



# *C-H Activated Trifluoromethylation*

**Reporter: Yan Fang**

**Superior: Prof. Yong Huang**

**Jun. 17<sup>th</sup> 2013**

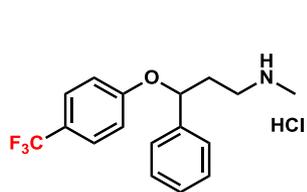
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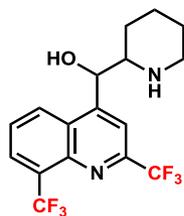
- *Background*
- *Trifluoromethylation of  $sp$ -Hybridized C-H Bonds*
- *Trifluoromethylation of  $sp^2$ -Hybridized C-H Bonds*
- *Trifluoromethylation of  $sp^3$ -Hybridized C-H Bonds*
- *Summary & Acknowledgement*

# Background:

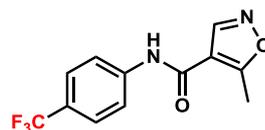
## ➤ Commercially Available Pharmaceuticals



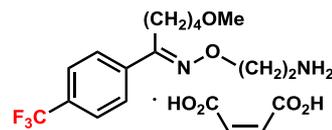
Prozac (antidepressant)



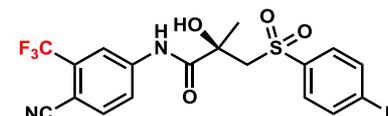
Lariam (antimalarials)



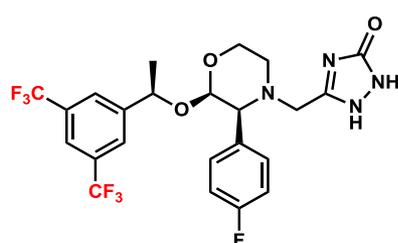
Arava (immunomodulatory)



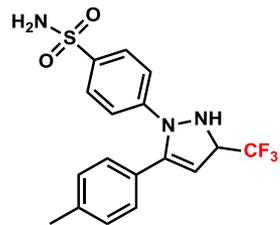
Luvox (antidepressant)



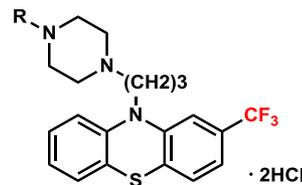
Casodex (anticancer)



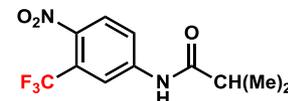
Emend (antiemetic)



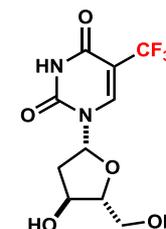
Celebrex (antiinflammatory)



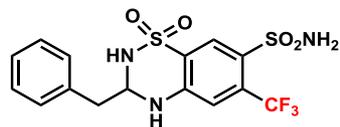
Prolixin (R = -(CH<sub>2</sub>)<sub>2</sub>OH, antipsychotic)  
Stelazine (R = -CH<sub>3</sub>, antipsychotic)



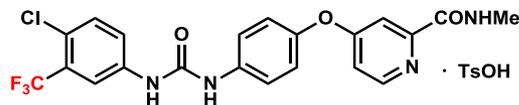
Eulexin (anticancer)



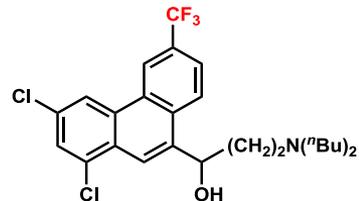
Viroptic (antiviral)



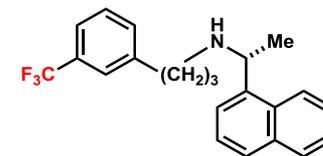
Naturetin (antihypertensive)



Nexavar (anticancer)



Halfan (antimalarial)

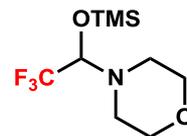
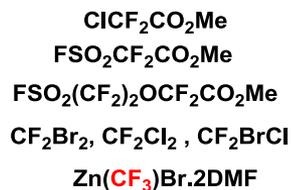
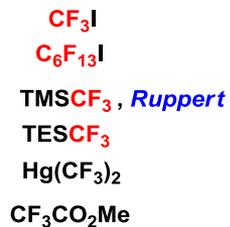


Sensipar (calcimimetic)

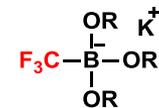
# Background:

## ➤ Trifluoromethyl Sources

### nucleophilic reagents



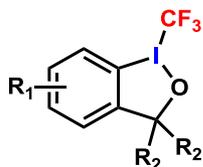
*Langlois*



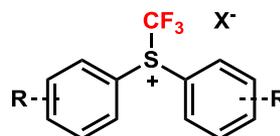
R = Me, Bn,  $\text{CH}_2\text{CH}_2\text{OMe}$   
2-methyltetrahydrofuran

*Gooben*

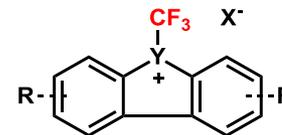
### electrophilic reagents



$\text{R}_1=\text{H}$ ,  $\text{R}_2=\text{Me}$   
 $\text{R}_1=\text{H}$ ,  $\text{R}_2=\text{O}$ , *Togni*  
 $\text{R}_1=\text{H}$ ,  $\text{R}_2=\text{CF}_3$   
 $\text{R}_1=p\text{-Me}$ ,  $\text{R}_2=\text{CF}_3$



X =  $\text{BF}_4$ , OTf



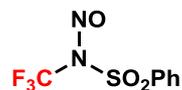
X =  $\text{BF}_4$ , OTf

R=H, Y=S, *Umemoto*  
Y=Se  
Y=Te

### radical reagents



X=Na, *Langlois*  
X=K  
X=( $\text{NH}_3$ )<sub>2</sub>



*Umemoto*



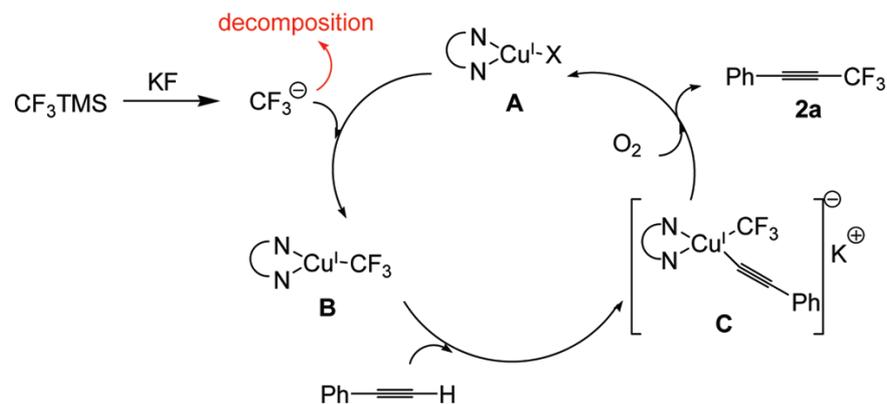
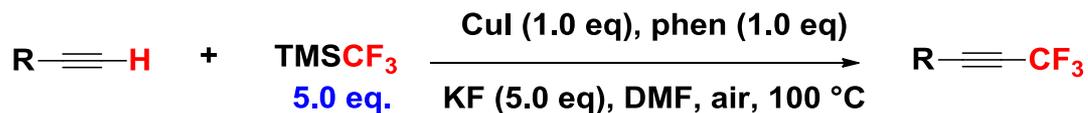
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# Sp C-H :

## Copper-Mediated Oxidative Trifluoromethylation of Terminal Alkynes



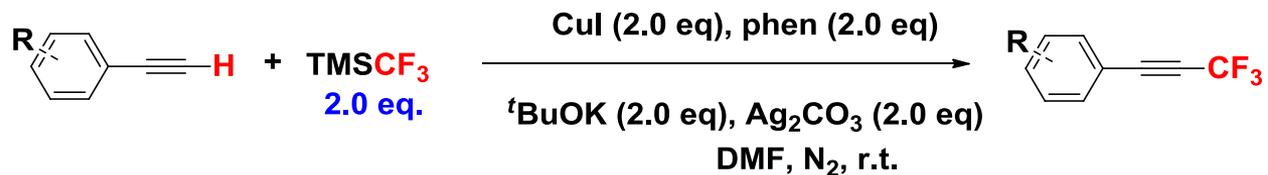
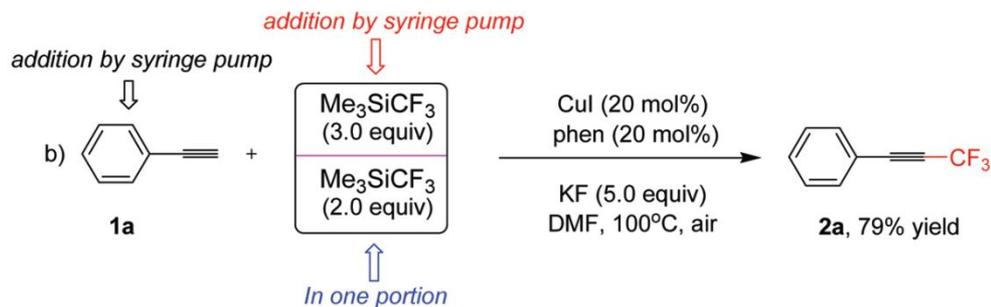
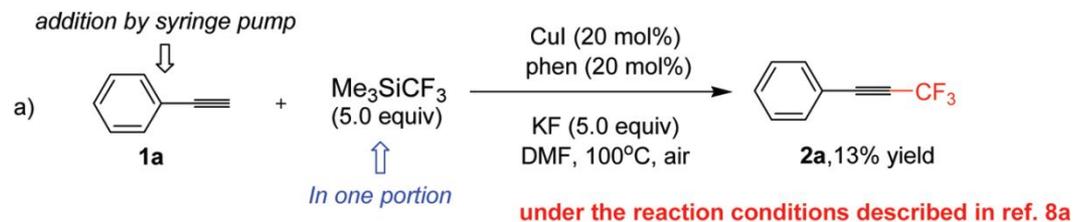
F.-L. Qing *J. Am. Chem. Soc.* **2010**, *132*, 7262–7263.

F.-L. Qing *Org. Lett.*, **2012**, *14*, 94–97.

F.-L. Qing *J. Org. Chem.* **2012**, *77*, 1251–1257.

# Sp C-H :

## Copper-Mediated Oxidative Trifluoromethylation of Terminal Alkynes



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- *Summary & Acknowledgement*

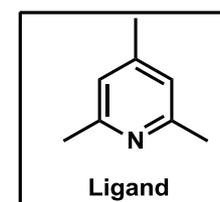
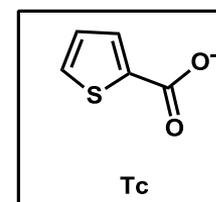
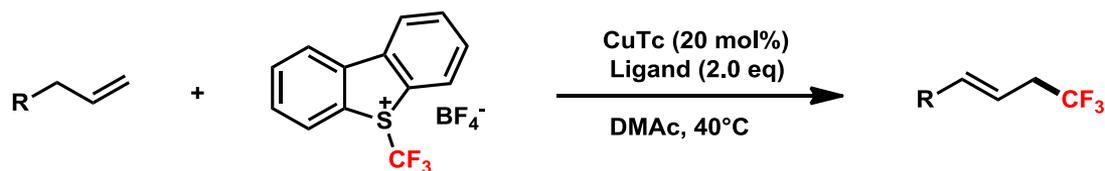
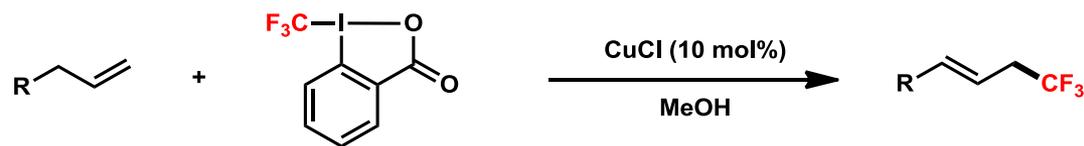
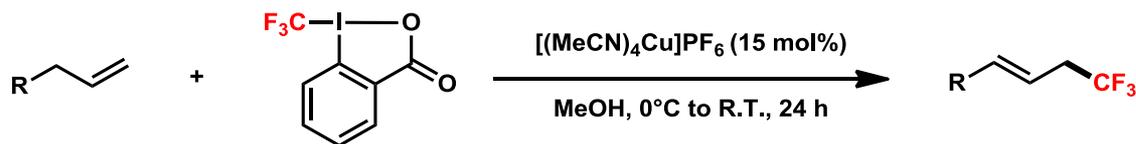
# *Sp<sup>2</sup> C-H Trifluoromethylation*



