

Literature Seminar  
2013. 10. 19 (Sat)  
Keiichi Kaneko (D1)

# Introduction of Fluorine- Containing Functional Groups & The Many Roles for Fluorine in Medicinal Chemistry

## Contents

1. Introduction
2. Fluorination
3. Difluoromethylation
4. Trifluoromethylation
5. Summary



## Physical Properties of Fluorine

Table 2. van der Waals Radii and Pauling Electronegativities<sup>10</sup>

	van der Waals radius (Å)	Pauling electronegativity
C	1.70	2.55
H	1.20	2.20
F	1.47	3.98
O	1.52	3.44
N	1.55	3.04
Cl	1.75	3.16

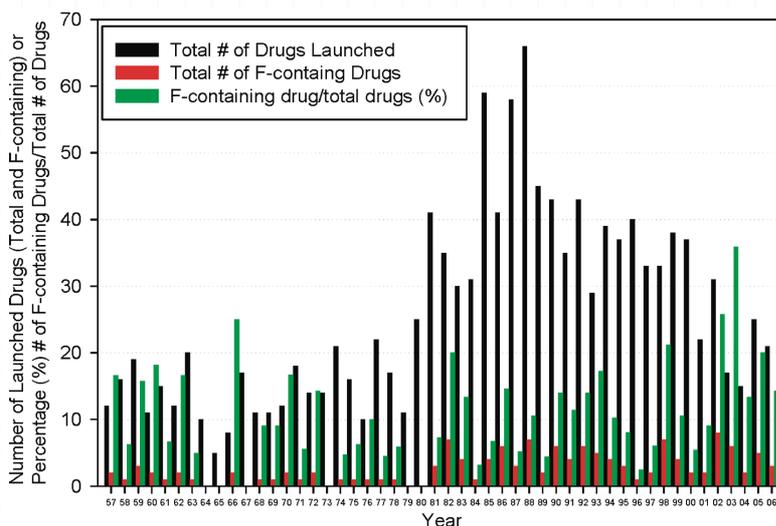
- Its van der Waals radius is closer to that of oxygen as is its electronegativity
- The strongly electron withdrawing nature of fluorine substitution is especially evident in its effect on **the acidity** of neighboring functional groups.



Changes in pKa can have effects on a number of different parameters in lead optimization including physicochemical properties (solubility, log *D*), binding affinities (potency, selectivity), and **absorption, distribution, metabolism, excretion (ADME)**.

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## Launched Drugs Containing Fluorine 1957-2006



- ✧ The number of fluorine-containing launched drugs as a percentage of the total number of launched drugs has remained relatively constant (green bars)
- ✧ Fluorinated drugs have constituted approximately 5-15% of the total number of launched drugs worldwide over the past 50 years with a noticeable increase in the past 5 years.

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# Fluorine in Pharmaceuticals

## 1. Selectivity (off target effects)

## 2. Metabolic Clearance

A particularly labile site of metabolic oxidation can be blocked by fluorination without adversely effecting affinity.

## 3. Brain Penetration

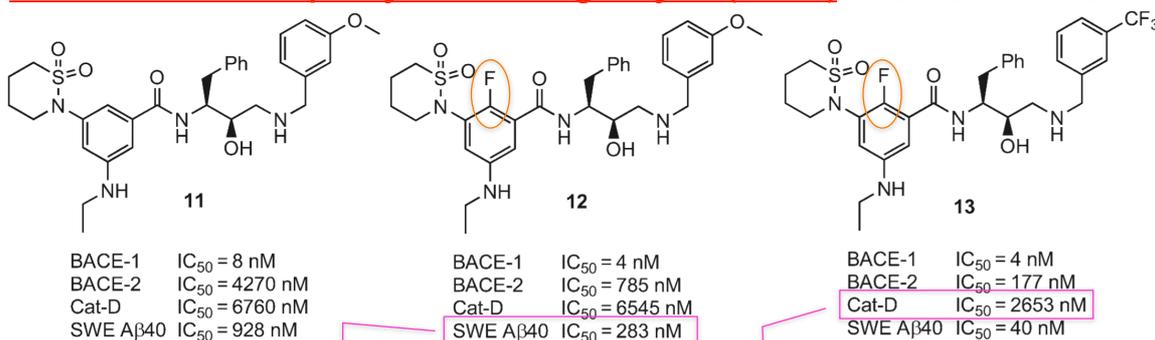
## 4. Protein Binding

These interactions may occur between fluorine and a protein directly, may be bridged by a sphere of solvation, or may occur by alterations in the conformation of the molecule.

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# Modulating Potency & Selectivity by Introduction of Fluorine (1)

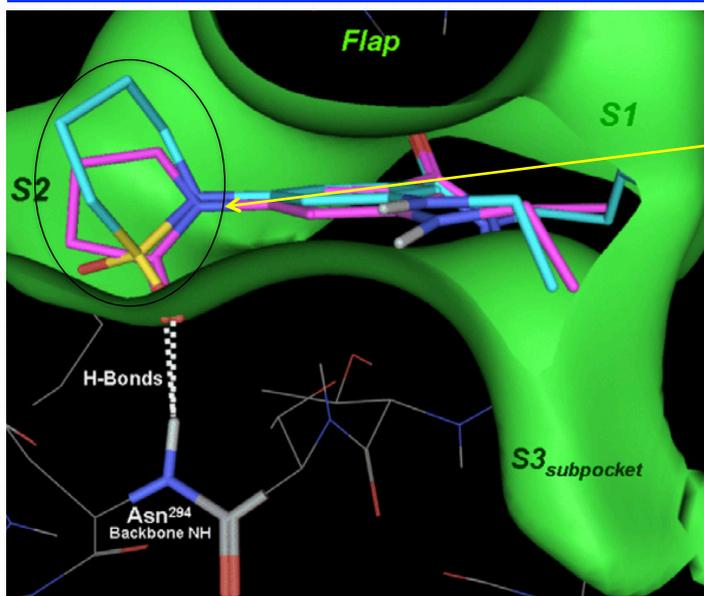
## Potent inhibitors of $\beta$ -amyloid cleaving enzyme (BACE)



Threefold improvement  
in cellular potency

excellent selectivity  
could be achieved,  
particularly against  
Cat-D

## Modulating Potency & Selectivity by Introduction of Fluorine (2)



Superimposition of 6-sultam

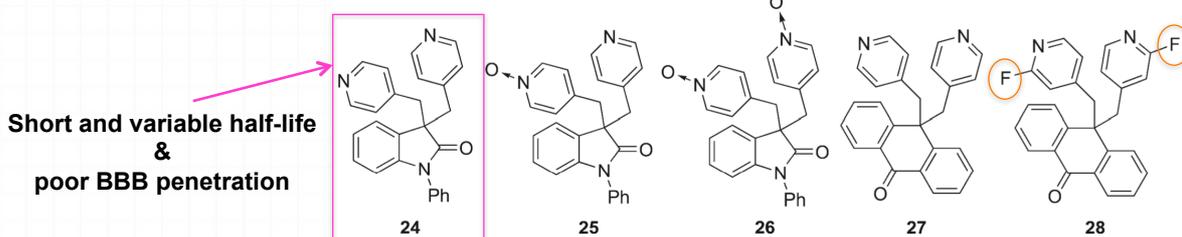
The substituents which had been shown to form a H-bond to Asn-294, or which would bind more tightly in the S1 pocket is needed.

➔ **Effect of fluorine might be observed in the sultam series.**

*Bioorg. Med. Chem. Lett.* 2008, 18, 1022. 7

## Effects of Fluorine on Pharmacokinetic Parameters & Drug-Like Properties (Metabolic Stability)

Linopirdine (24) was among the first clinical compounds that enhanced potassium-evoked release of acetylcholine in preclinical models of AD.



Compound	ACH release EC <sub>50</sub> (μM)	CLogP	Rat PO PK		
			T <sub>1/2</sub>	F	B/P
24	4.5	2.97	0.5 h	30%	1/6
25	Inactive	—	—	—	—
26	Inactive	—	—	—	—
27	0.45	4.65	—	—	—
28	0.83	5.11	2.0 h	30%	1/1

- ✓ **Lowering pK<sub>a</sub> and reducing metabolic N-oxidation**
- ✓ **Led to a significant improvement in brain-to-plasma ratio**

*J. Med. Chem.* 1998, 41, 4615. 8



## Small Summary (1)

- The presence of this one atom can **influence metabolic stability, brain exposure, off-target selectivity, protein binding, and affinity for the primary biological target.**
- Therefore, striking the correct balance of drug-like properties will remain a recurring challenge in lead optimization but strategies utilizing fluorine's impact on these properties will continue to influence the success of many drug discovery programs.

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- 2. Fluorination**
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**Antozonite (2012)**



**Liquid Fluorine**

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## Fluorinating Reagents

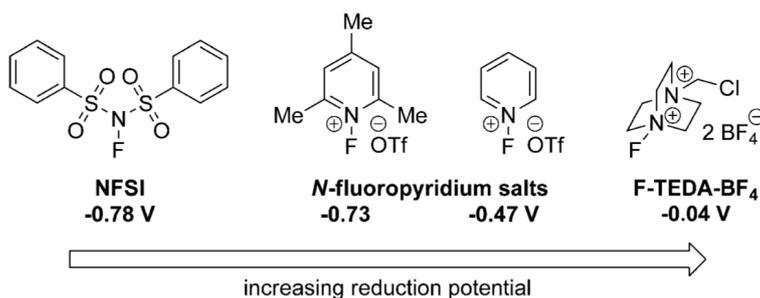
- Fluorine gas, hypofluorites, fluoroxysulfates, perchloryl fluoride

➔ **High reactivity**

- XeF<sub>2</sub> : more stable electrophilic fluorination source

➔ **Still limits the tolerance of this reagent to FG.**

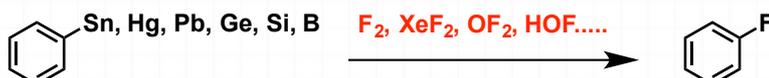
- Crystalline, benchtop-stable fluorinating reagents



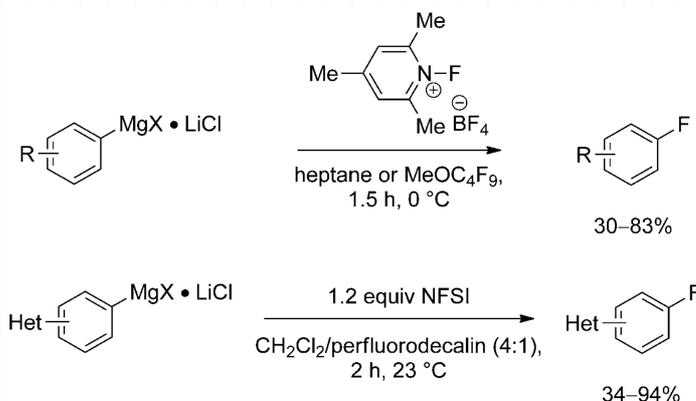
**Figure 1.** Comparison of the redox potentials of crystalline, benchtop-stable fluorinating reagents (versus SCE).

