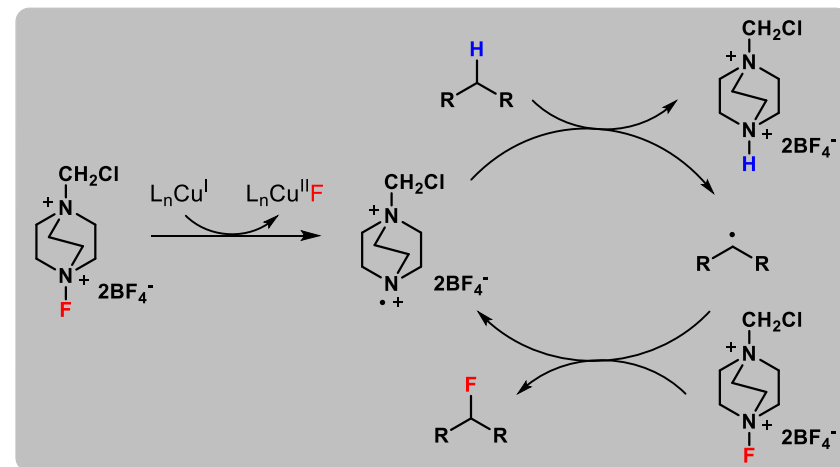
UV/Vis study: Addition of **Selectfluor** give rise to weak bands indicative of Cu^{II} and they disappear rapidly, concomitant with the appearance of a **prominent I_3^-** band. In turn, addition of **NHPI** results in consumption of I_3^- . Presumably, **CuI** is regenerated as well.

The complex conditions limited both applicability and understanding of this reaction.

Lectka, T.; et al. *Angew. Chem. Int. Ed.* **2012**, 51, 10580-10583.



Spectroscopic evidence and synthetic experiments confirm a radical chain mechanism initiated by an inner-sphere SET from copper(I) to Selectfluor (as opposed to a mechanism where copper plays a role in the catalytic cycle).

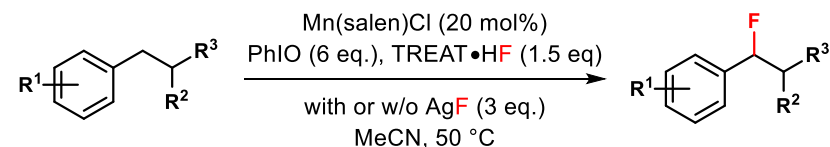


Lectka, T.; et al. *J. Am. Chem. Soc.* **2014**, 136, 9780-9791.

- Manganese-catalyzed oxidative benzylic C-H fluorination**

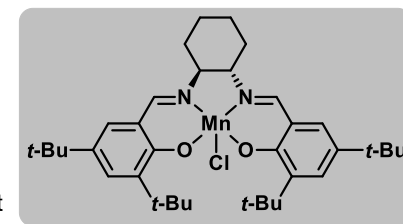
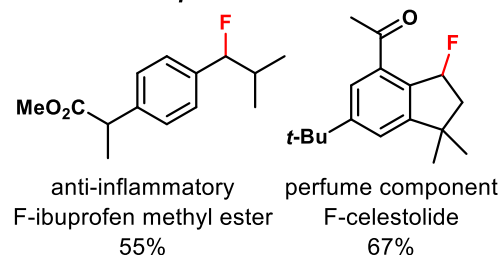
* Mn-catalyzed aliphatic fluorination protocol, when applied to benzylic C-H bonds, resulted in significant amounts of oxygenated side products.

* The rationale for byproducts was the relatively low oxidation potential of benzylic radicals, which leads to rapid carbon radical rebound to the $\text{Mn}^{\text{IV}}\text{-OH}$ intermediate.

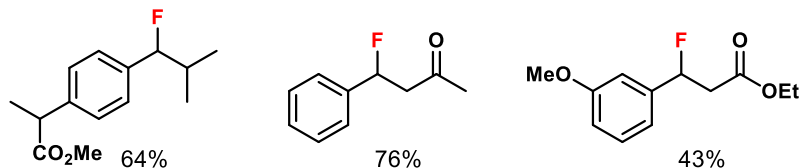
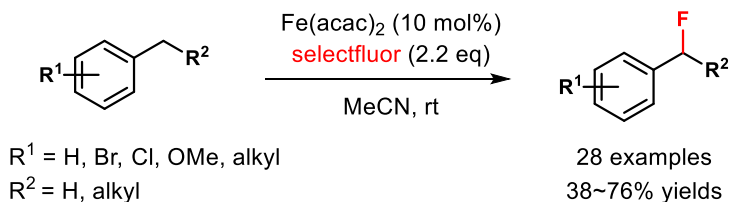