# *Sp<sup>2</sup> C-H (I):*

## *Copper-Catalyzed Trifluoromethylation of Terminal Alkenes*

### ➤ Electrophilic Trifluoromethylating



S. L. Buchwald *Angew. Chem. Int. Ed.* **2011**, *50*, 9120–912.

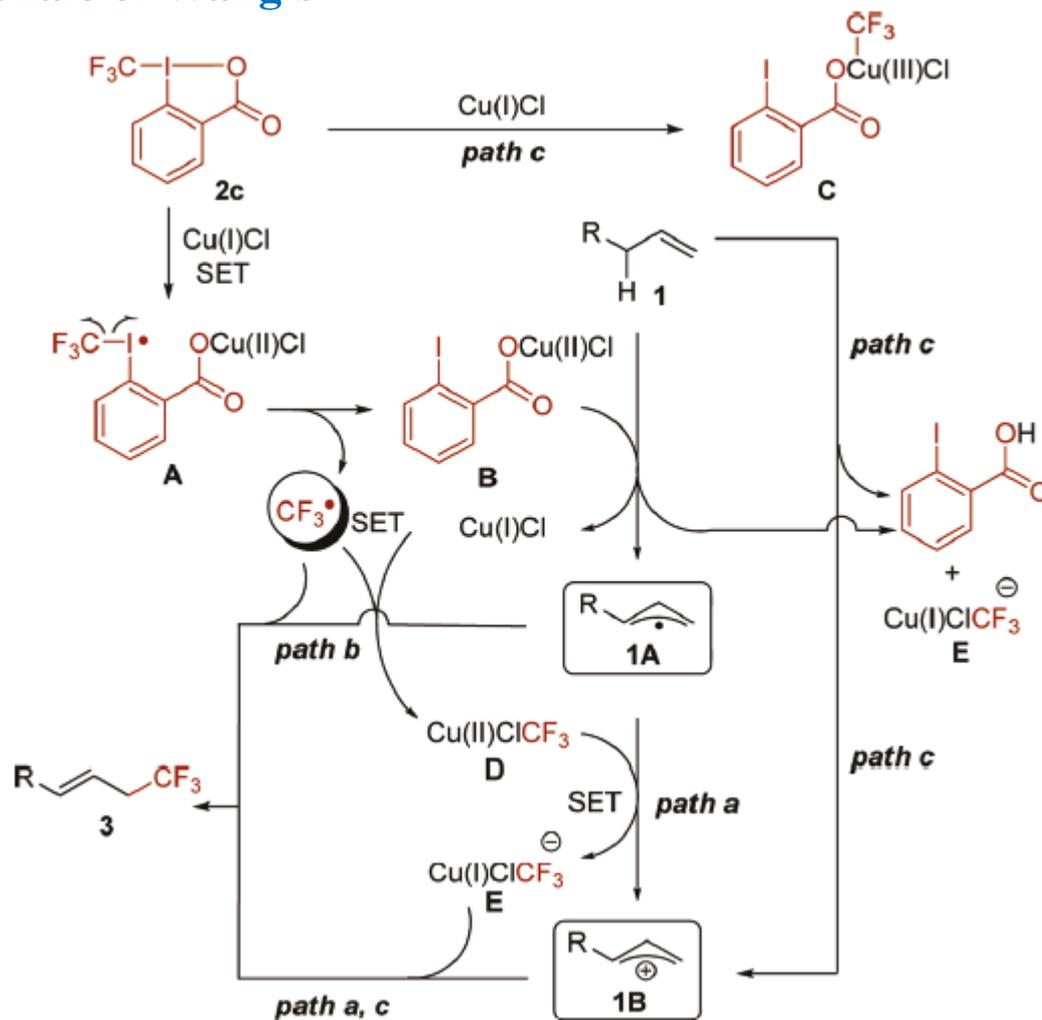
J.-B. Wang *J. Am. Chem. Soc.* **2011**, *133*, 16410–16413.

L. Liu *J. Am. Chem. Soc.* **2011**, *133*, 15300–15303. 3

# *Sp<sup>2</sup> C-H (I):*

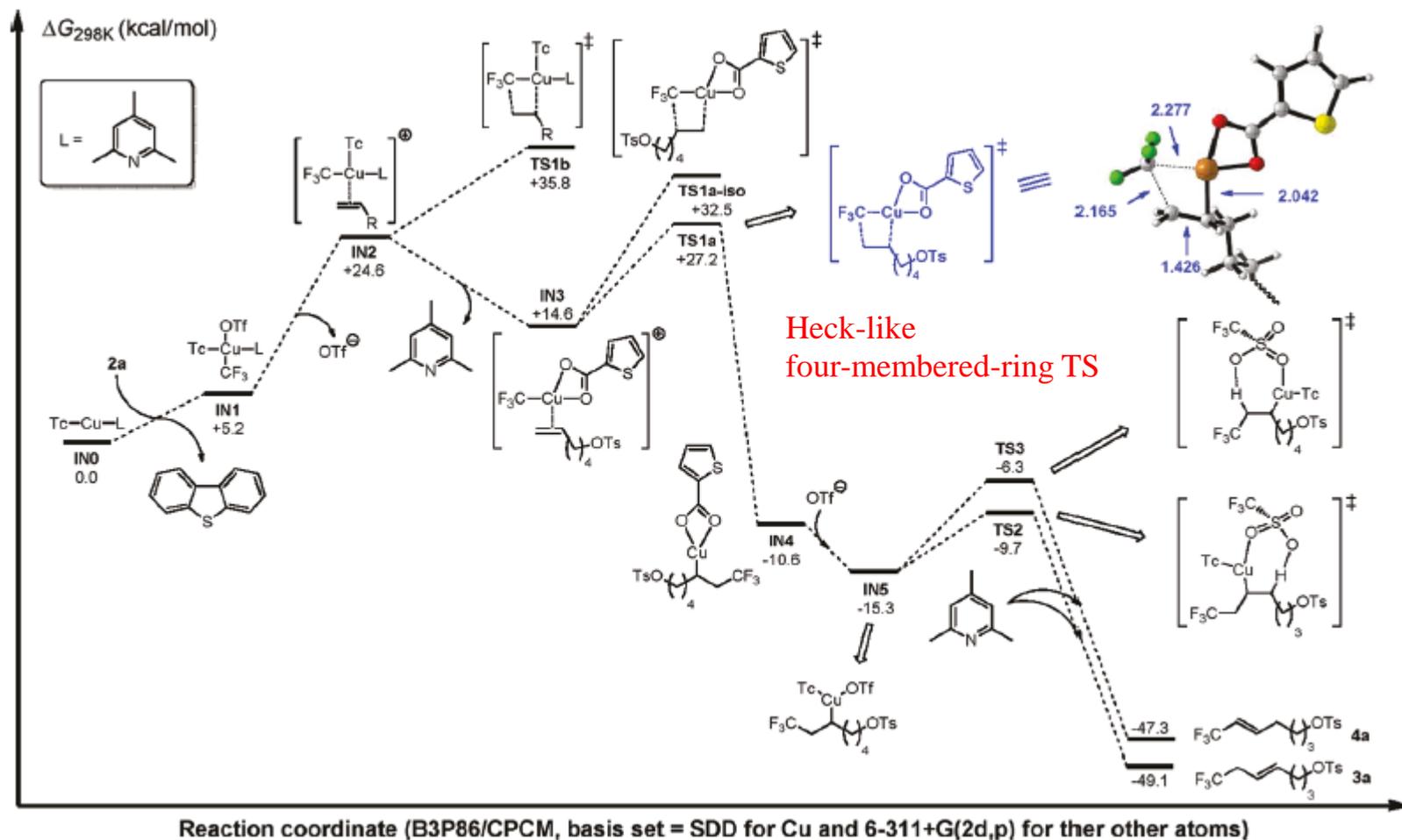
## *Copper-Catalyzed Trifluoromethylation of Terminal Alkenes*

### ➤ Mechanistic Rationale of Wang's



# *Sp<sup>2</sup> C-H (I): Copper-Catalyzed Trifluoromethylation of Terminal Alkenes*

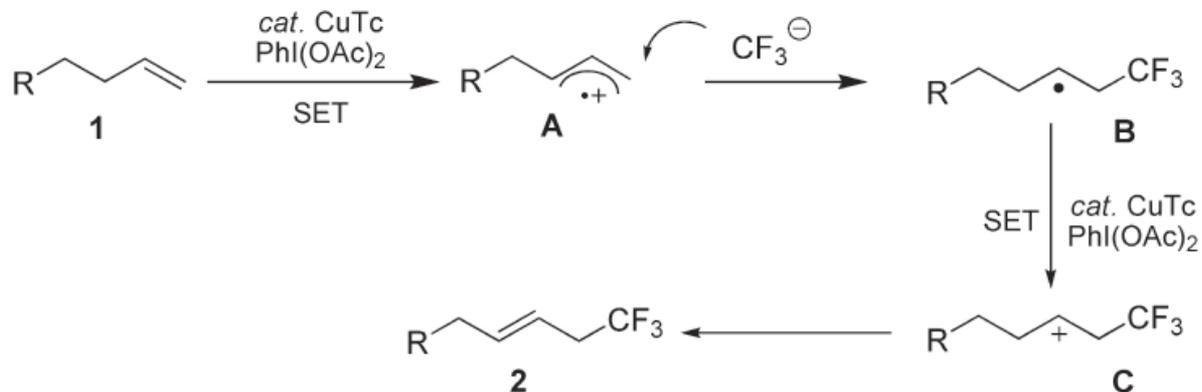
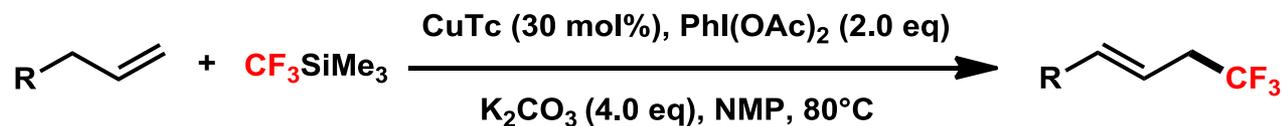
## ➤ Proposed mechanism and corresponding theoretical calculations of Liu's



# *Sp<sup>2</sup> C-H (I):*

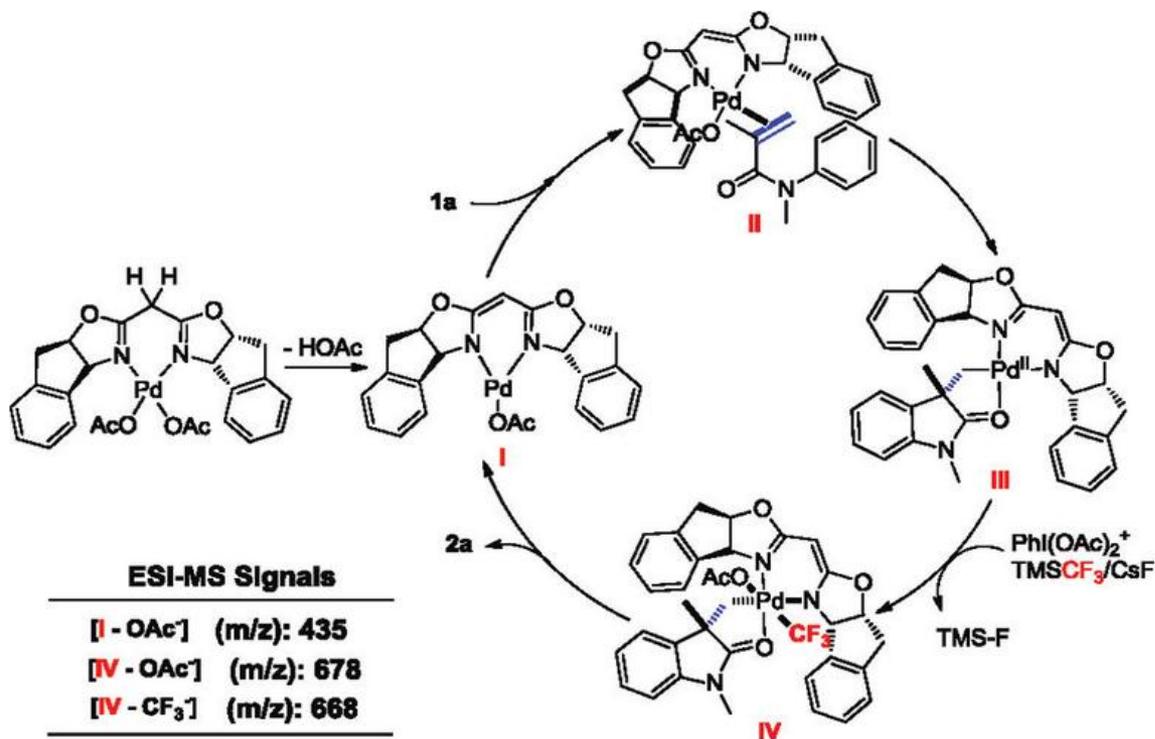
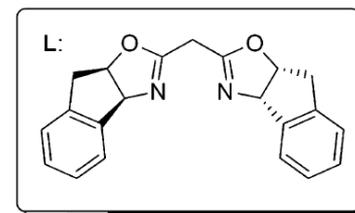
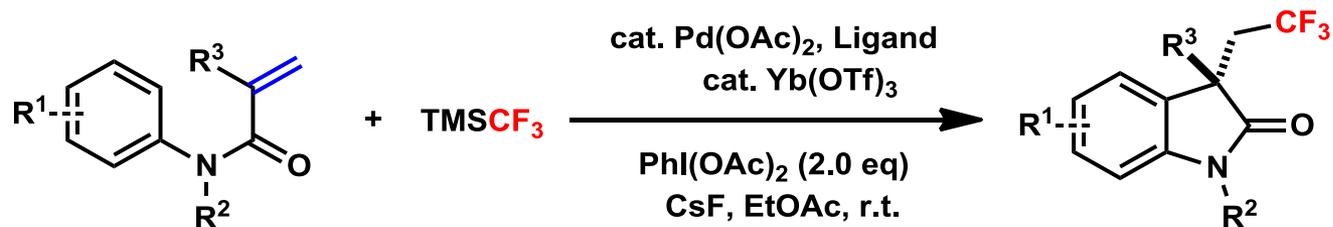
## *Copper-Catalyzed Trifluoromethylation of Terminal Alkenes*