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## The Fluorination of Arenes (C-M to C-F)



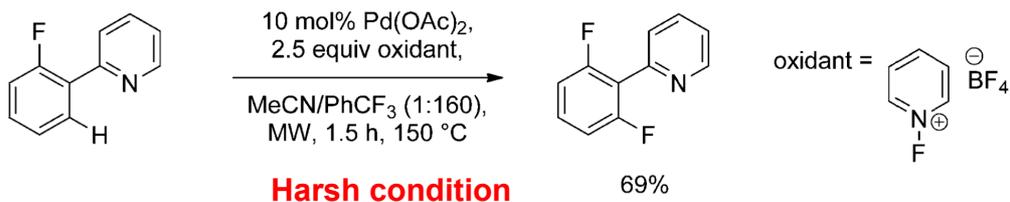
**However, the substrate scope is limited due to the high reactivity of the reagent, and often results in unselective fluorination.**



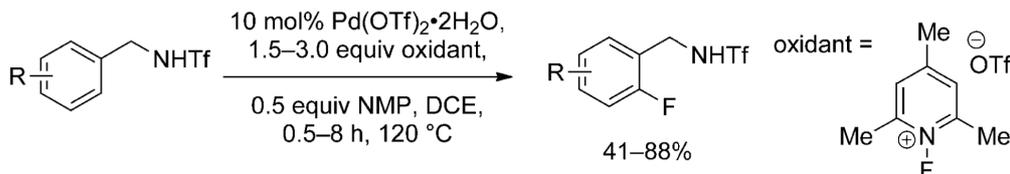
**The fluorination of Grignard reagents with electrophilic is narrow in scope due to the basicity and nucleophilicity of the aryl magnesium reagents.**

## Palladium-Catalyzed *ortho*-Fluorination

M. S. Sanford, *et al.* *JACS*, **2006**, *128*, 7134.



J. -Q. Yu, *et al.* *JACS*, **2009**, *131*, 7520.



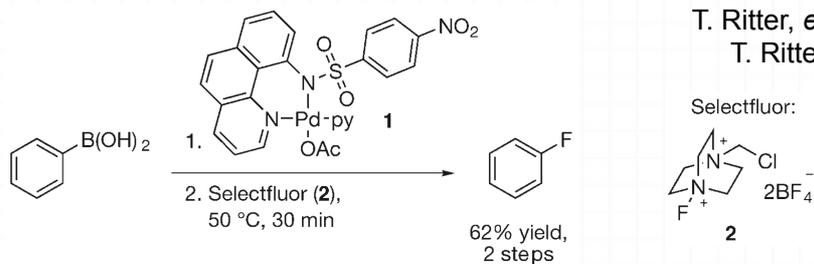
Limited to orthoposition  
Couldn't prevent the difluorination

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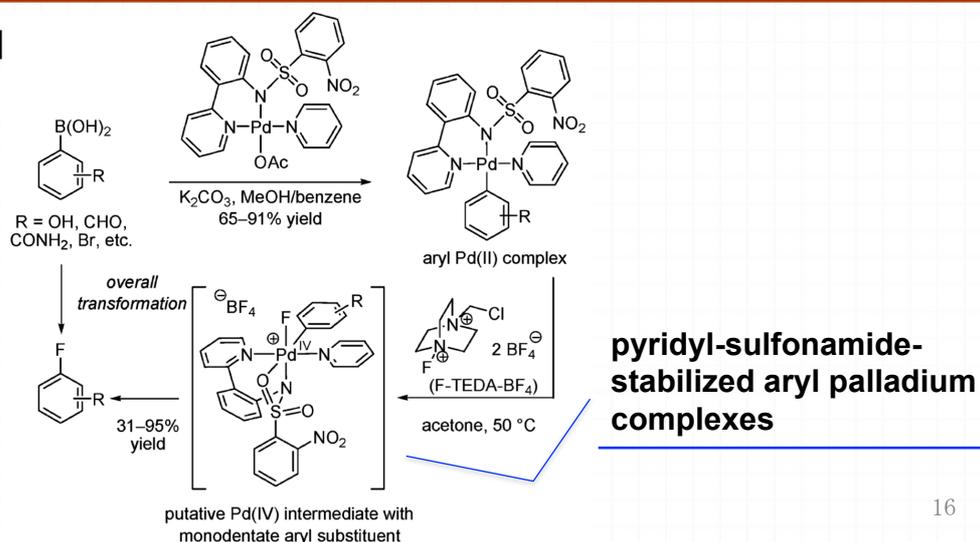
## Carbon-Fluorine Reductive Elimination (1)

T. Ritter, *et al.* *JACS*, **2008**, *130*, 10060.

T. Ritter, *et al.* *ACIE*, **2008**, *47*, 5993.

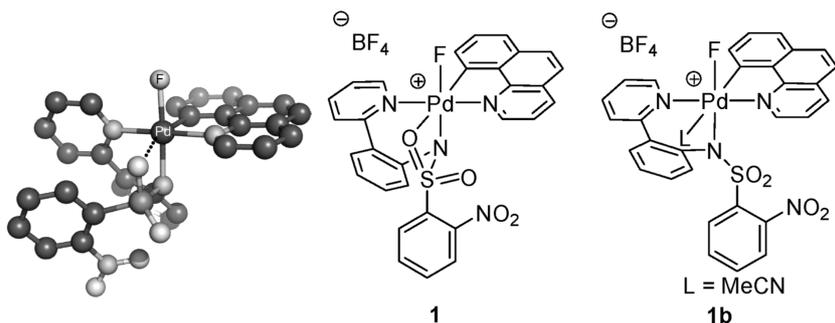


### [Mechanism]



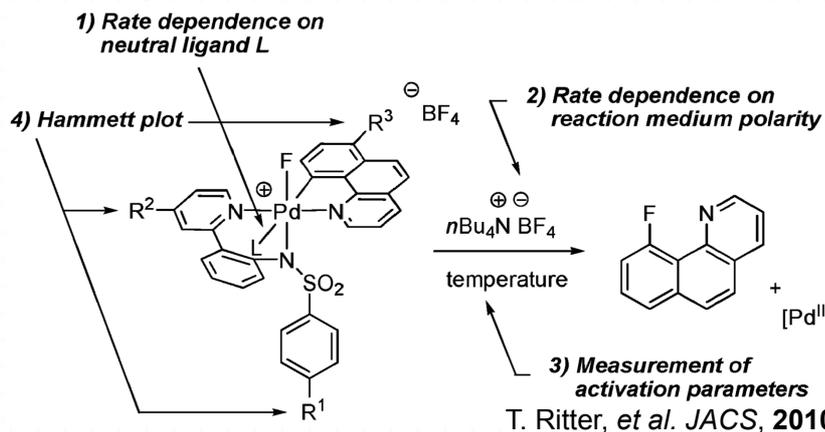
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## Carbon-Fluorine Reductive Elimination (2)

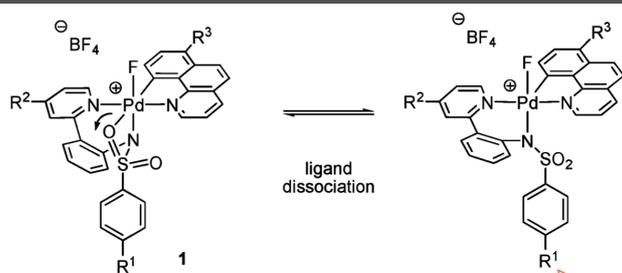


The computed energy difference ( $\Delta H_{298}$ ) between 1 and 1b is 2.2 kcal $\cdot$ mol $^{-1}$  favoring 1.

### • Methods employed in this mechanistic study



## Proposed Mechanism of C-F Reductive Elimination

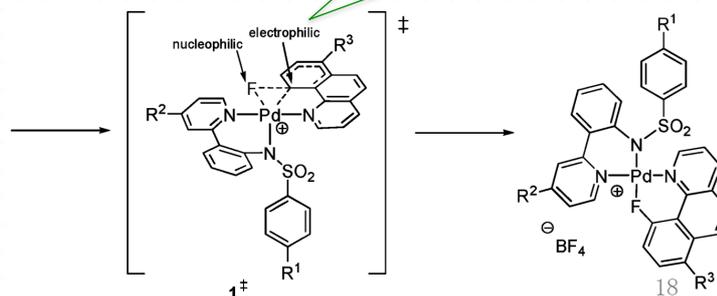


T. Ritter, *et al.* JACS, 2010, 132, 3793.

**O-sulfonamide dissociation of the hexacoordinate Pd(IV) complex 1 to form a cationic, pentacoordinate complex**

**Ligand rearrangement may take place for C-F reductive elimination.**

**Reductive elimination from pentacoordinate transition metal complexes likely proceeds from distorted trigonal bipyramidal structures.**



## Palladium(III)-Catalyzed Fluorination (1)

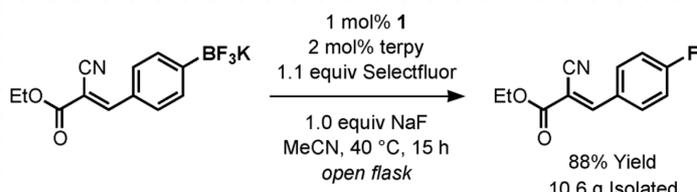
Only two catalytic reactions have been reported that provide a general route to functionalized aryl fluorides.



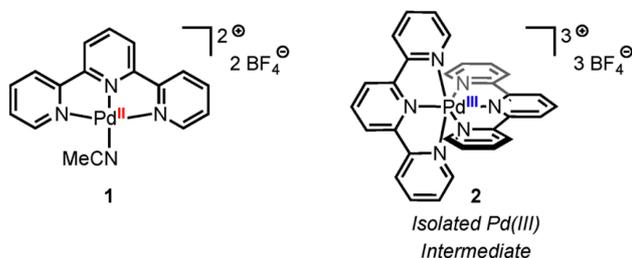
Buchwald, S. L. *et al. Science*, **2009**, 325, 1661.  
Ritter, T. *et al. JACS*, **2010**, 132, 12150.

• Ritter, T. *et al. JACS*, **2013**, 135, 14012.