18 examples
44~70% yields

selected examples

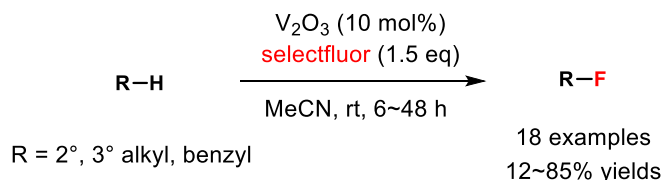


Groves, J. T.; et al. *Angew. Chem. Int. Ed.* **2013**, 52, 6024-6027.

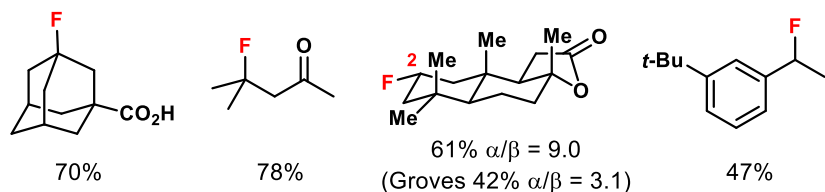
• **Iron(II)-catalyzed benzylic fluorination**

* A solution to the long-standing problem of mild conjugate addition of fluoride.

Lectka, T.; et al. *Org. Lett.* **2013**, *15*, 1722-1724.

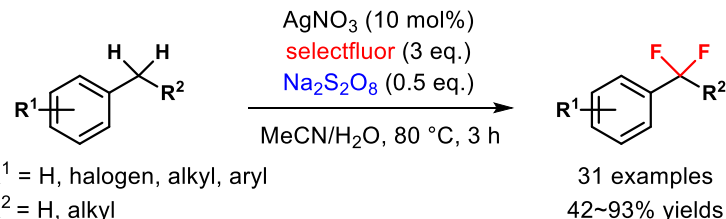
• **Vanadium-catalyzed $C(sp^3)$ -H fluorination**

- * Tertiary C-H groups are significantly more reactive than secondary C-H groups.
- * The fluorine atom of benzylic fluorides can eliminate under the reaction conditions, leading to low yields for the more electron-rich substrates.
- * Catalyst can be easily removed by filtration along with the selectfluor by-product.



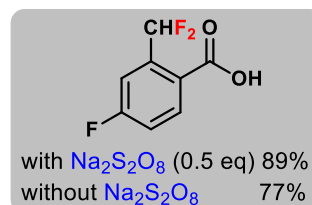
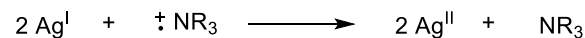
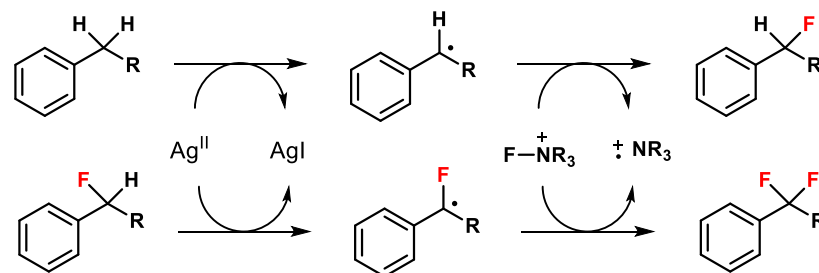
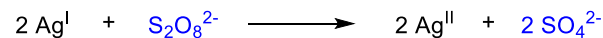
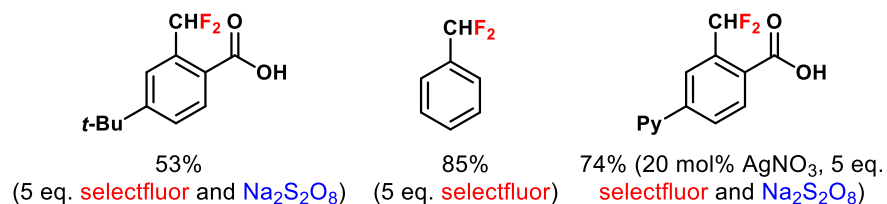
* While the nature of the active catalyst is not clear, it's believed that a vanadium (II/III) or (III/IV) cycle rather than a vanadium(III/V) cycle was involved.