### ➤ Nucleophilic Trifluoromethylating



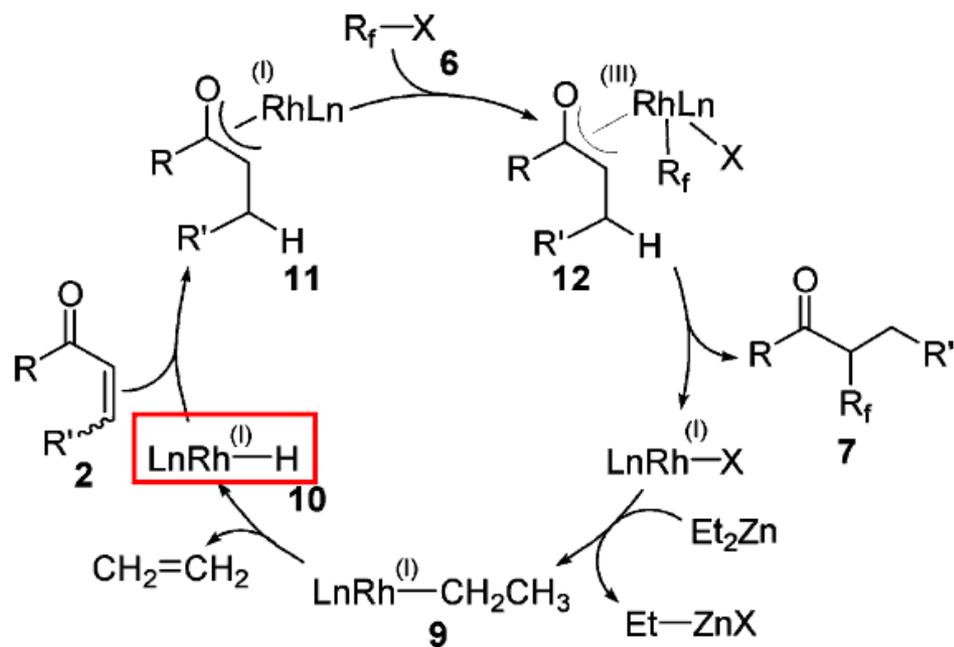
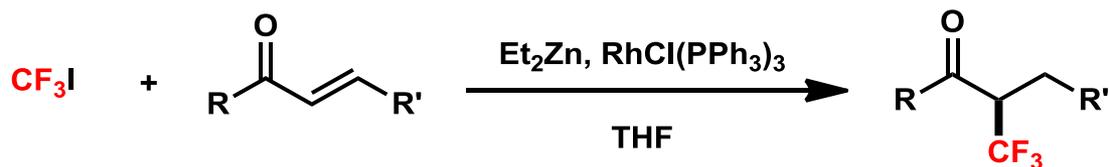
# *Sp<sup>2</sup> C-H (I):*

## *Palladium-Catalyzed Oxidative Trifluoromethylation of Activated Alkenes*

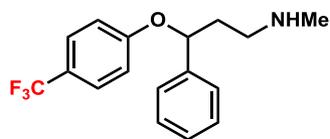
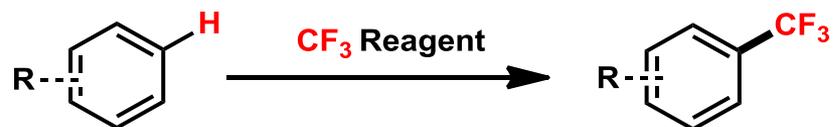


# *Sp<sup>2</sup> C-H (I):*

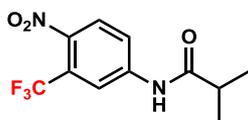
## *Rhodium-Catalyzed Trifluoromethylation of $\alpha, \beta$ -Unsaturated Ketones*



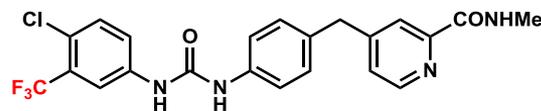
# *Sp<sup>2</sup> C-H Trifluoromethylation (II)*



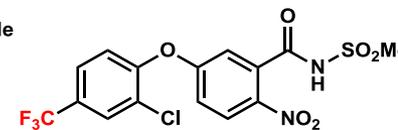
Fluoxetine



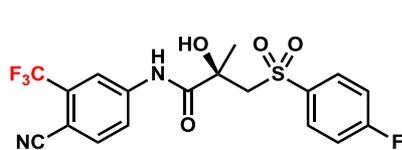
Flutamide



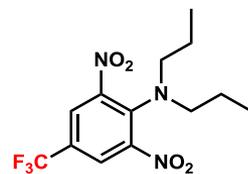
Sorafenib



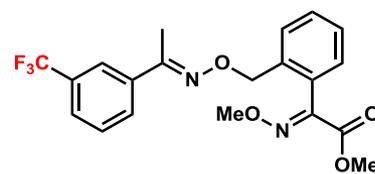
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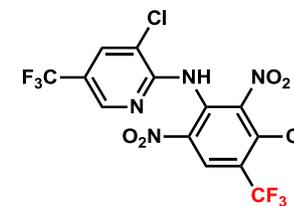
Casodex



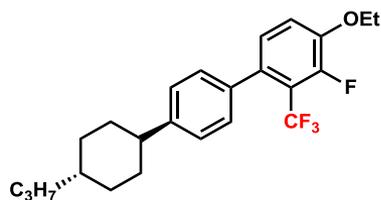
Trifluralin



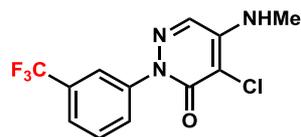
Trifloxystrobin



Fluazinam

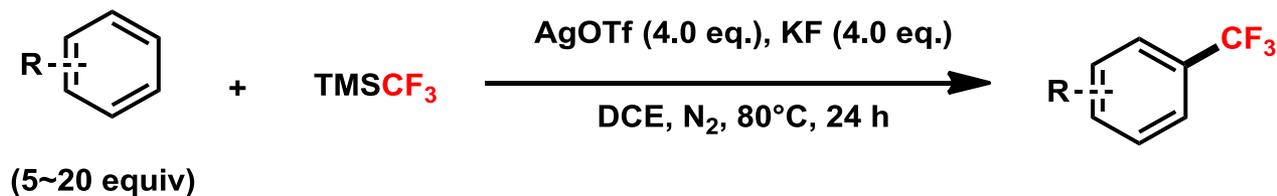


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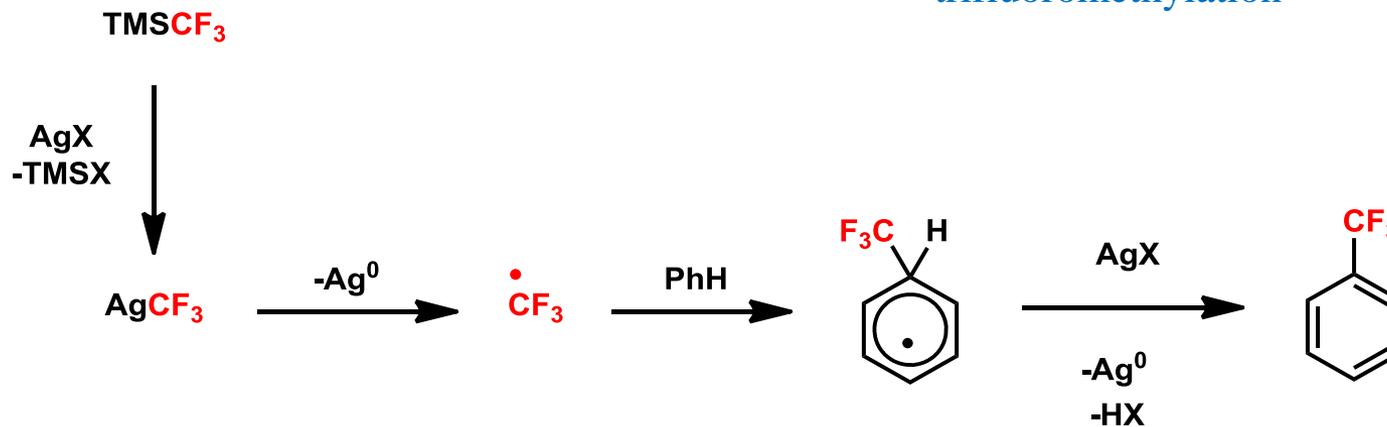


Norflurazon

## *Sp<sup>2</sup> C-H (II): Silver-Mediated Trifluoromethylation of Arenes*



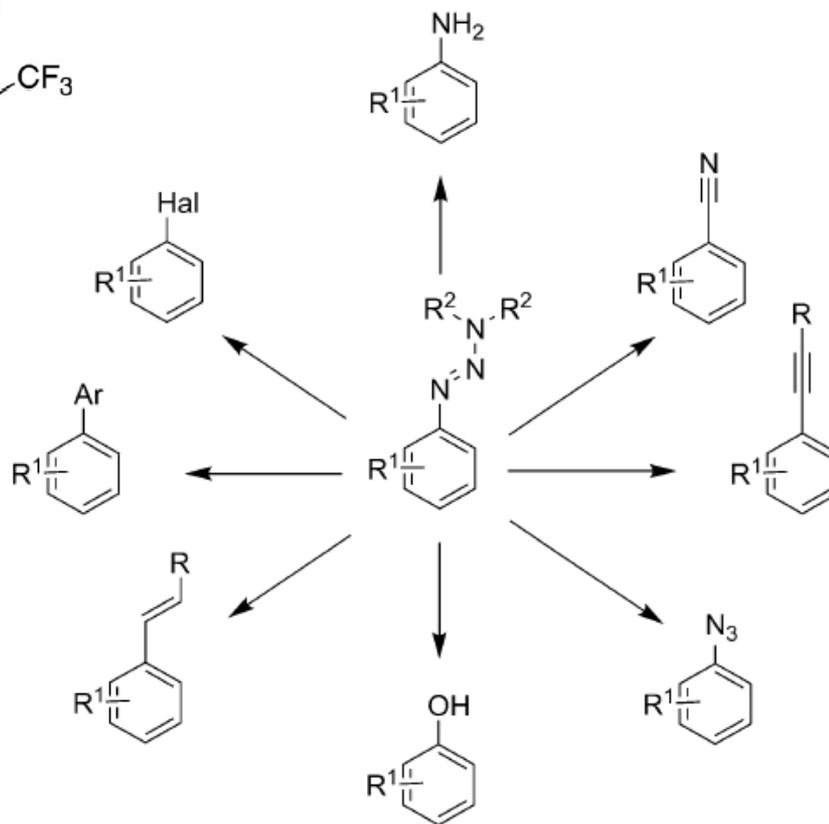
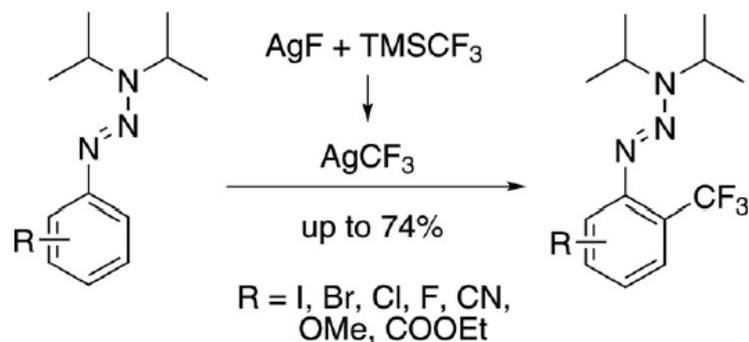
TMSCF<sub>3</sub> as a precursor to radical arene trifluoromethylation