For arylboronic acid derivatives, **slow transmetalation of the arene from boron to the transition metal complex** is frequently a hurdle.



propose a mechanism that proceeds without the formation of organopalladium intermediates.

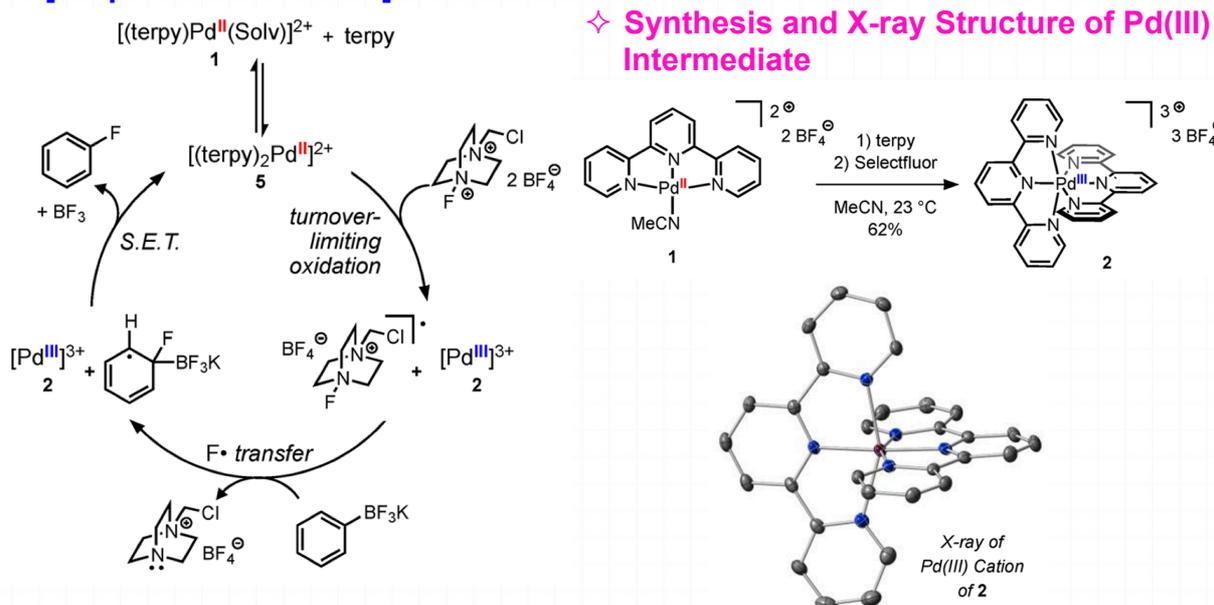


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## Palladium(III)-Catalyzed Fluorination (2)

T. Ritter, *et al. JACS*, **2013**, 135, 14012.

### [Proposed Mechanism]



For recent reviews of Pd(III) complexes;

Ritter, T. *et al. JACS*, **2012**, 134, 12002.

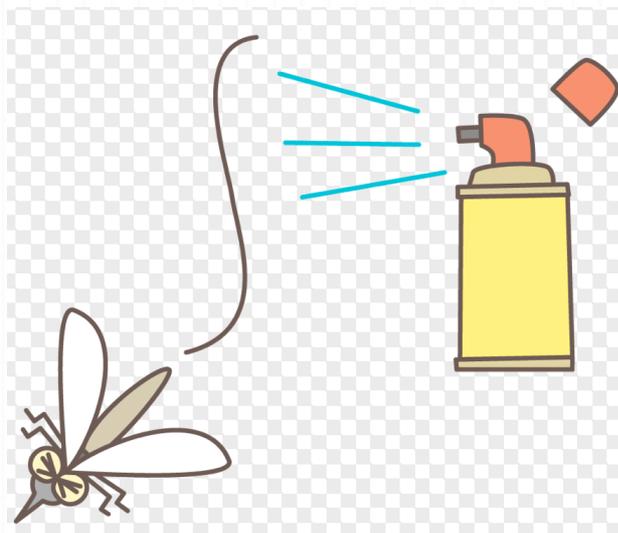
Ritter, T. *et al. Top. Organomet. Chem.* **2011**, 503, 129.

Ritter, T. *et al. Acc. Chem. Res.* **2012**, 45, 840.

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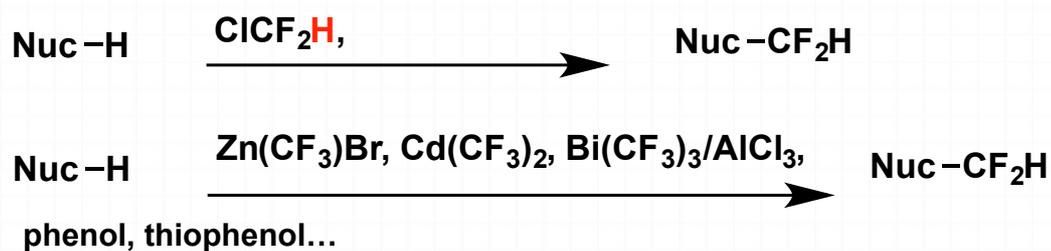
1. Introduction
2. Fluorination
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## Difluoromethylation (introduction)

The increased acidity of  $\text{XF}_2\text{C-H}$  compared to  $\text{XFHC-H}$  facilitates the formation of  $\text{F}_2\text{CX}^-$



*JACS.* 1985, 107, 5014.

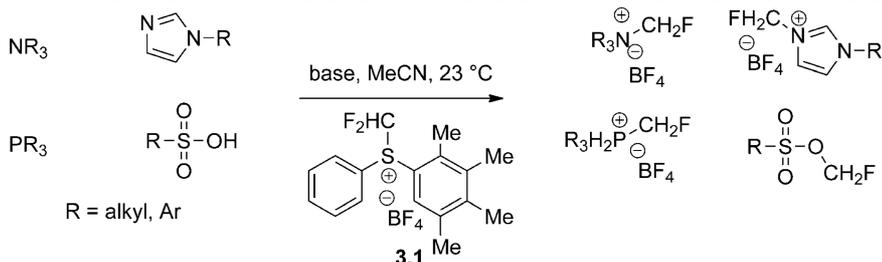
All of which react through difluorocarbene intermediates.

➔ An electrophilic reagent for the direct introduction of a “ $\text{CF}_2\text{H}^+$ ” building block is yet to be reported.

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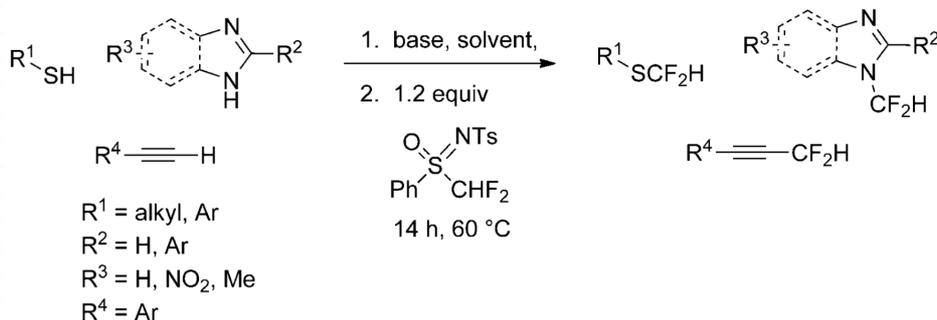
## Electrophilic Difluoromethylation

G. K. S. Prakash, *et al. Org. Lett.* **2007**, *9*, 1863.



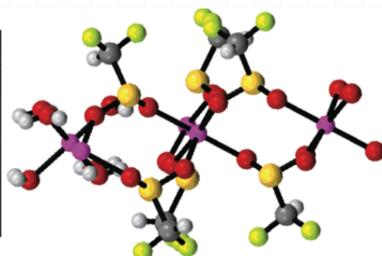
The reagent did not give the corresponding difluoromethylated products with either phenols, carbon-based nucleophiles, or primary/secondary amines.

### • The successful difluoromethylation of S, N, and C nucleophiles

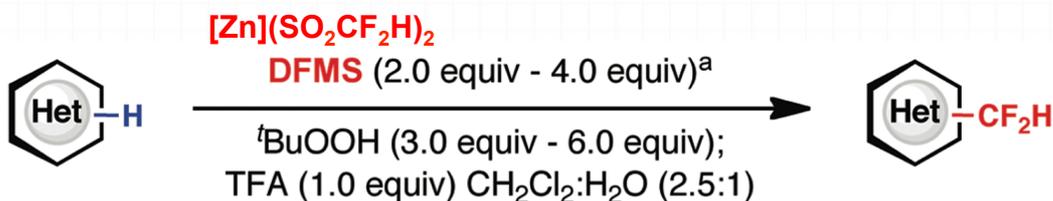


Hu, J. *et al. Org. Lett.* **2009**, *11*, 2109. 23

## Radical Difluoromethylation of Heteroarene



- air stable
- free-flowing powder
- X-ray (polymeric crystal)
- 150g prepared



- 22 examples<sup>b</sup>
- Displays high regioselectivity
- Proceeds at ambient temperature
- Runs in aqueous conditions under air
- Compatible with halogen functionalities
- Both electron rich and deficient heterocycles

Baran, P. S. *et al. JACS.* **2012**, *134*, 1494. 24

## Contents

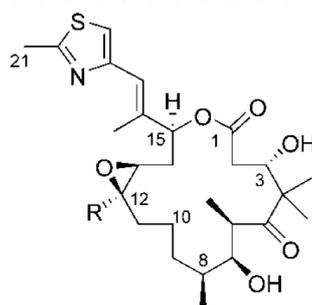
### 1. Introduction

### 2. Fluorination

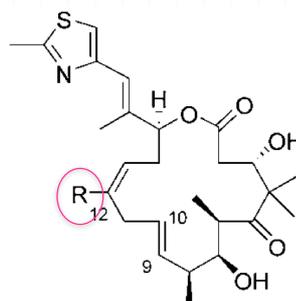
### 3. Difluoromethylation

### 4. Trifluoromethylation

### 5. Summary



6: epothilone A (EpoA), R = H  
7: epothilone B (EpoB), R = CH<sub>3</sub>



8: (*E*)-9,10-dehydro-dEpoB, R = CH<sub>3</sub>  
9: 26-trifluoro-(*E*)-9,10-dehydro-dEpoB,  
R = CF<sub>3</sub> (fludelone)

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## Trifluoromethylation (introduction)

### ➤ Difficulties of Trifluoromethylation

Only one other substituent can be varied.

Transition-metal-mediated trifluoromethylation is complicated by the strong metal-CF<sub>3</sub> bond .