Chen, C.; et al. *Org. Chem. Front.* **2014**, *1*, 468-472.

• **Silver-catalyzed benzylic difluorination**

Various functionalities, such as ketone, ester, carboxylic acid, amide, sulfonamide, fluoride, chloride, or bromide, and heteroaromatic substrates were well tolerated.

* Additional optimization of reaction conditions was needed for different substrates.

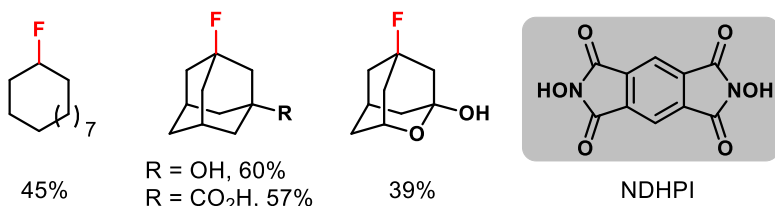
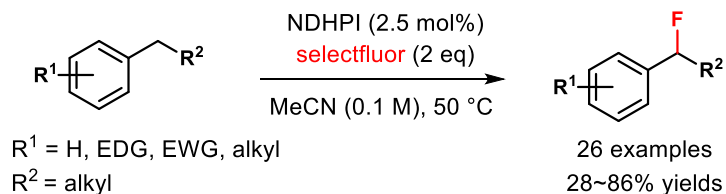


$\text{Na}_2\text{S}_2\text{O}_8$ is believed to oxidize the silver(I) salt to a silver(II) species and to facilitate the formation of difluoromethylated arenes.

A Ag(I)-Ag(III) cycle could also not be ruled out.

Tang, P.; et al. *Angew. Chem. Int. Ed.* **2014**, *53*, 5955-5958.

• **Metal-free fluorination of $C(sp^3)$ -H bonds using a catalytic *N*-oxyl radical**

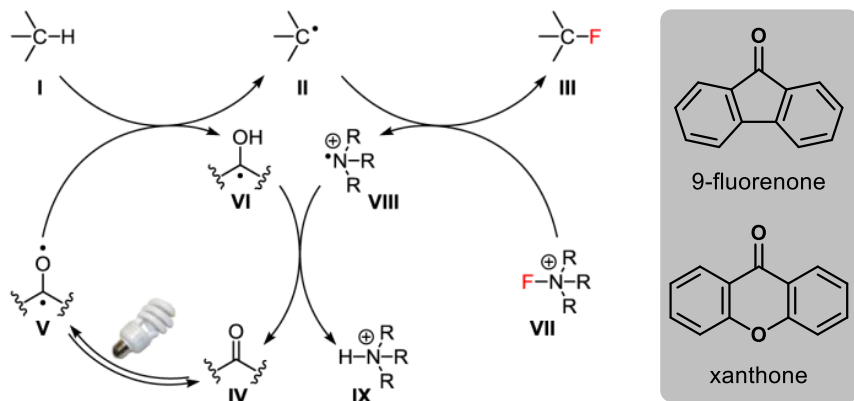


* NHPI gave low yield along with a significant quantity of unreacted SM.

* A longer reaction time resulted in dramatic lower yield.

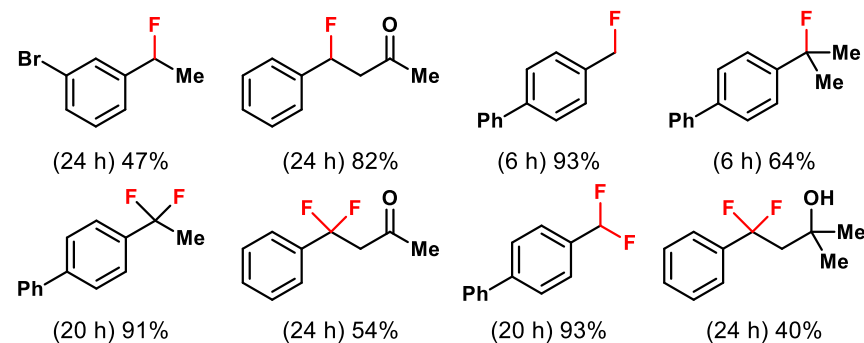
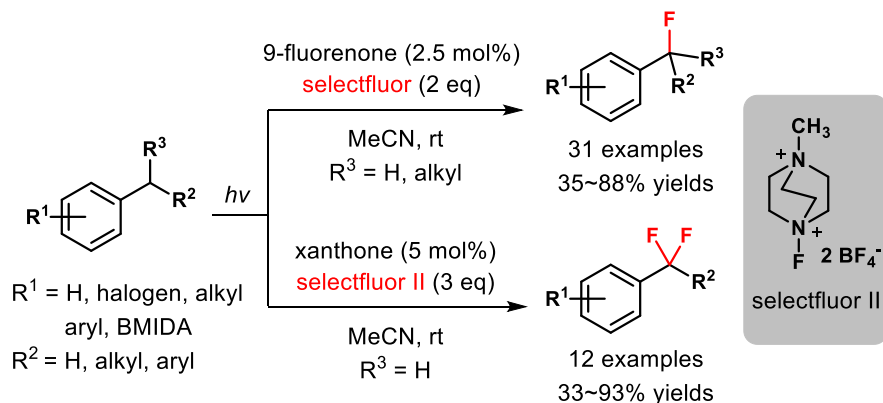
Inoue, M.; et al. *Org. Lett.* **2013**, *15*, 2160-2163.