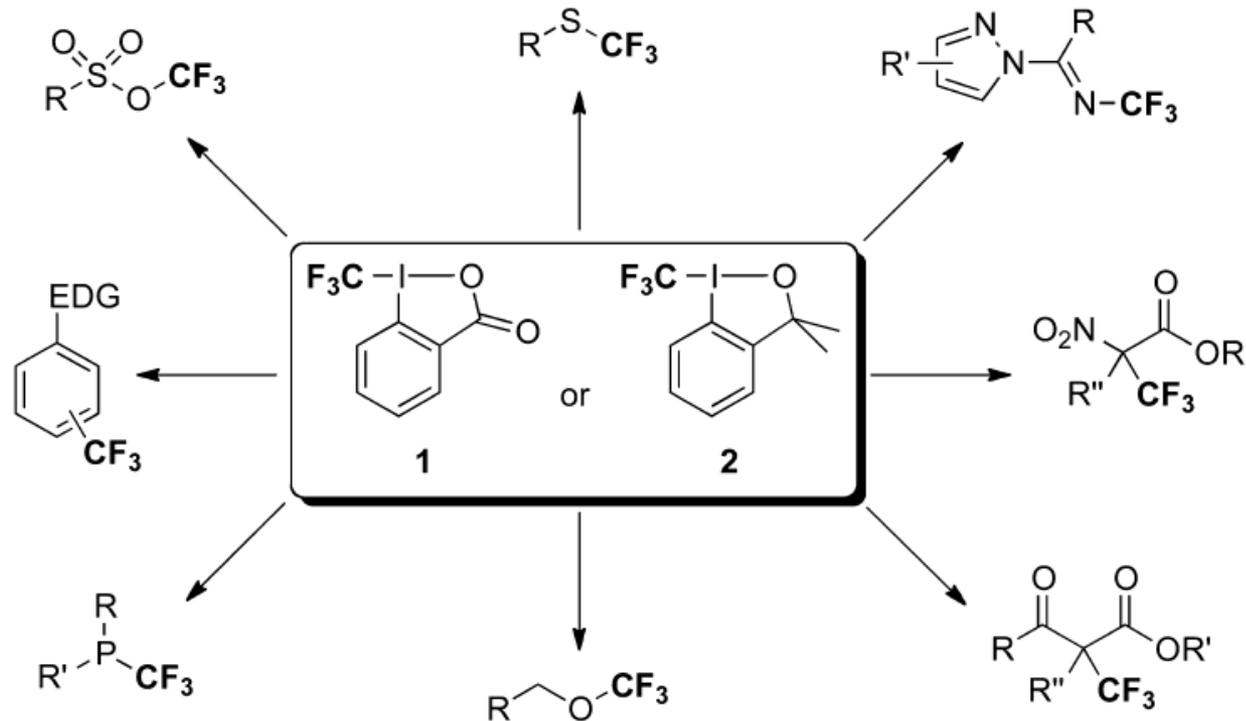
excess of required aromatic compound  
a low regioselectivity

## *Sp<sup>2</sup> C-H (II):*

### *Silver-Mediated Ortho-Trifluoromethylation of Functionalized Aromatic Triazenes*



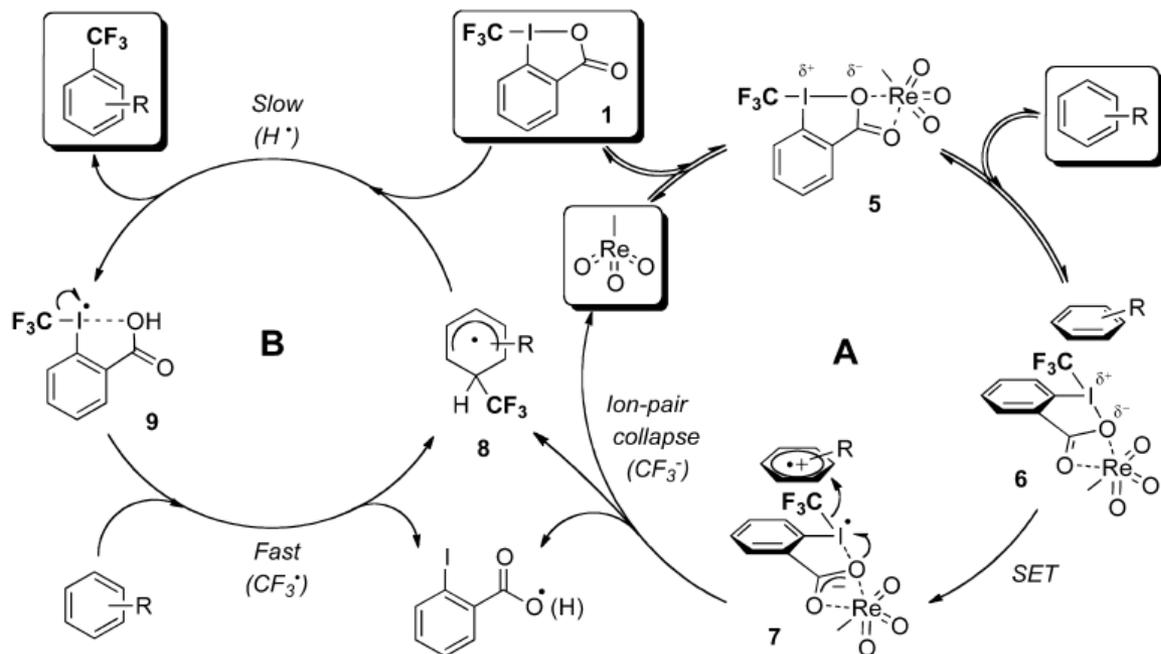
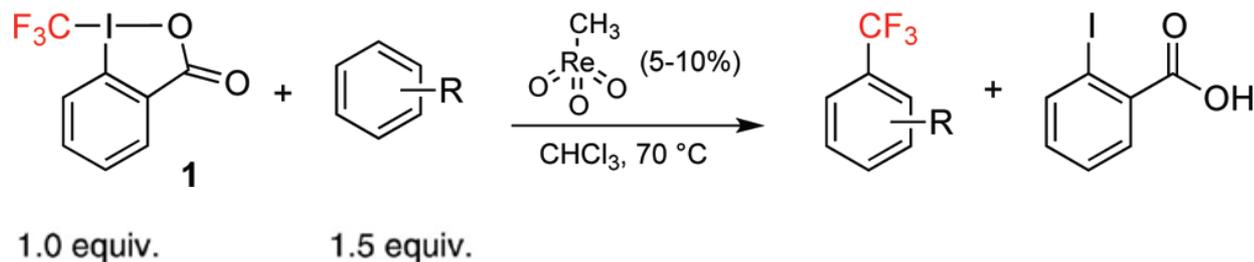
# *Sp<sup>2</sup> C-H Trifluoromethylation (II)*



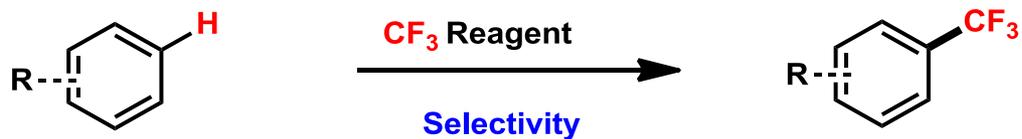
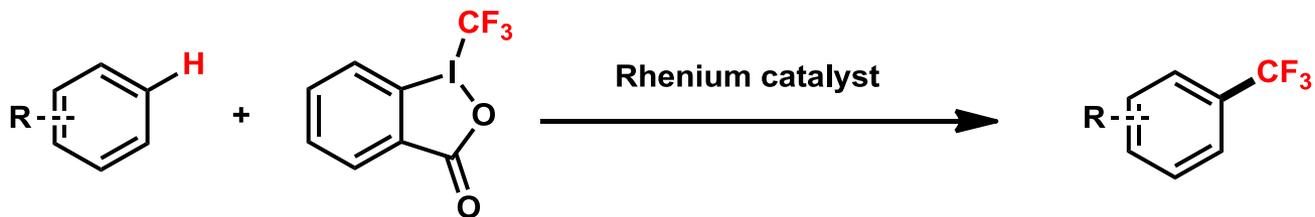
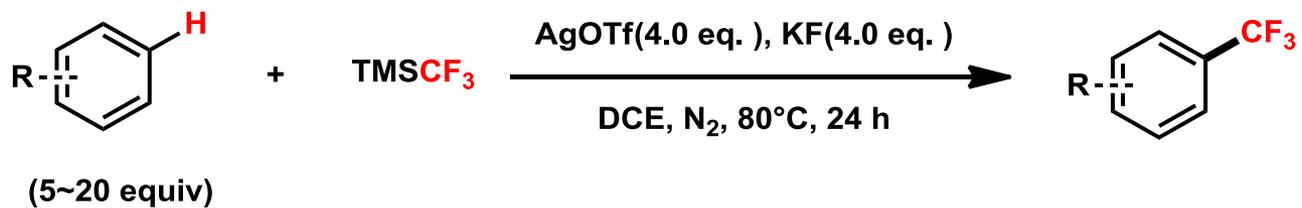
## *Sp*<sup>2</sup> C-H (II):

# Rhenium-Catalyzed Trifluoromethylation of Arenes and Heteroarenes

### ➤ using MTO as catalyst

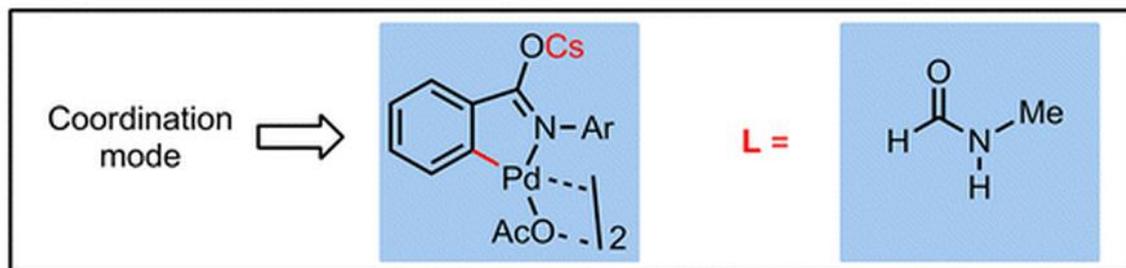
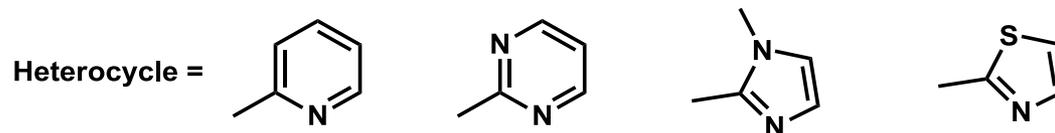
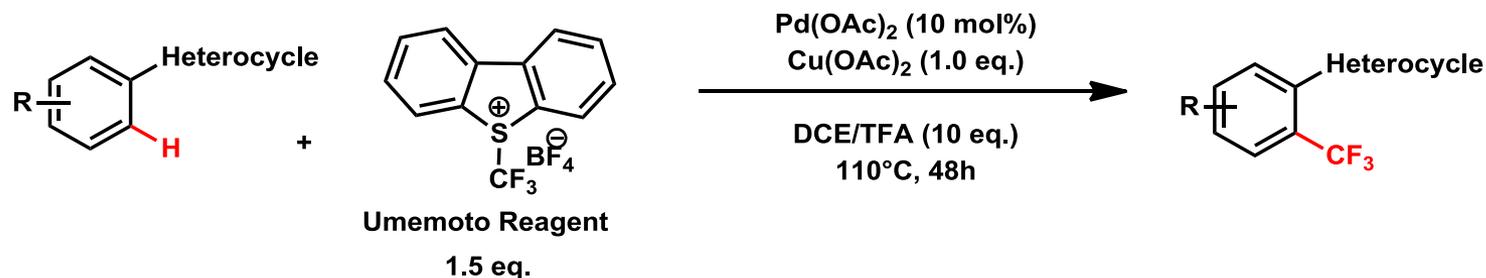