1. the polar contribution of the bond

2. backbonding from filled metal d orbitals into the s\*C-F bonds

### ➤ Electrophilic trifluoromethylating reagents

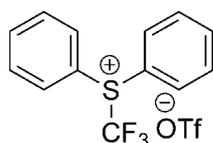
#### In laboratory settings

Crystalline

Easily weighable reagents



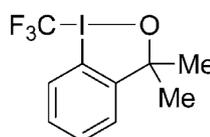
S-(trifluoromethyl)diarylsulfonium salts



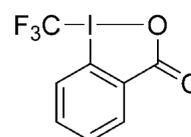
#### In industrial process

Lower cost reagents

Such as CF<sub>3</sub>H, CF<sub>3</sub>I



Togni reagent

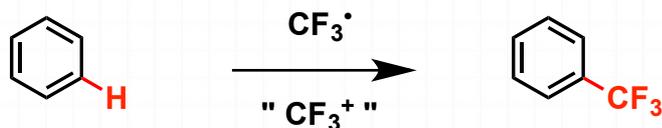


Togni reagent II

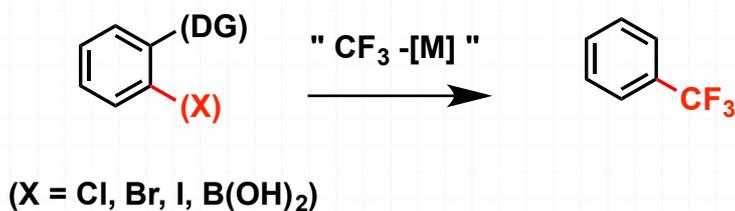
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## Pathway to Trifluoromethyl arenes

### 1. Innate Trifluoromethylation



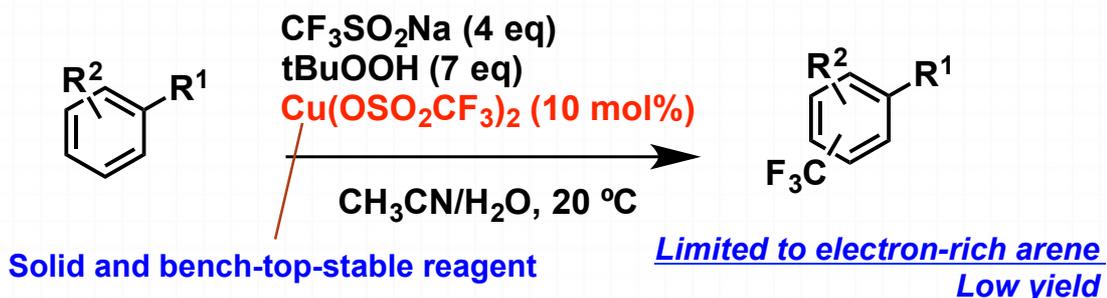
### 2. Programmed Trifluoromethylation



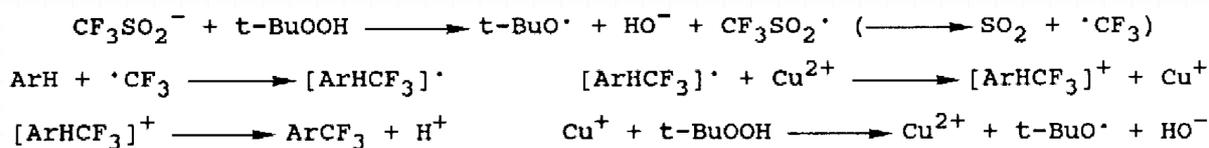
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## Cu-Catalyzed Trifluoromethylation of Aromatic compound

Langlois, B. R. *et al. Tetrahedron. Letters.* 1991, 32, 7525.



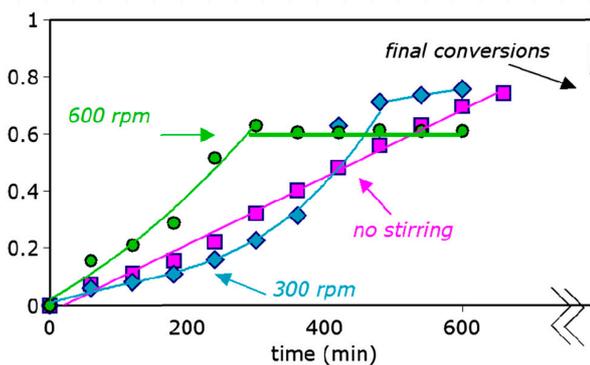
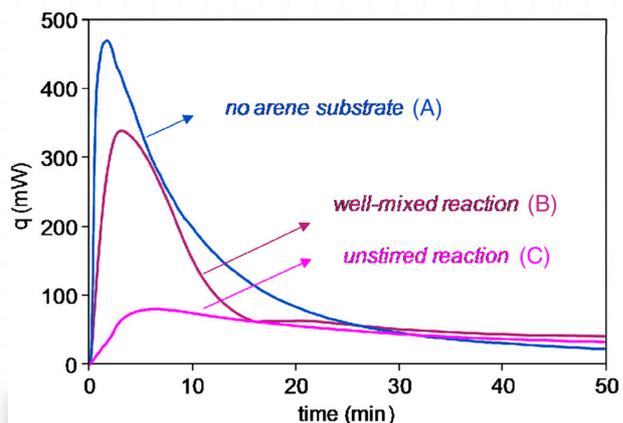
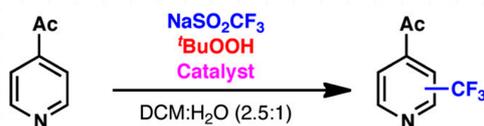
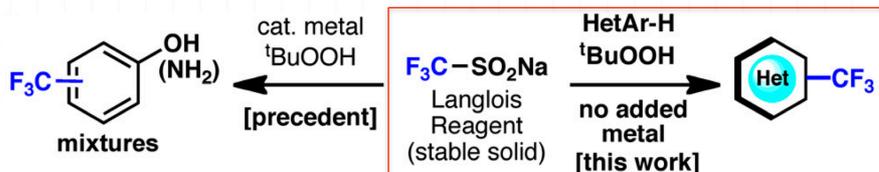
### [Mechanism]



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## Radical Trifluoromethylation of Heteroarenes (1)

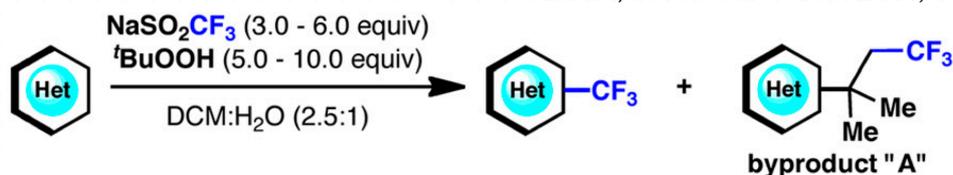
Baran, P. S. et al. *PNAS*. 2011, 108, 14411.



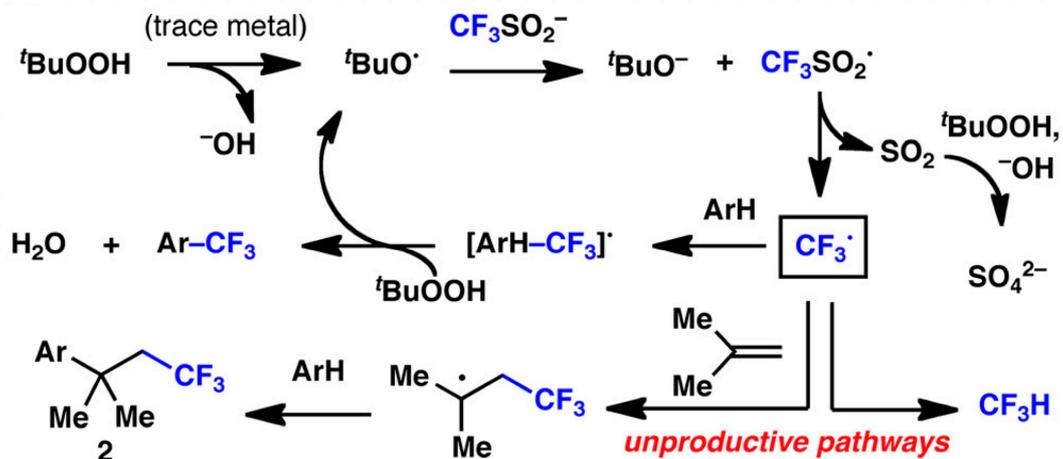
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## Radical Trifluoromethylation of Heteroarenes (2)

Baran, P. S. et al. *PNAS*. 2011, 108, 14411.



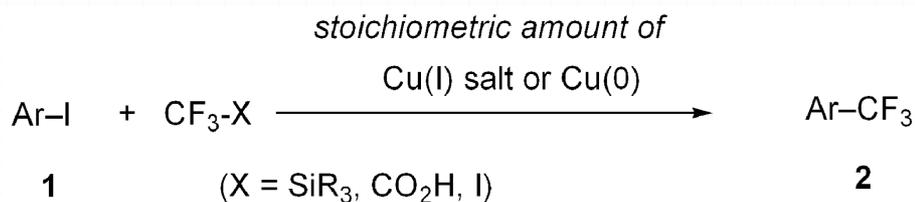
### [Putative Mechanism]



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## Aromatic trifluoromethylation catalytic in copper (1)

### Urata and Fuchikami's Works



**Drawback of the protocols is the loading of CuI (1–1.5 equiv.) to complete the desired reactions.**

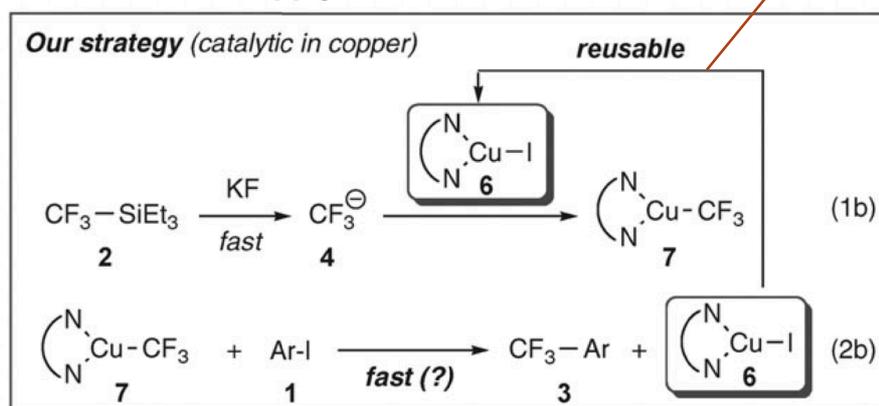
### Amii's Work



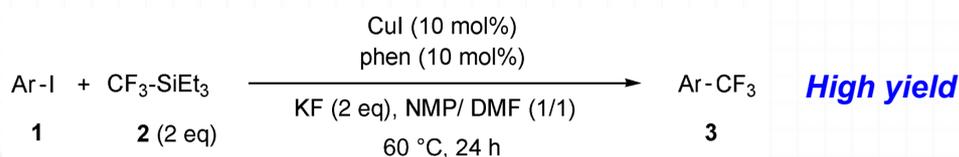
Amii, H. *et al. Chem. Commun.* **2009**, 1909. 31