• **Visible light-promoted metal-free C-H fluorination**



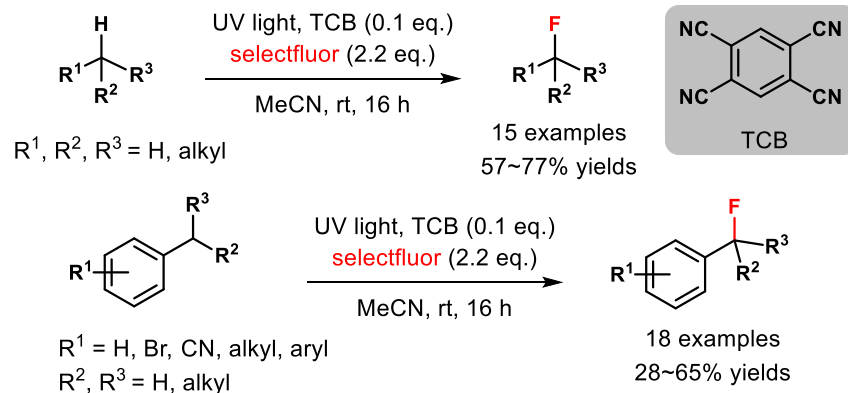
* Photoexcited ketone **V** is short-lived and can potentially react with all accessible hydrogen atoms, Breslow covalently linked benzophenone to a remote position of the substrate to enhance the reaction efficiency and regioselectivity.

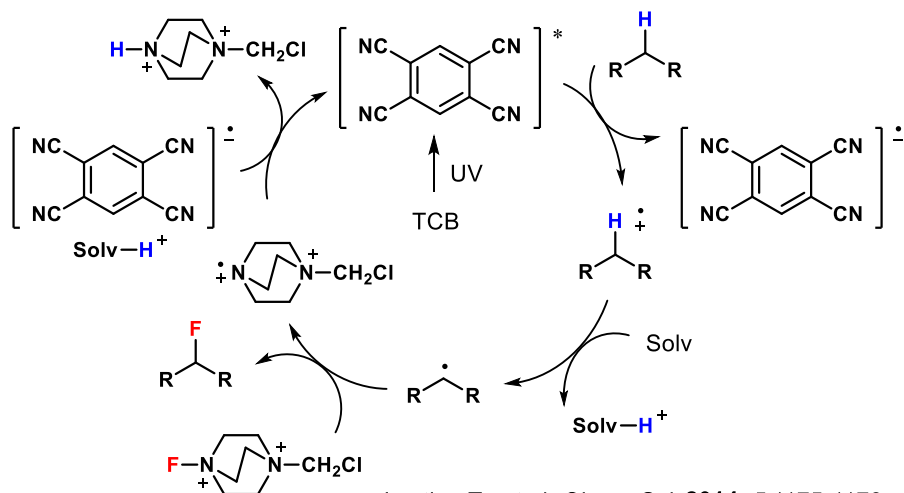
* Accumulation of **VI** would lead to its dimerization and loss of the catalyst, giving low or no catalyst turnover. They envisioned that aminium radical cation **VIII** would be highly energetic, and could effectively turn over the catalyst.



Chen, C.; et al. *J. Am. Chem. Soc.* **2013**, *135*, 17494-17500.