## *Sp<sup>2</sup> C-H Trifluoromethylation (II)*



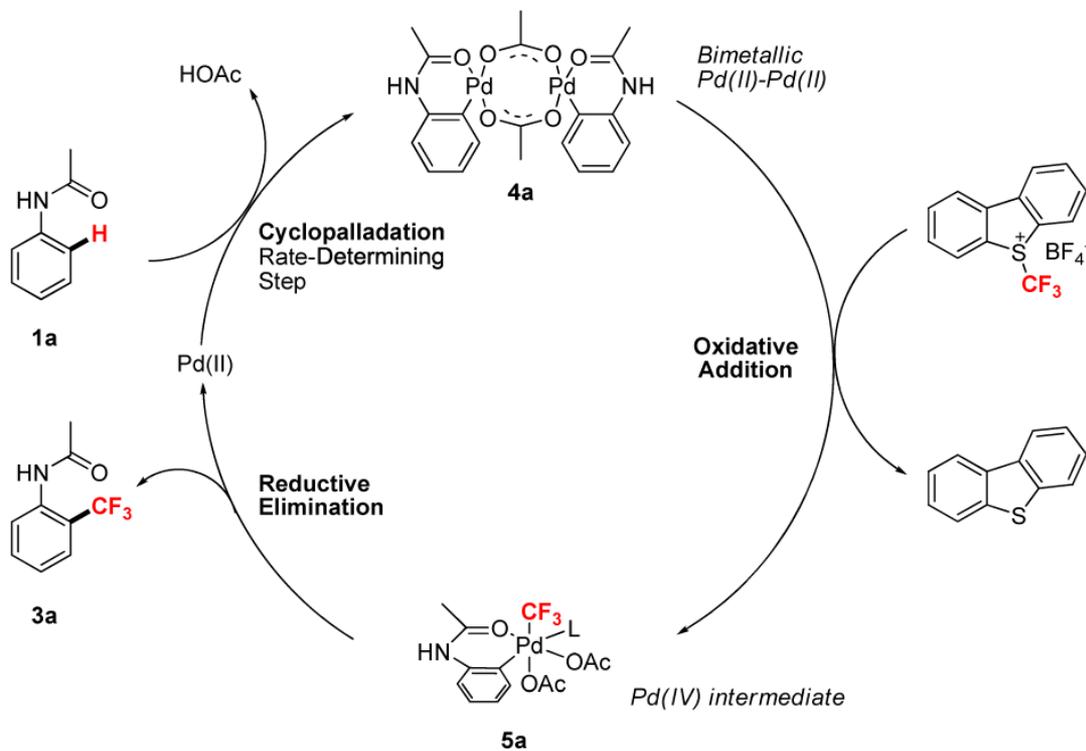
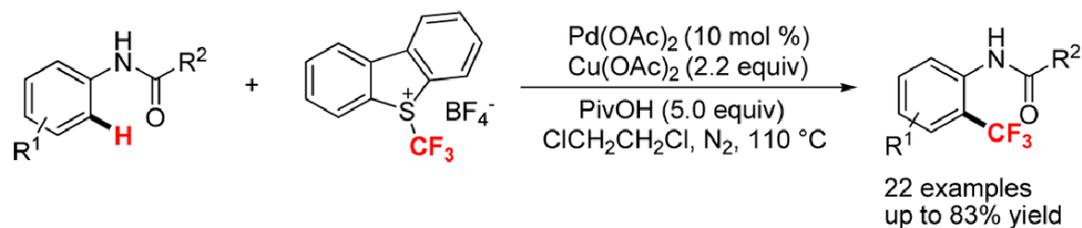
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### *Palladium-Catalyzed ortho-Trifluoromethylation of Arenes*



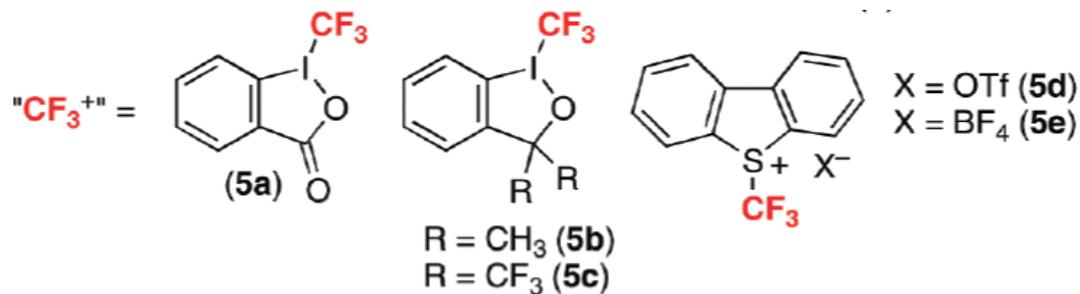
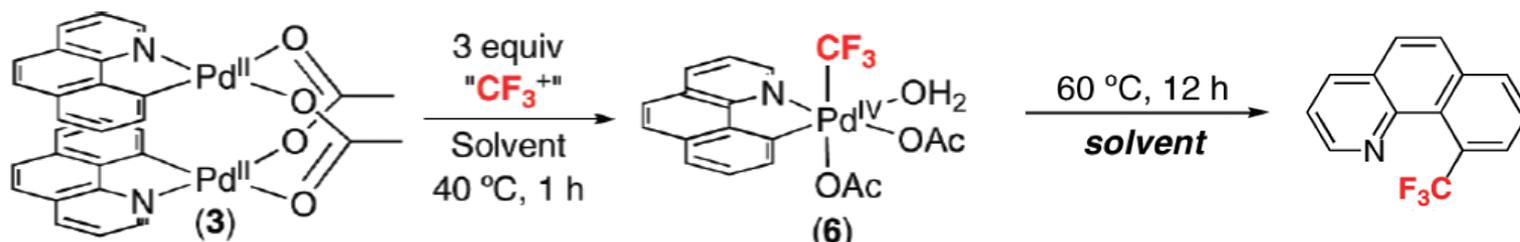
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# *Palladium-Catalyzed ortho-Trifluoromethylation of Arenes*



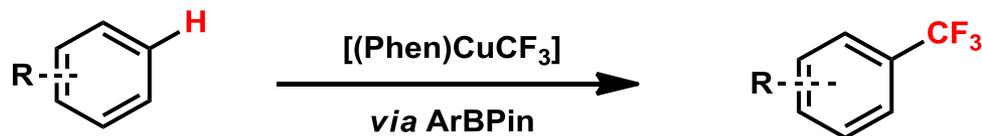
## *Sp<sup>2</sup> C-H (II):*

### *Trifluoromethylation with "CF<sub>3</sub><sup>+</sup>" reagents via a Monomeric Palladium(IV) Complex*

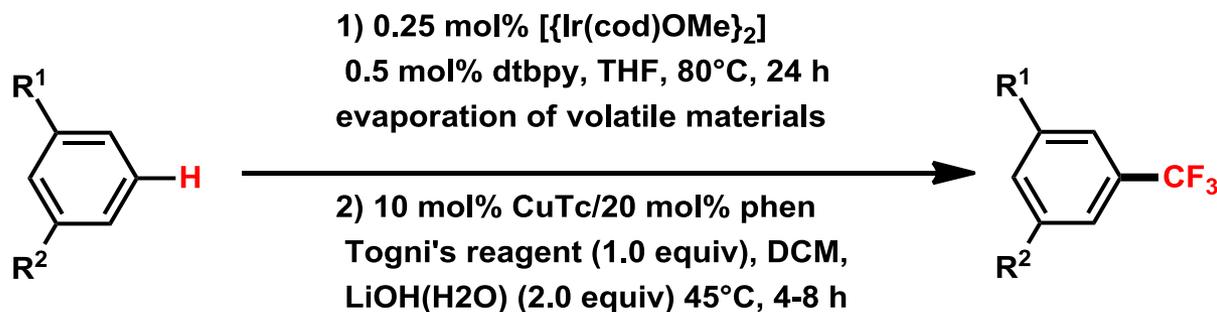


## *Sp<sup>2</sup> C-H (II):*

### *Iridium-Catalyzed Selective Trifluoromethylation of 1,3-Disubstituted Arenes*

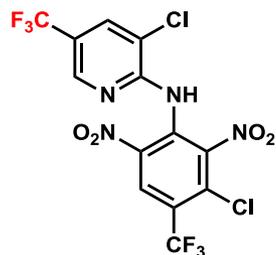
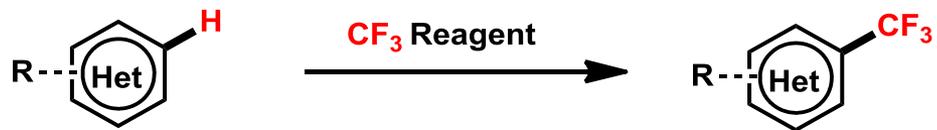


#### ➤ iridium-catalyzed borylation and copper-catalyzed trifluoromethylation of arenes

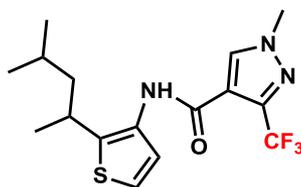


a variety of functional groups could be tolerated,  
which might lead to a number of biologically  
active molecules

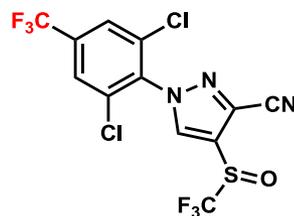
# *Sp<sup>2</sup> C-H Trifluoromethylation (III)*