## Aromatic trifluoromethylation catalytic in copper (2)

**Due to the sluggish regeneration of CuI in the second step, the net transformation cannot supply sufficient amount of CuI.**



**[Diamine ligand]**  
 increase electron density at the metal centers  
 improve the nucleophilicity of the CF<sub>3</sub>  
 stabilize the soluble Cu(I) complexes

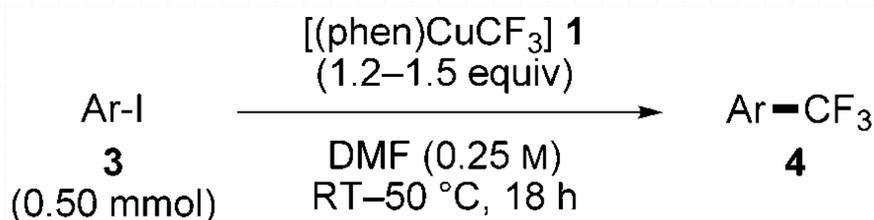
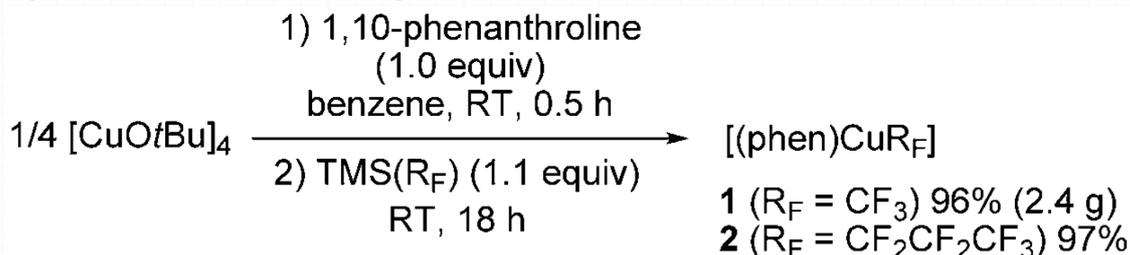


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## A Broadly Applicable Copper Reagent

Hartwing, J. F. *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 3793.

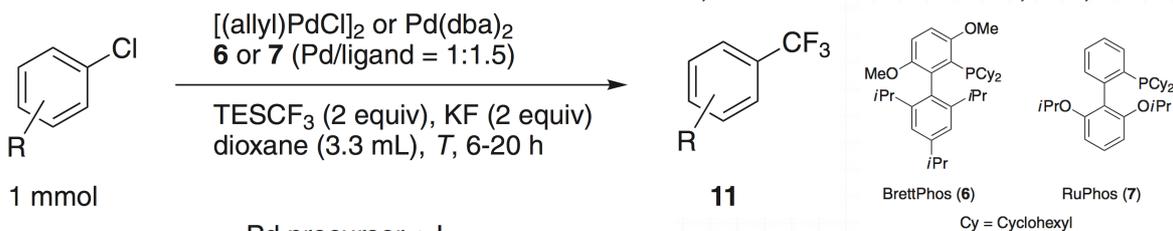
### Synthesis of 1,10-phen.-ligand



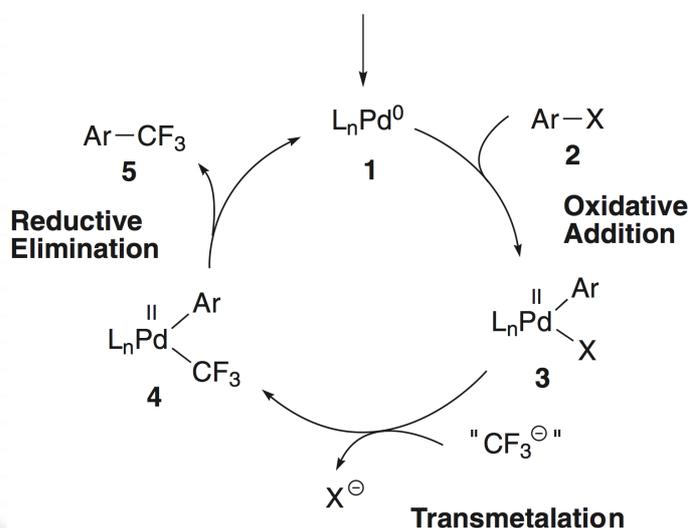
Up to 99% yield 33

## Palladium-Catalyzed Trifluoromethylation

Buchwald, S. L. *et al. Science* **2010**, *328*, 1670.



**No catalytic system with this system was reported.**



See also  
Grushin, V. V. *et al. JACS*,  
2006, *128*, 12644.

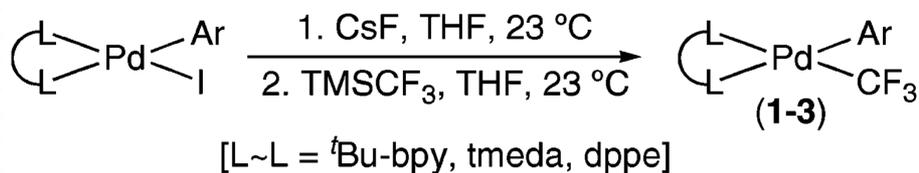
**They use quantitative amount of [(Xantphos)Pd(CF<sub>3</sub>)Ph].**

## Aryl-CF<sub>3</sub> Bond-Forming Reductive Elimination (1)

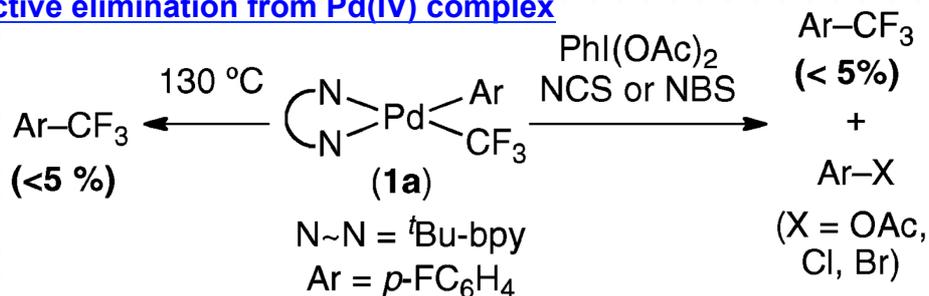
Sanford, M. S. *et al.* *JACS.* **2010**, *132*, 2878.

Pd(II)-mediated ArylCF<sub>3</sub> bond-forming reactions remain limited by the requirement for specialized and expensive phosphine ligands, relatively high reaction temperatures, and the need for expensive Et<sub>3</sub>SiCF<sub>3</sub>.

### Synthesis of Pd(II) complexes



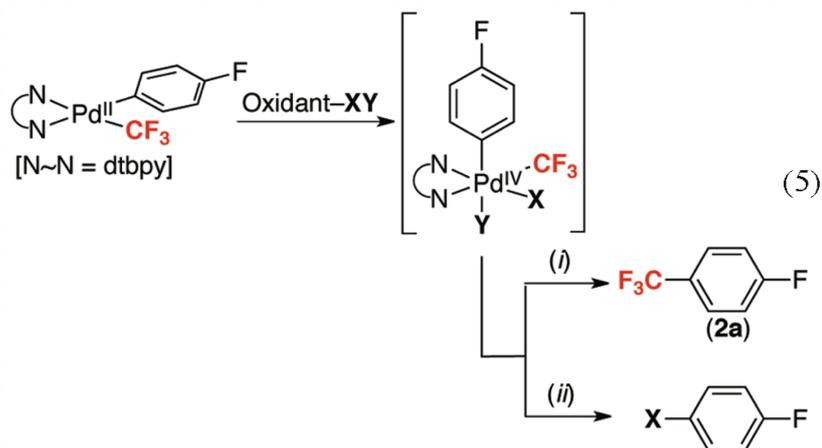
### Reductive elimination from Pd(IV) complex



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## Aryl-CF<sub>3</sub> Bond-Forming Reductive Elimination (2)

Sanford, M. S. *et al.* *JACS.* **2011**, *133*, 7577.



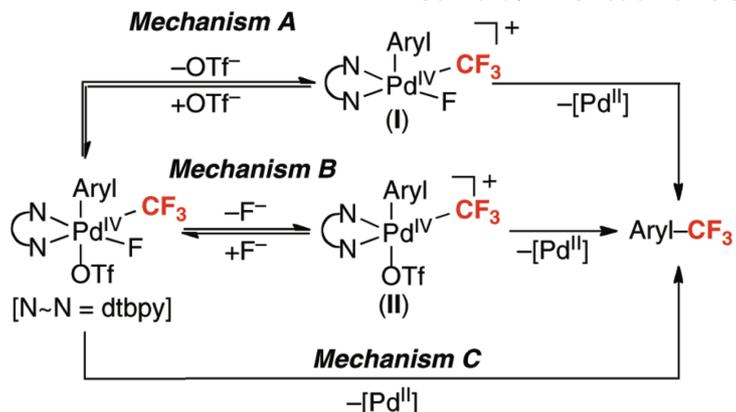
Fluoride (the X-type ligand introduced to Pd(IV) by F<sup>+</sup>sources) might undergo slower reductive elimination than CF<sub>3</sub>.



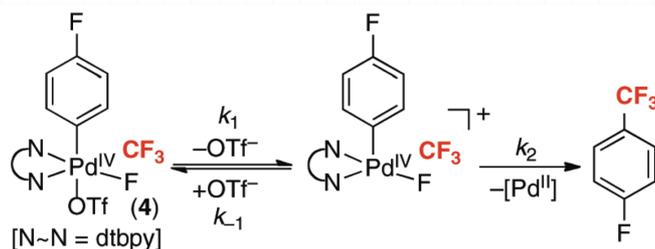
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## Aryl-CF<sub>3</sub> Bond-Forming Reductive Elimination (3)

Sanford, M. S. et al. *JACS*. 2011, 133, 7577.