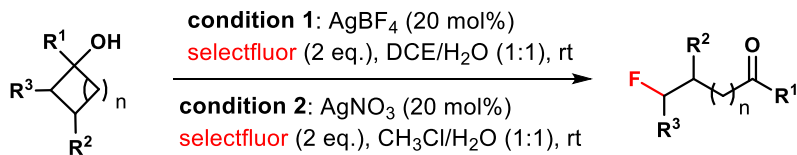
• **TCB-catalyzed $C(sp^3)$ -H fluorination**



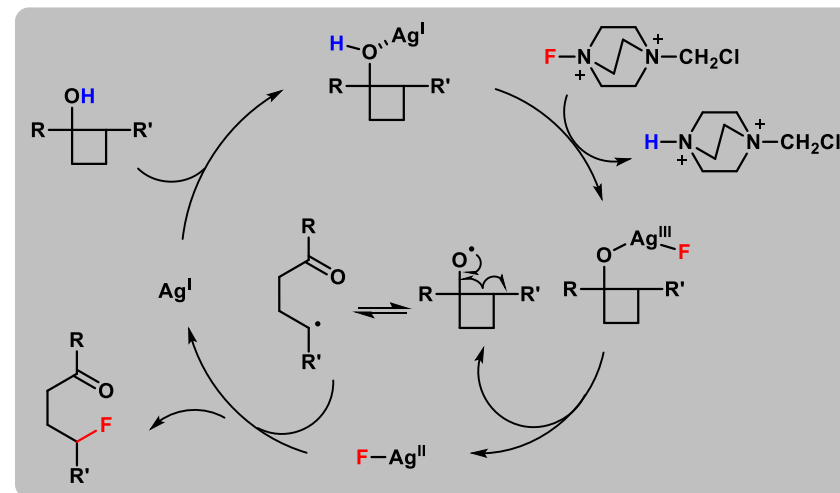
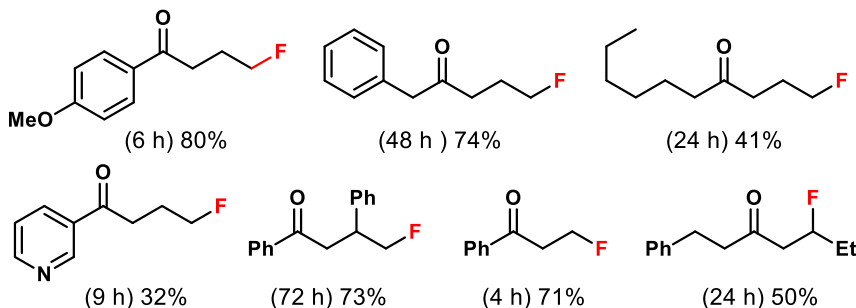
Lectka, T.; et al. *Chem. Sci.* **2014**, *5*, 1175-1178.Lectka, T.; et al. *Org. Lett.* **2014**, *16*, 6338-6341.

* They suggest the formation of distinct intermediate radical cations in the key radical forming step, as opposed to a concerted hydrogen atom transfer process.

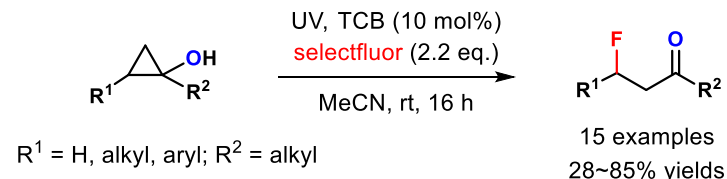
□ C-C Bond Activation



n = 0 (condition 2), 1 (condition 1)

R¹ = alkyl, benzyl, aryl, heteroarylR² = H, Me, Ph; R³ = H, Et34 examples
30~83% yieldsZhu, C.; et al. *J. Am. Chem. Soc.* **2015**, *137*, 3490-3493.Murakami, M.; et al. *Chem. Lett.* **2015**, *44*, 821-823.Loh, T.-P.; et al. *Org. Biomol. Chem.* **2015**, *13*, 5105-5109.

• Photocatalyzed C-C bond activation/fluorination

R¹ = H, alkyl, aryl; R² = alkyl15 examples
28~85% yieldsLectka, T.; et al. *Chem. Eur. J.* **2015**, *21*, 8060-8063.

III. Conclusions

* While electrophilic and nucleophilic fluorinations have been extensively developed over the last century, selective radical fluorination has experienced a renaissance with the development of numerous new methods in recent years, due to the uncovering of novel sources of atomic fluorine.

* Fluorinated compounds can now be efficiently synthesized from carboxylic acids, alkenes, trifluoroborate derivatives as well as aliphatic and benzylic substrates using mild conditions.

* Asymmetric radical fluorination is a challenge and also an opportunity.