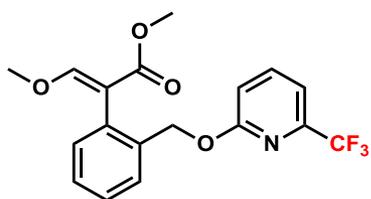
Fluazinam



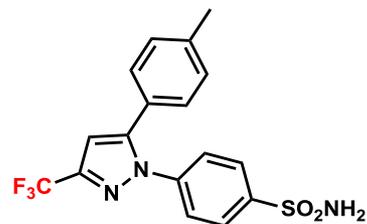
Penthiopyrad



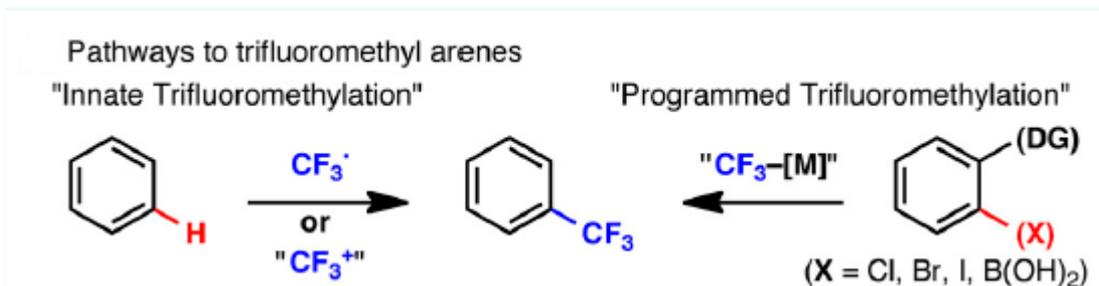
Fipronil



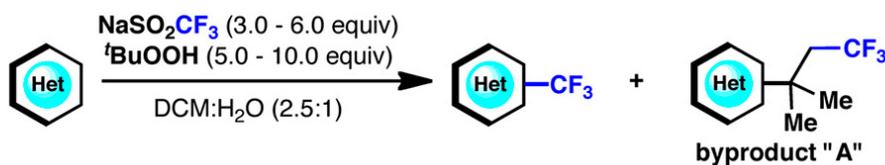
Picoxystrobin



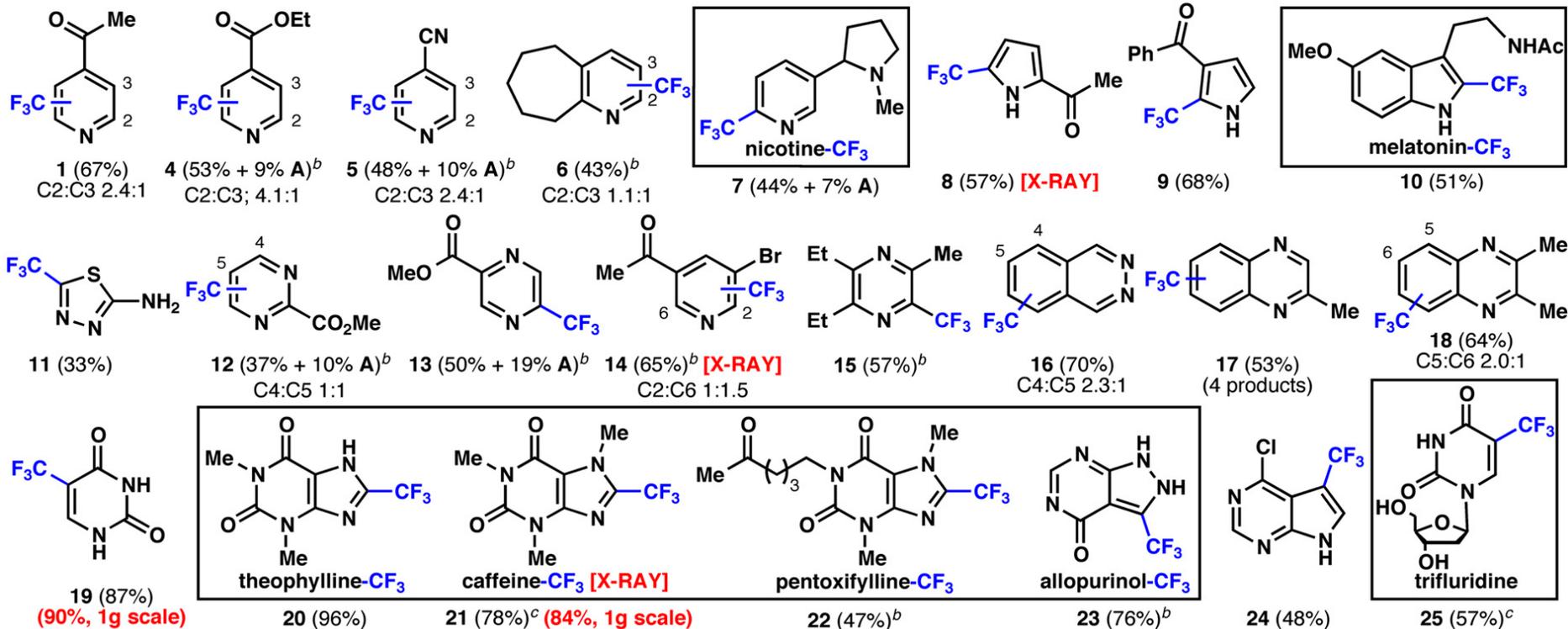
Celecoxib



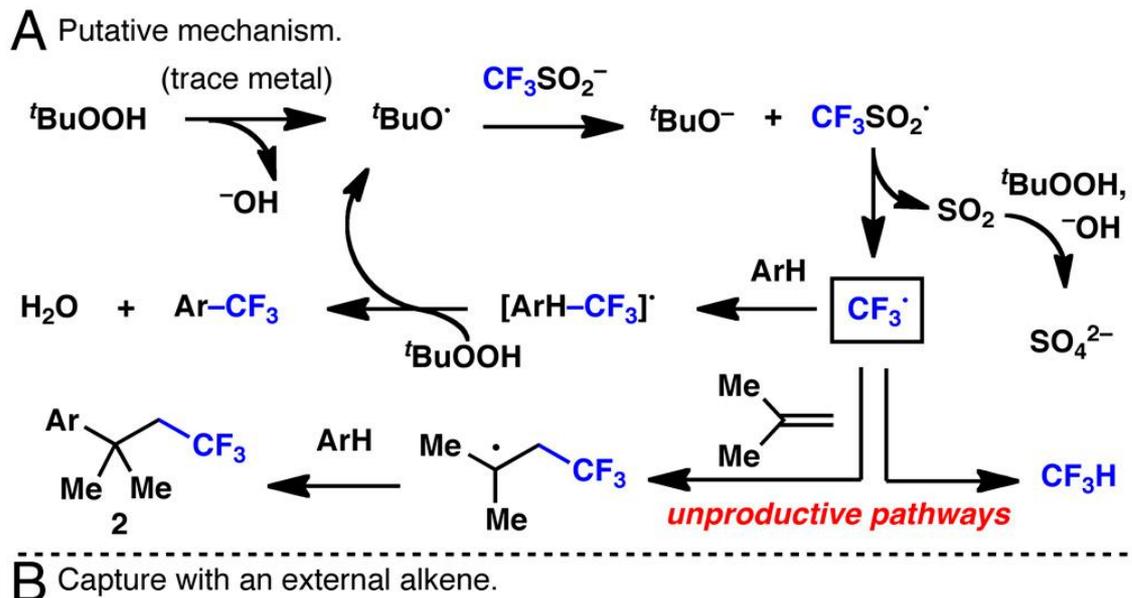
# *Sp<sup>2</sup> C-H (III): Innate C-H Trifluoromethylation of Heterocycles*



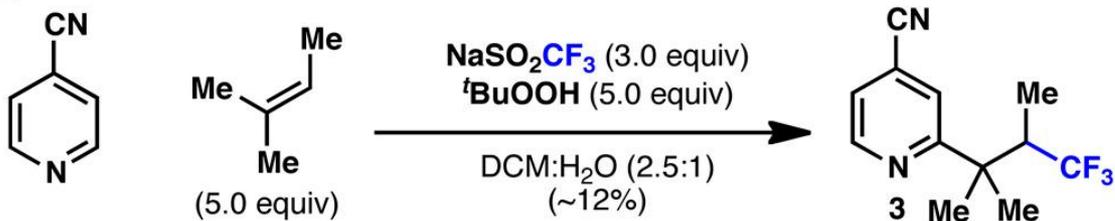
- 23 examples
- Proceeds at ambient temperature
- Runs in aqueous conditions under air
- High functional group tolerance
- Broad scope in heterocycle electronics
- No added metal required



# *Sp<sup>2</sup> C-H (III): Innate C-H Trifluoromethylation of Heterocycles*

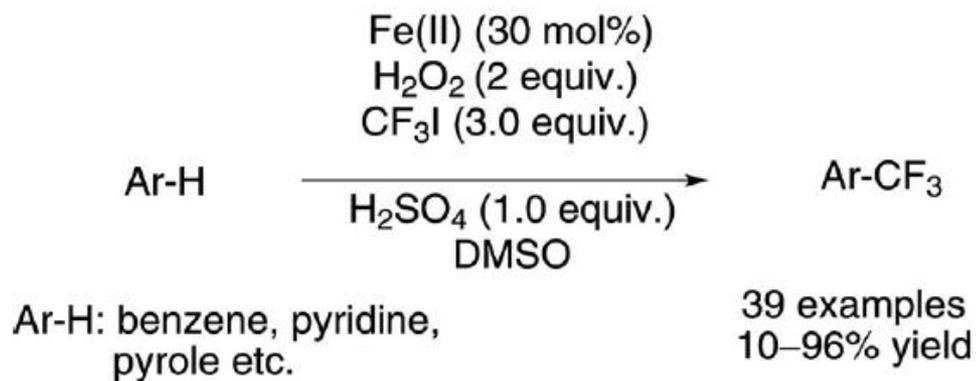


**B** Capture with an external alkene.



## *Sp<sup>2</sup> C-H (III):*

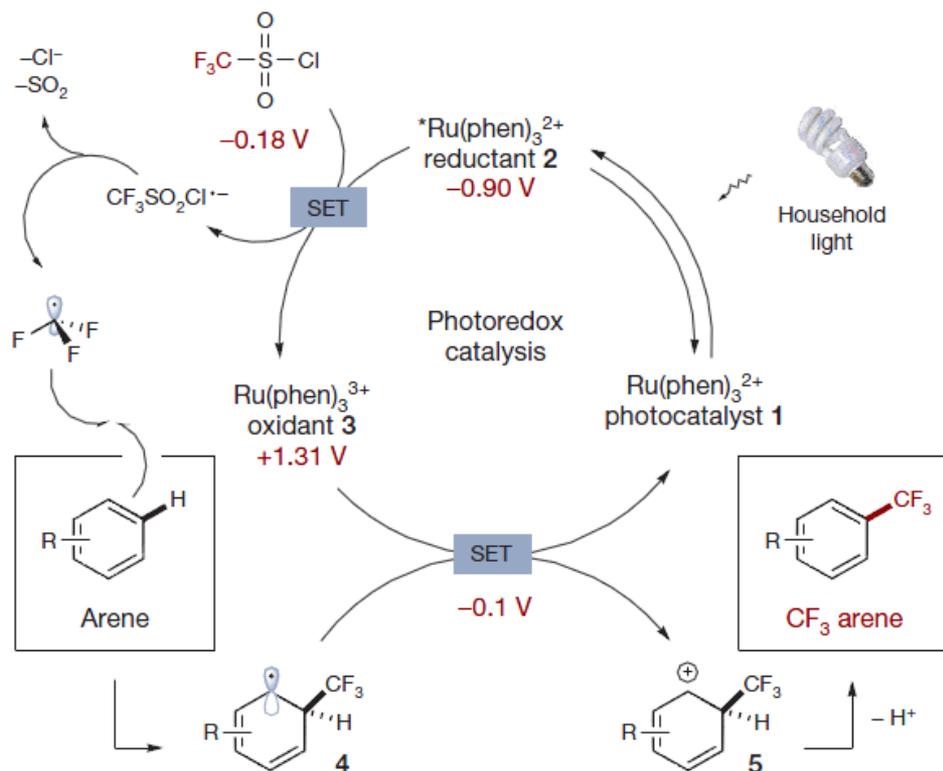
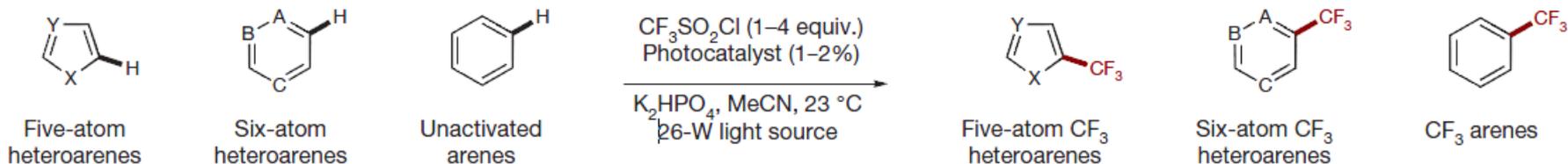
### *Iron(II)-catalyzed trifluoromethylation of aromatic and heteroaromatic compounds*



The regioselectivity is oriented by the general trend of electrophilic substitution of aromatic compounds with some exceptions.

# *Sp<sup>2</sup> C-H (III):*

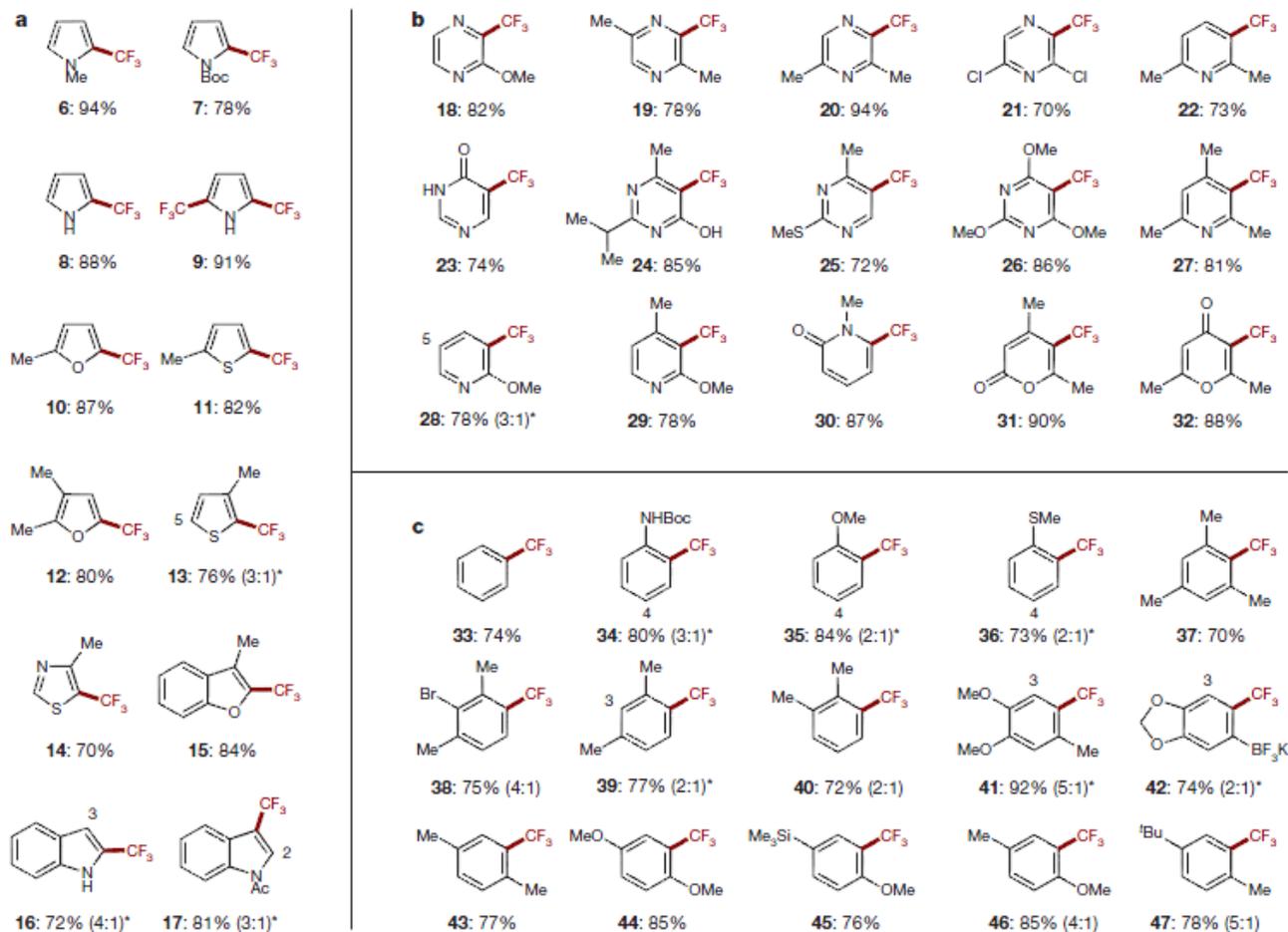
## *Trifluoromethylation of Arenes and Heteroarenes by Photoredox Catalysis*