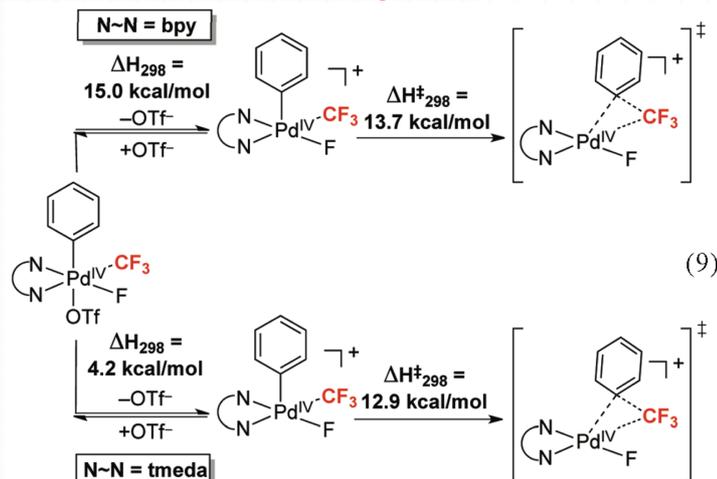
**The addition of 1 equiv of NBu<sub>4</sub>OTf to the thermolysis of 4 significantly slowed the initial rate of formation of Ar-CF<sub>3</sub>.**



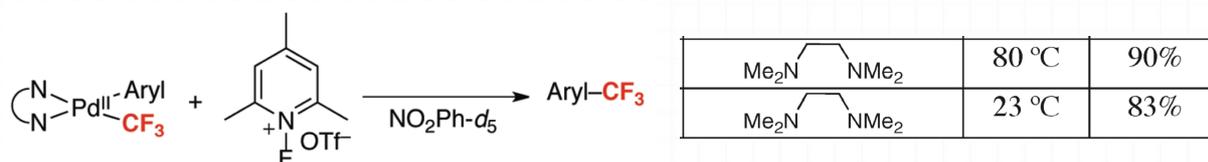
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## Aryl-CF<sub>3</sub> Bond-Forming Reductive Elimination (4)

• Room Temperature Arene Trifluoromethylation



• Reactivity of (tmeda)Pd(Aryl)(CF<sub>3</sub>) Complexes



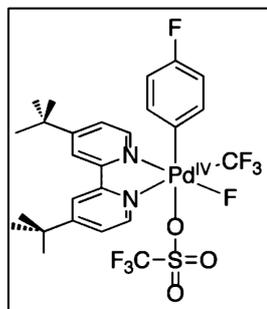
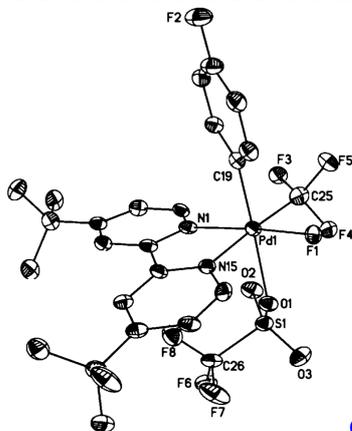
Sanford, M. S. et al. *JACS*. 2011, 133, 7577. 38

## Aryl-CF<sub>3</sub> Bond-Forming Reductive Elimination (5)

Sanford, M. S. *et al.* *JACS.* **2011**, *133*, 7577.

Sanford, M. S. *et al.* *JACS.* **2010**, *132*, 2878.

The first isolated example of a Pd(IV) complex containing a perfluoroalkyl ligand.



octahedral Pd(IV) species

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## Small Summary (2)

The most significant, conceptual advances over the past decade in the area of fluorination were made in the reactions that led to the formation of C-F and C-CF<sub>3</sub> bonds, most prominently by organo- and transition-metal catalysis.

The most challenging transformation remains the formation of the parent C-F bond, primarily due to

1. the high hydration energy of fluoride,
2. strong metal-fluorine bonds,
3. and the highly polarized nature of bonds to fluorine.

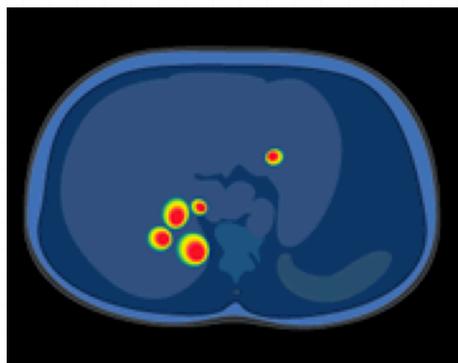


Fluorination reactions still lack general predictability and practicality.

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## Contents

1. Introduction
2. Fluorination
3. Difluoromethylation
4. Trifluoromethylation
5. Summary



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## Positron Emission Tomography (PET)

Positron emission tomography (PET) is a noninvasive imaging technology used to observe and probe biological processes in vivo.

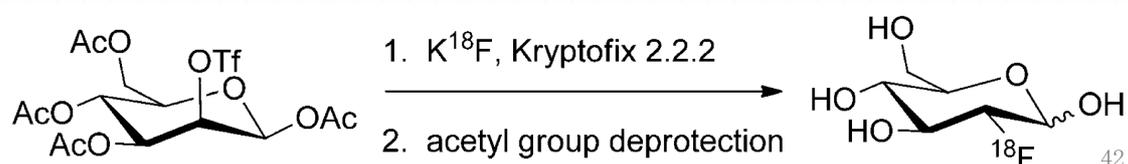
Although several **positron-emitting isotopes** can be used for PET imaging, fluorine-18 ( $^{18}\text{F}$ ) is the most clinically relevant radioisotope.

( $^{15}\text{O}$  : 2 min,  $^{13}\text{N}$  : 10min,  $^{11}\text{C}$  : 20 min,  $^{18}\text{F}$  : 110 min)



**Conventional [ $^{18}\text{F}$ ]fluoride chemistry has been limited to nucleophilic fluorination reactions.**

### ✧ Nucleophilic radiochemical fluorination with [ $^{18}\text{F}$ ]fluoride

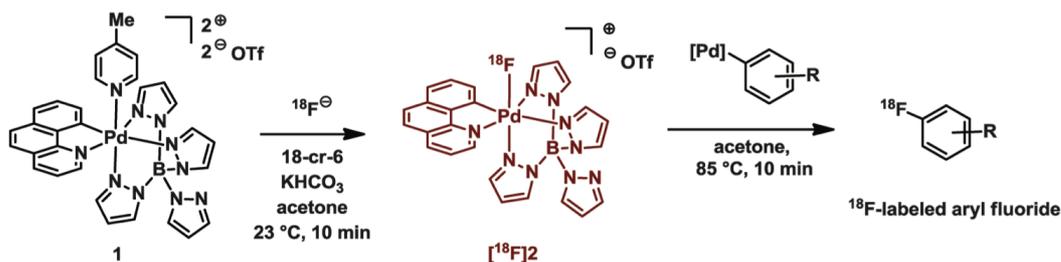


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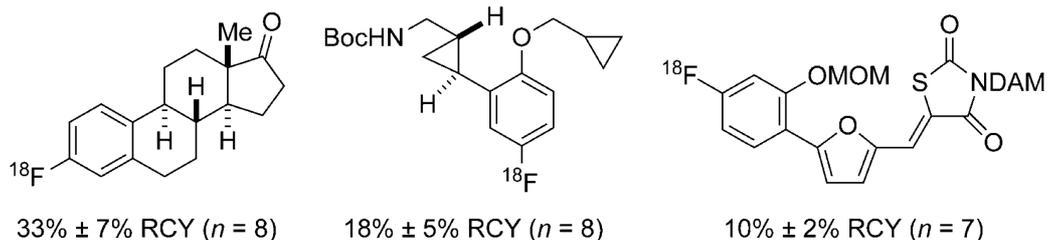
## Late-Stage Fluorination Reagent for PET Imaging

Ritter, T. *et al. science* 2011, 334, 639.

### [Electrophilic $^{18}\text{F}$ -Pd(IV) fluorinating reagent]



### • Late-stage fluorination to form $^{18}\text{F}$ -labeled aryl fluorides



- ✓ overall synthesis time of less than 60 min.
- ✓ Radiochemical yields (RCYs) as low as 5% can provide meaningful PET imaging

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## Small Summary (3)

Despite these limitations, modern fluorination methods have made fluorinated molecules more readily available than ever before.

In particular, the modern methods have started to have an impact on research areas that do not require large amounts of material, **such as drug discovery and PET.**

The ideal fluorination reaction would be **predictable, general, and functional-group tolerant, and a readily available, inexpensive catalyst.**

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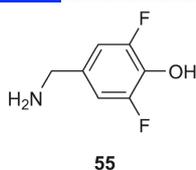
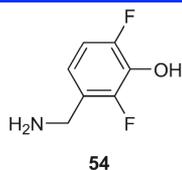
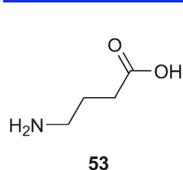
## References

T. Ritter, *et al.* *Angew. Chem. Int. Ed.* **2013**, *52*, 8214.

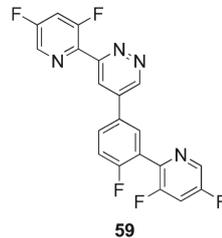
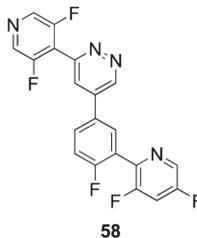
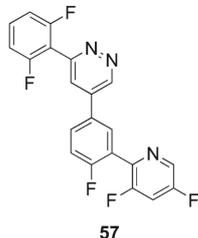
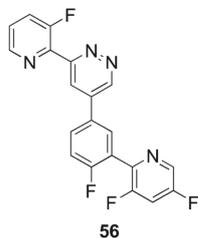
W. K. Hagmann, *J. of Med. Chem.* **2008**, *51*, 4359.