# *Sp*<sup>2</sup> C-H (III):

## Trifluoromethylation of Arenes and Heteroarenes by Photoredox Catalysis

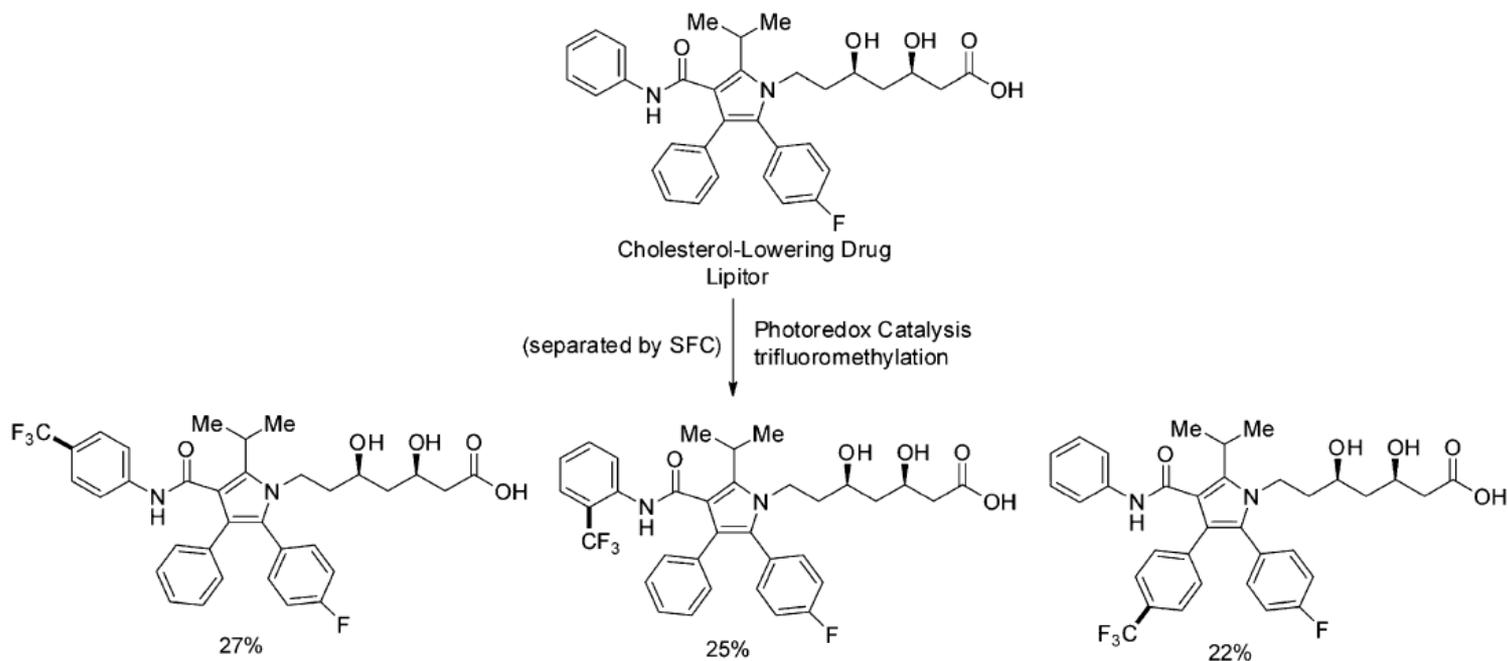
### ► wide substrate scope



## *Sp<sup>2</sup> C-H (III):*

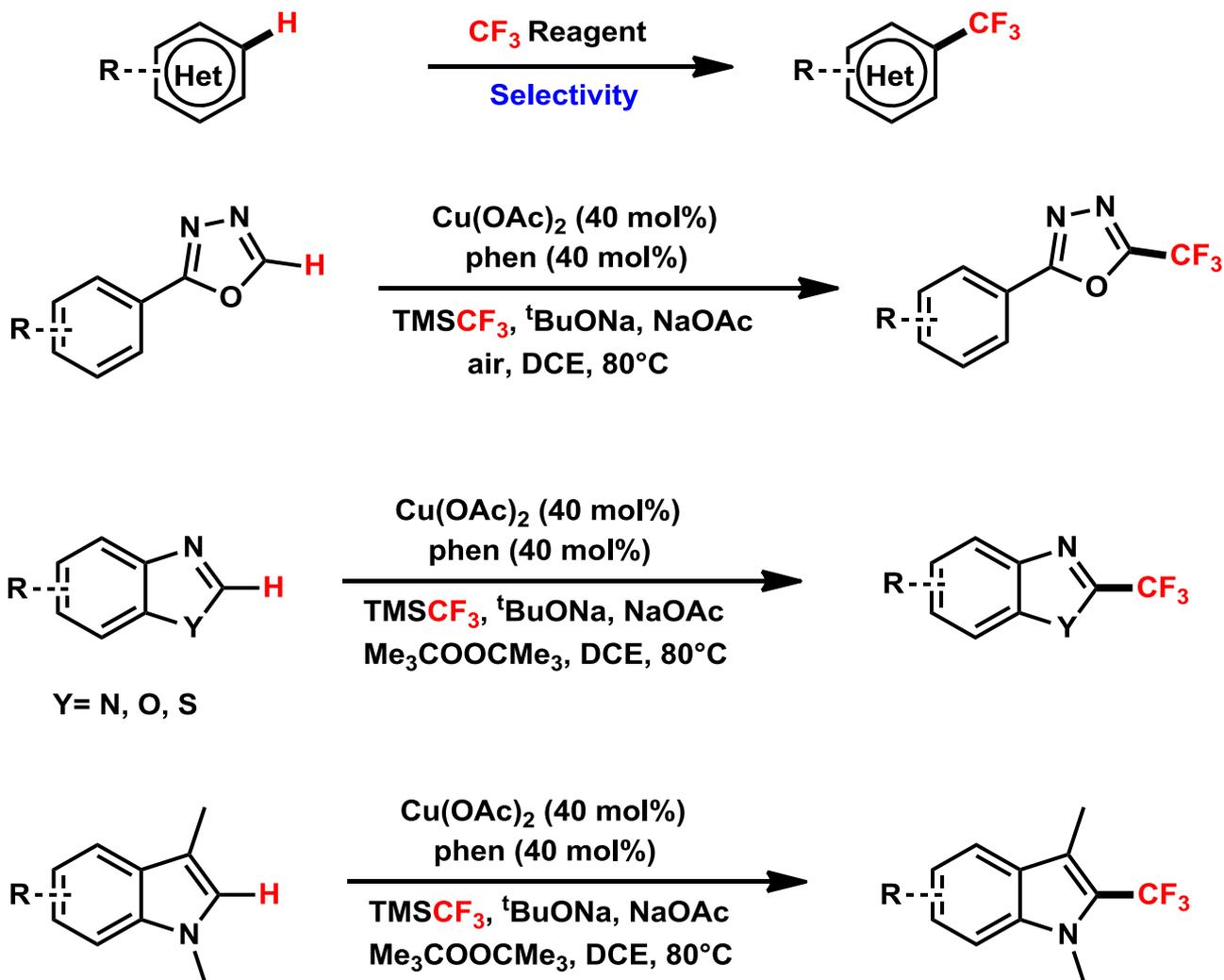
# *Trifluoromethylation of Arenes and Heteroarenes by Photoredox Catalysis*

## ➤ Application in the synthesis of Lipitor



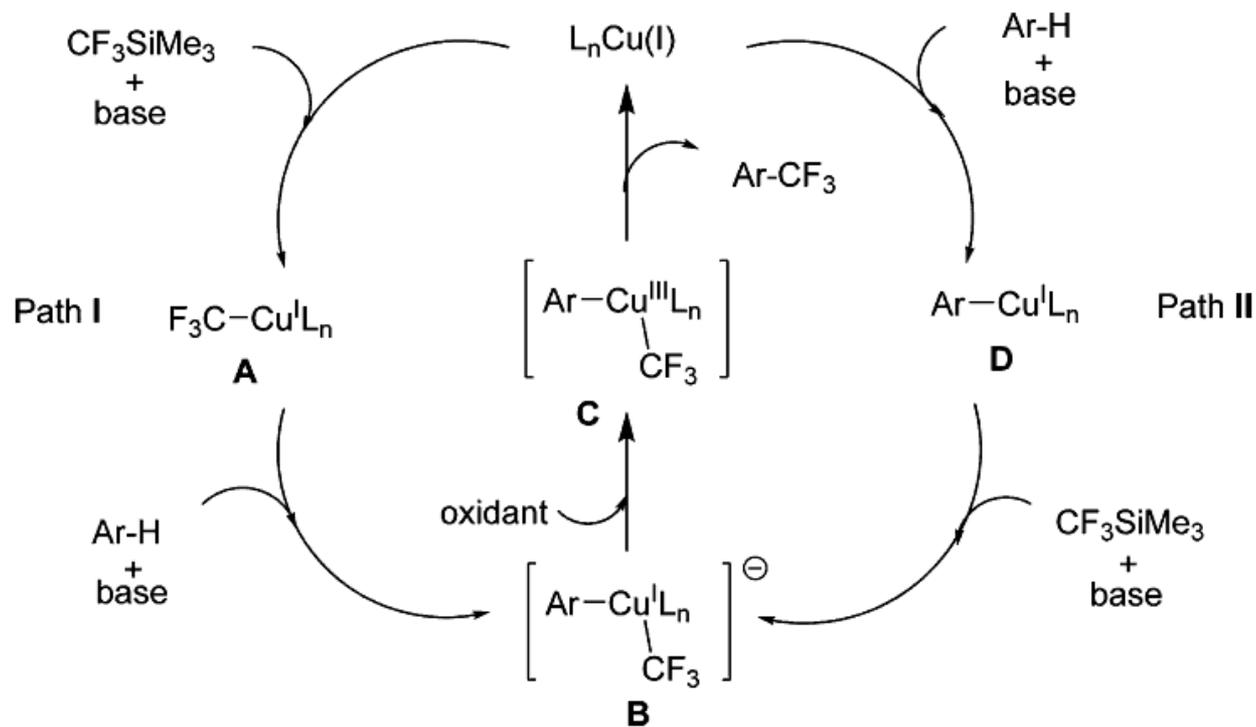
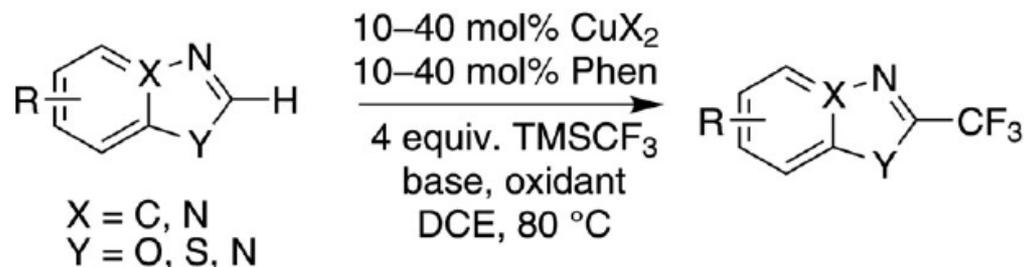
## *Sp<sup>2</sup> C-H (III):*