K. J. Hodgetts, *et al.* *Annual Reports in Medicinal Chemistry* **2010**, *45*, 429.

## Fluorine as a Bioisostere



Bioisosteric replacement  
for a carboxylate anion



**Table 9** Efficacy and rat pharmacokinetic data for fluorinated GABA<sub>A</sub> agonists

Compound	Ki (nM)			Efficacy				Rat PK		
	α1	α3	α5	α1	α2	α3	α5	Cl (ml/min/kg)	T <sub>1/2</sub> (h)	F(%)
56	0.5	1.4	2.4	-30%	—	0.4	—	—	—	—
57	0.1	0.4	0.3	-5%	—	0.24	—	—	—	—
58	1.8	6.3	6.0	-3%	0.28	0.39	-5%	59	1.6	50
59	1.5	8.5	12.1	-7%	0.12	0.44	0.01	1.3	53	88

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## Metabolic Stability (Experimental Date)

**Table 2.** Acetylcholine Release Enhancement Data

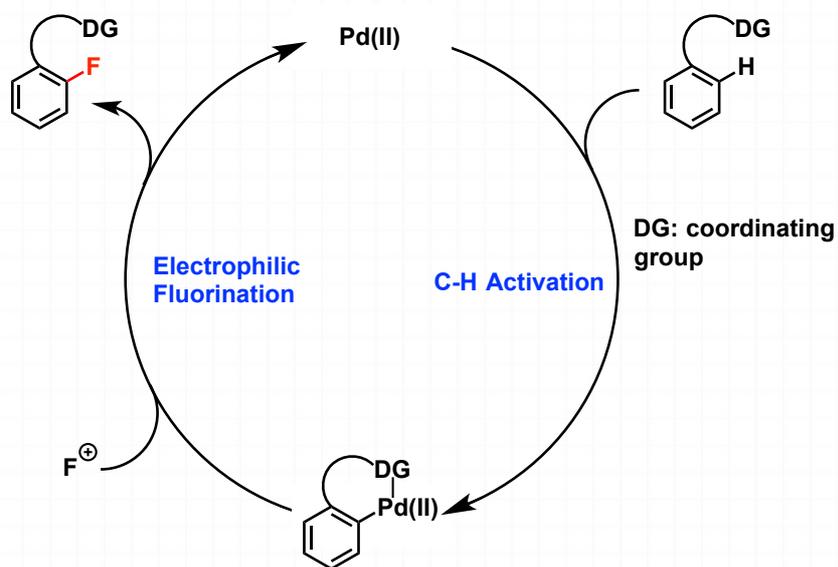
compd	in vitro ACh release EC <sub>50</sub> (μM)	in vitro ACh release max efficacy <sup>a</sup>	in vivo microdialysis ACh release (po)		
			dose, vehicle <sup>b</sup>	peak <sup>c</sup>	duration <sup>d</sup>
1 (linopirdine)	4.5 ± 1.24	337% at 10 μM	20, methocel	117 ± 36	140
			10, methocel	65 ± 13	80
			5, water	50 ± 16	20
2	4.12 ± 2.28	725% at 10 μM	10, methocel	IA	
			10, water	127 ± 31	100
			5, water	18 ± 15	NSP
3	0.45 ± 0.12	600% at 10 μM	10, methocel	27 ± 38	NSP
			10, water	52 ± 10	>40
			5, water	47 ± 32	NSP
4	10.0 ± 10.1	433% at 10 μM	5, methocel	75 ± 12	100
			10, methocel	44 ± 32	NSP
			5, methocel	201 ± 68	>80
5	1.08 ± 0.2	317% at 10 μM	1, methocel	74 ± 29	120
			1, methocel	115 ± 27	>120
			0.5, methocel	40 ± 21	NSP
6	0.41 ± 0.23	452% at 1 μM			
7	15.2 ± 6.67	326% at 10 μM			
8	1.60 ± 0.95	440% at 3 μM			
9	0.83 ± 0.28	413% at 3 μM			

<sup>a</sup> Percent control, control = 100%, at the dose specified; determined as described previously.<sup>47</sup> <sup>b</sup> Doses in mg/kg; methocel, compound suspended in 25% methocel in water and bead-milled overnight. <sup>c</sup> Percent increase over control, control = 0; IA, inactive. <sup>d</sup> Number of consecutive minutes at significance; NSP, no significant points.

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## General Scheme of Directed electrophilic fluorination

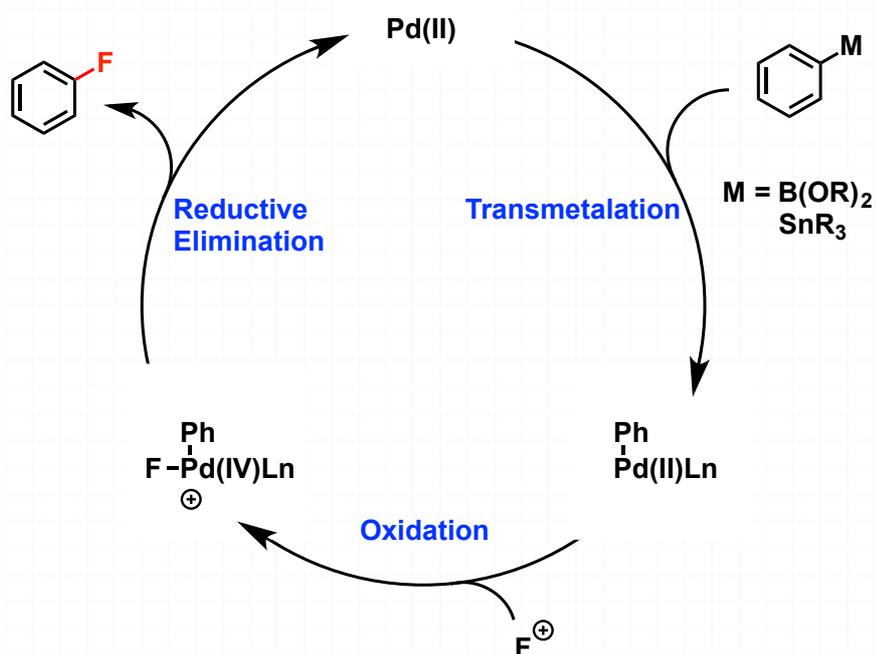
### Sanford & Yu's Works



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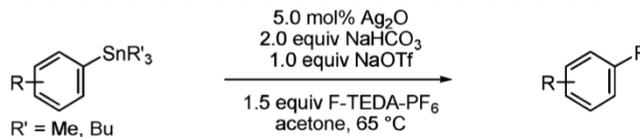
## General Scheme of electrophilic fluorination

### Ritter's Works

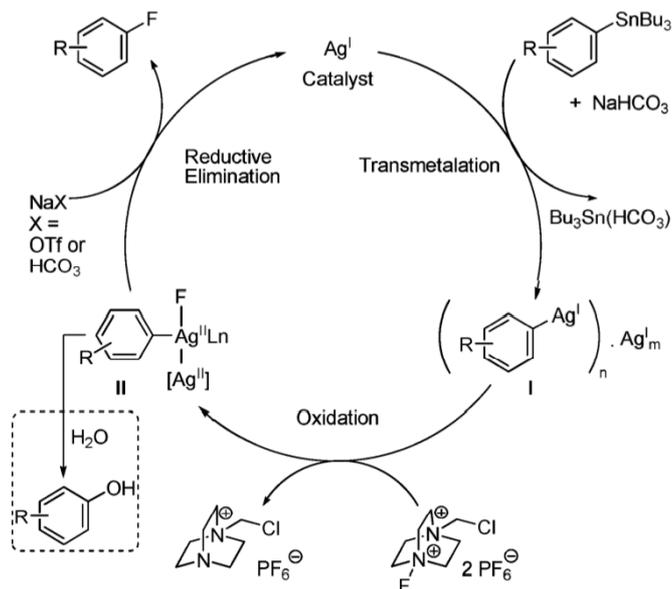


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## Silver-Catalyzed Fluorination



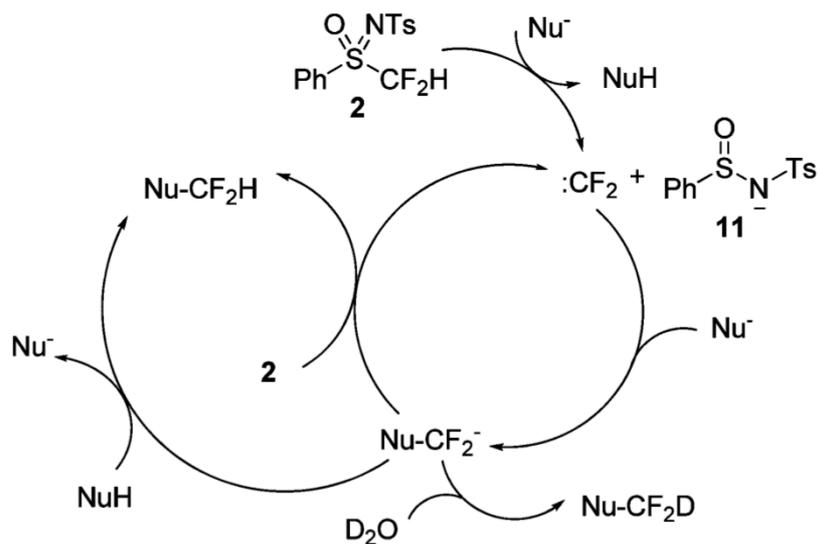
**Scheme 2.** Proposed Mechanism for Silver-Catalyzed Fluorination



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## Difluorination

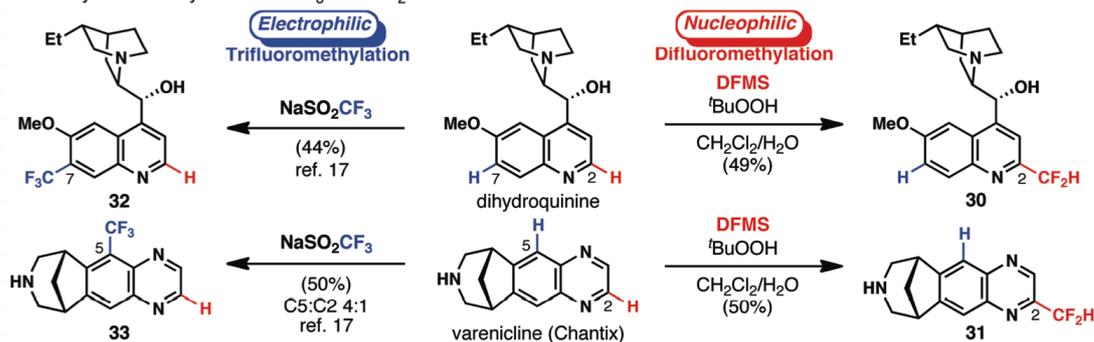
**Scheme 4.** Proposed Reaction Mechanism



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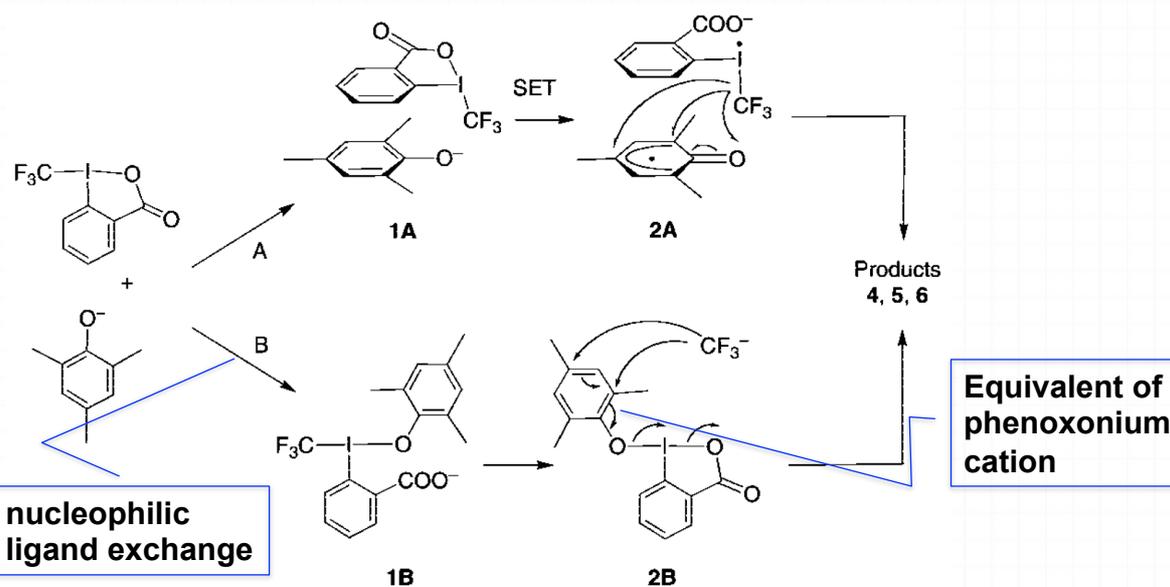
## Difluoromethylation and Trifluoromethylation

Reactivity of fluoroalkyl radicals:  $\cdot\text{CF}_3$  and  $\cdot\text{CF}_2\text{H}$



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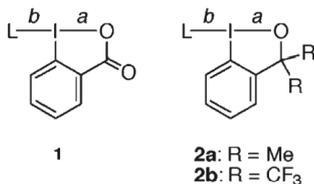
## Possible Mechanism of Toni's Reagent



The exact mechanisms for the trifluoromethylation have not been firmly established in many cases; the mechanism could occur **by two SET or one two-electron transfer concurrent with or followed by trifluoromethyl group transfer.**

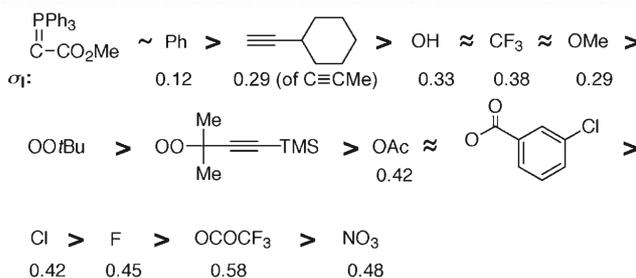
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## Possible Mechanism of Toni's reagent (1)



**Table 1:** Selected bond lengths in hypervalent  $\lambda^3$ -iodanes 1–4.

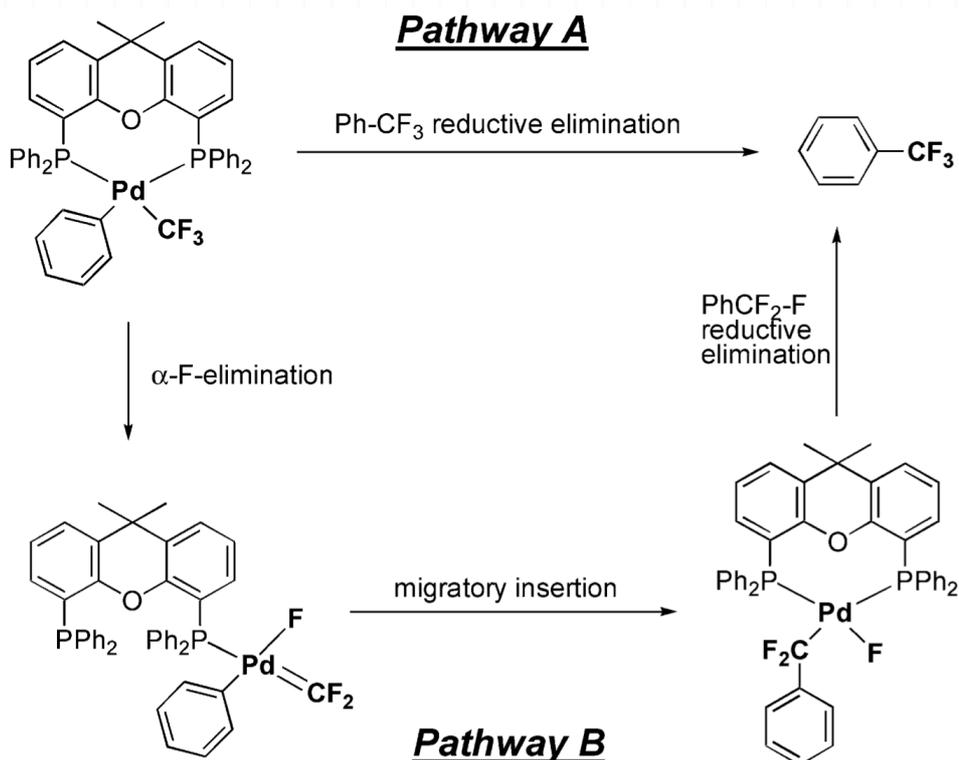
Entry	$\lambda^3$ -iodane (L)	Bond a [Å]	Bond b [Å]	$\sigma_1$	Ref.
1	1 (C(=PPh <sub>3</sub> )CO <sub>2</sub> Me)	2.484(2)	2.056(3)		[16]
2	1 (Ph)	2.478(4)	2.105(4)	0.12	[17]
3	1 (C≡C- <i>c</i> -C <sub>6</sub> H <sub>11</sub> )	2.34(1)	2.03(2)	0.29	[18]
4	1 (OH)	2.30	2.00	0.33	[19]
5	1 (CF <sub>3</sub> )	2.283(2)	2.219(4)	0.38	[20]
6	1 (OMe)	2.22(4)	1.98(4)	0.29	[21]
7	1 (OO <i>t</i> Bu)	2.181(5)	2.039(5)		[13a]
8	1 (OOCMe <sub>2</sub> C≡CSiMe <sub>3</sub> )	2.153(7)	2.032(6)		[22]
9	1 (OAc)	2.13(2)	2.11(2)	0.42	[23]
10	1 (OCOC <sub>6</sub> H <sub>4</sub> - <i>m</i> -Cl)	2.11	2.13		[24]
11	1 (Cl)	2.091(3)	2.461(1)	0.42	[25]
12	2a (Br)	2.050(5)	2.6927(8)	0.45	[26]
13	2b (CF <sub>3</sub> )	2.2014(15)	2.229(2)	0.38	[20]
14	2b (N <sub>3</sub> )	2.130(5)	2.182(7)	0.48	[27]
15	2b (Br)	2.118(6)	2.5945(11)	0.45	[26]
16	2b (Cl)	2.110(5)	2.438(2)	0.42	[25]
17	3a (OAc)	2.101(5)	2.234(4)	0.42	[6a]
18	3b (Cl)	2.06	2.56	0.42	[12]
19	3c (Cl)	2.113	2.563	0.42	[28]
20	3d (Ph)	2.455(6)	2.133(7)	0.12	[29]
21	4 (NHCO <i>i</i> Pr)	2.323(3)	2.010(4)	0.21	[6b]
22	4 (O <i>i</i> Pr)	2.271(2)	1.986(2)	0.34	[6a]



**Scheme 1.** Ligand order of decreasing *trans* influence in aryl  $\lambda^3$ -iodanes and Hammett inductive constants  $\sigma_1$ . TMS = SiMe<sub>3</sub>.

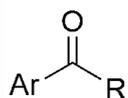
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## CF<sub>3</sub>-Ph Reductive Elimination

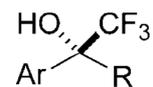


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## Nucleophilic CF<sub>3</sub>

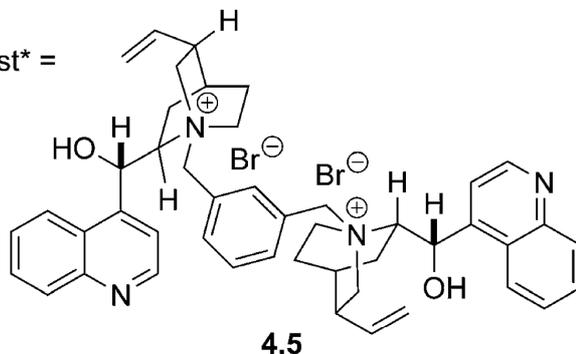


1. 10 mol% catalyst\*, 10 mol% TMAF, 2 equiv Me<sub>3</sub>SiCF<sub>3</sub>, 2:1 PhMe/CH<sub>2</sub>Cl<sub>2</sub>, 3–30 h, –60 °C
2. TBAF, H<sub>2</sub>O, THF, 1 h, 23 °C



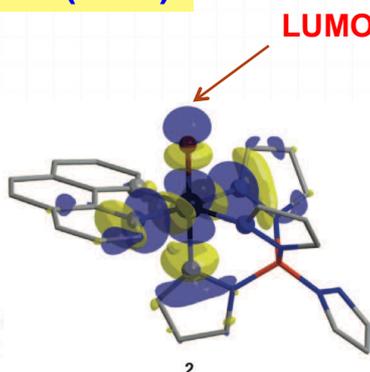
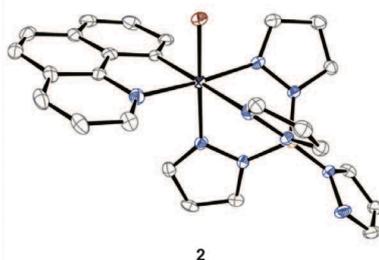
37–97%  
10–94% ee

catalyst\* =



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## Considerations of Pd-Complex (PET)



- ① carries three formal positive charges
- ② Late transition metals such as palladium, when in a high oxidation state, can function as an oxidant and transfer a ligand to a nucleophile.
- ③ Ligands are multidentate ligands that were selected to impart stability on both 1 and 2 toward undesired reductive processes.
- ④ An octahedral Pd(IV) complex was chosen to avoid undesired nucleophilic attack at the transition metal.
- ⑤ Multidentate ligands in 2 feature aromatic substituents to prevent nucleophilic attack on the carbon and nitrogen atoms coordinated to palladium.

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