### *Copper-Catalyzed Direct C–H Oxidative Trifluoromethylation of Heteroarenes*



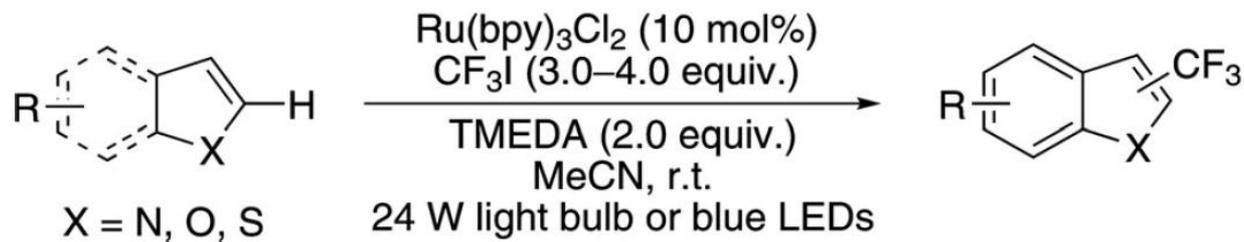
## *Sp<sup>2</sup> C-H (III):*

### *Copper-Catalyzed Direct C–H Oxidative Trifluoromethylation of Heteroarenes*



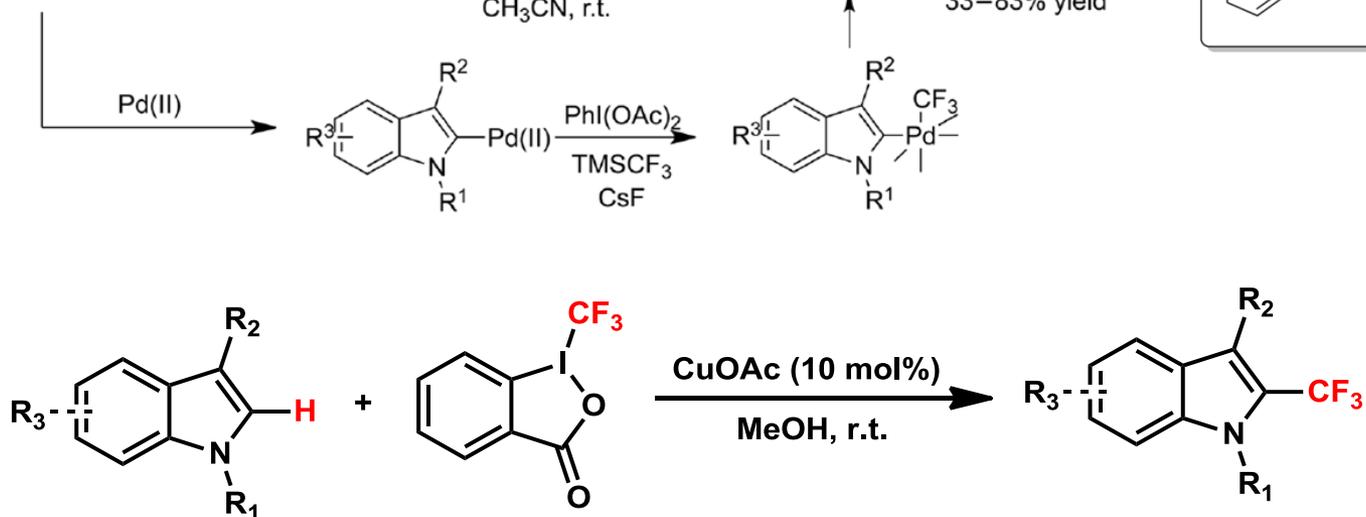
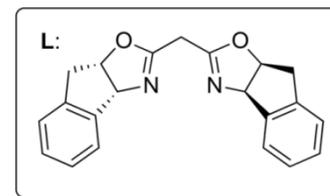
## *Sp<sup>2</sup> C-H Trifluoromethylation:*

### ➤ Visible light-induced trifluoromethylation



## *Sp<sup>2</sup> C-H (III):*

### *Palladium-Catalyzed Oxidative Trifluoromethylation of Indoles*



G. Liu *Chem. Eur. J.* **2011**, *17*, 6039-6042.

M. Sodeoka, *Tetrahedron Lett.* **2010**, *51*, 5947–5949.

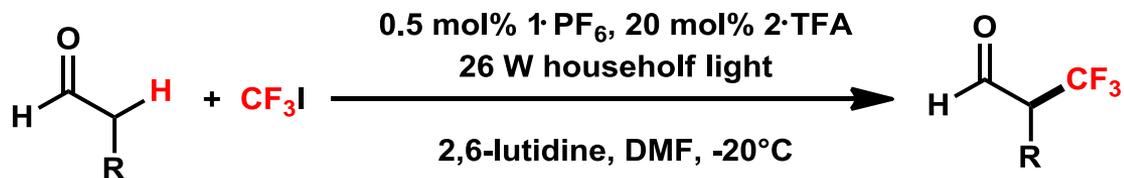
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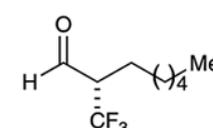
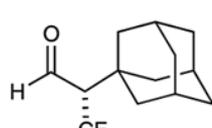
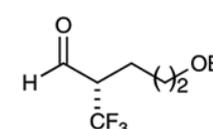
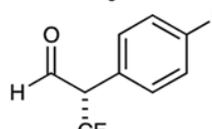
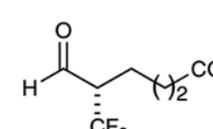
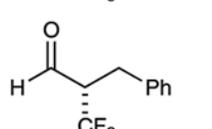
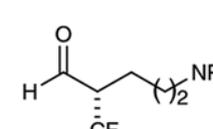
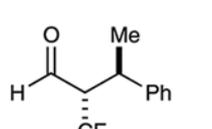
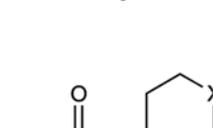
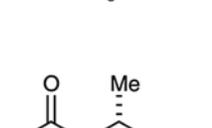
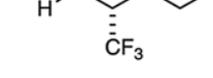
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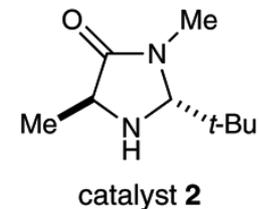
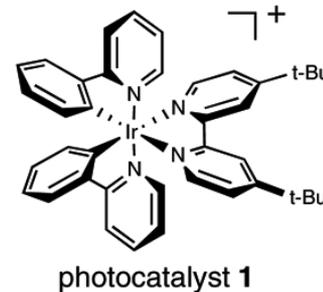
- *Background*
- *Trifluoromethylation of  $sp$ -Hybridized C-H Bonds*
- *Trifluoromethylation of  $sp^2$ -Hybridized C-H Bonds*
- ***Trifluoromethylation of  $sp^3$ -Hybridized C-H Bonds***
- *Summary & Acknowledgement*

# Sp<sup>3</sup> C-H :

## Photoredox Organocatalyzed Enantioselective $\alpha$ -Trifluoromethylation of Aldehydes

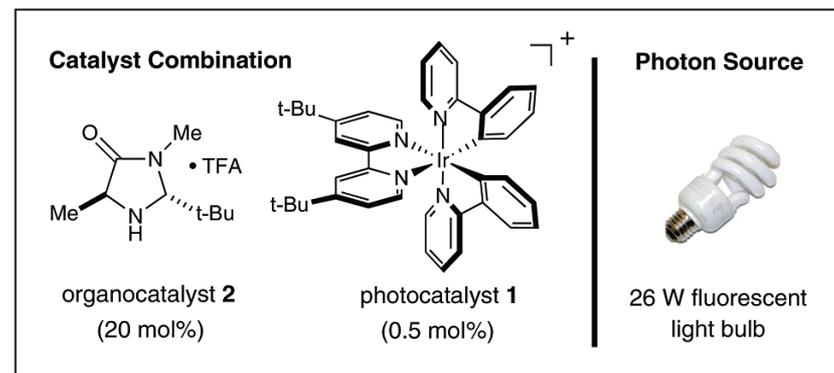
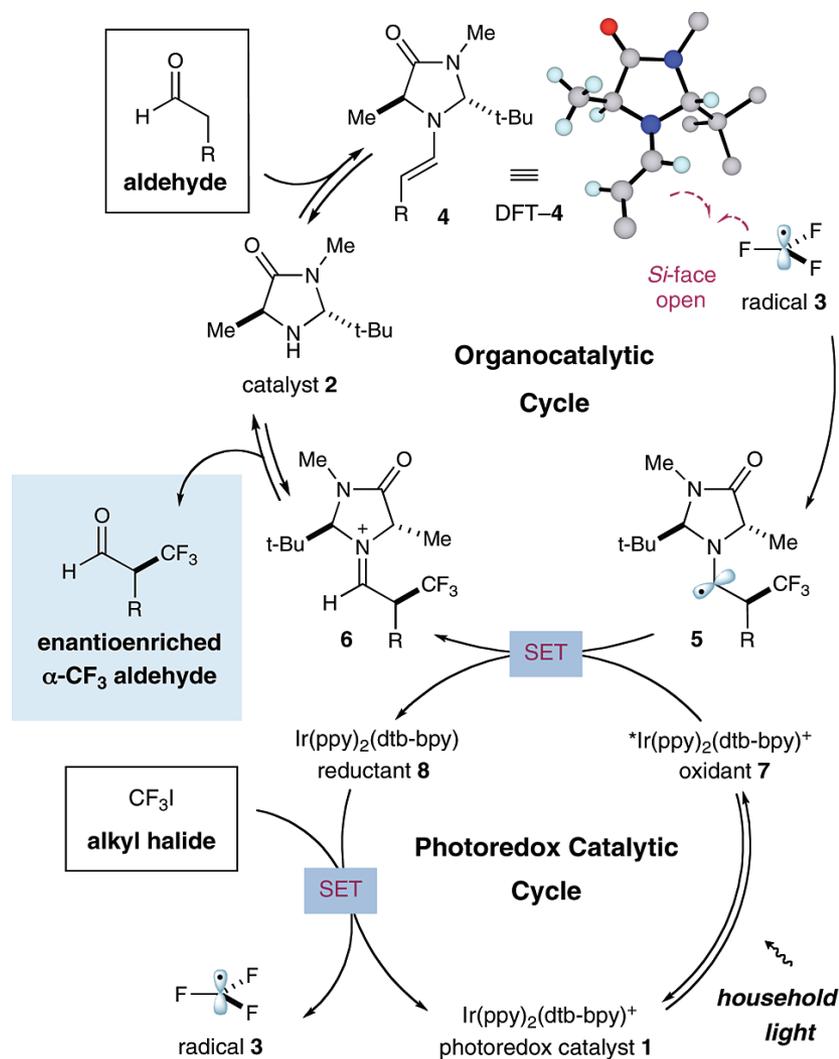


entry	product <sup>a</sup>	yield, <sup>b</sup> ee <sup>c</sup>	entry	product <sup>a</sup>	yield, <sup>b</sup> ee <sup>c</sup>
1		79% yield 99% ee	7		73% yield <sup>d</sup> 90% ee
2		72% yield 95% ee	8		61% yield 93% ee
3		86% yield 97% ee	9		75% yield 97% ee
4		78% yield 98% ee	10		68% yield >20:1 dr 99% ee
5		X = CH <sub>2</sub> 70% yield 99% ee	11		62% yield >20:1 dr 99% ee
6		X = NBoc 70% yield 98% ee			



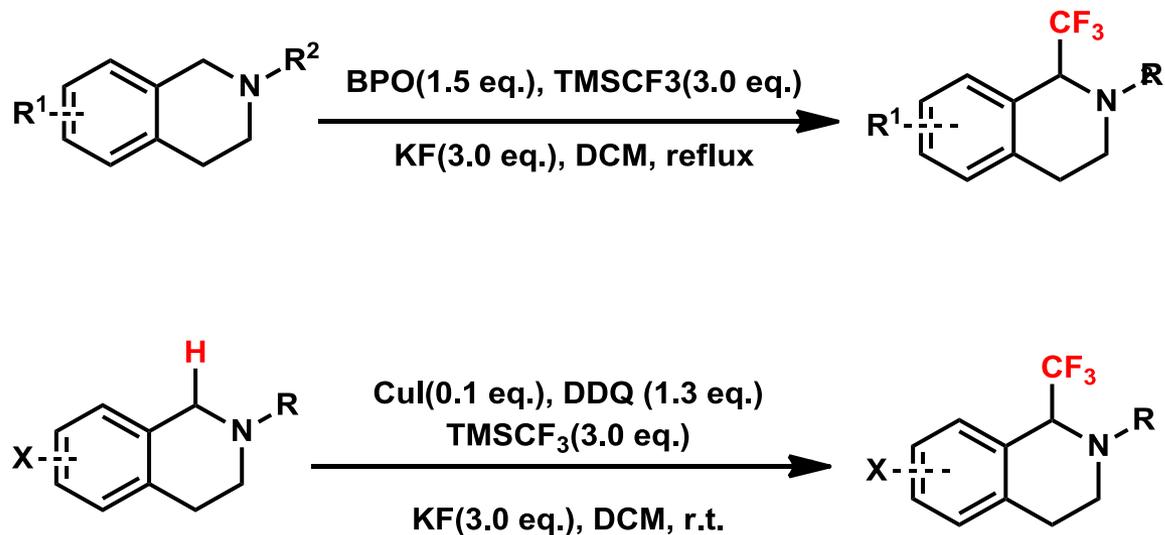
# *Sp<sup>3</sup> C-H :*

## *Photoredox Organocatalyzed Enantioselective $\alpha$ -Trifluoromethylation of Aldehydes*



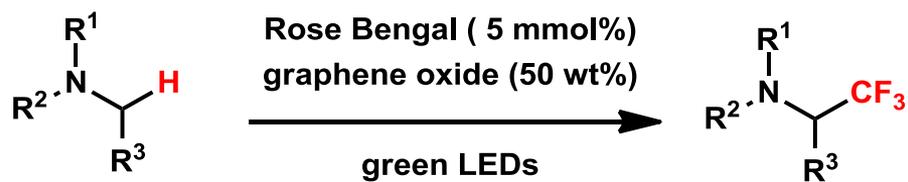
## *Sp<sup>3</sup> C-H :*

### *Trifluoromethylation of Tetrahydroisoquinoline and amines*

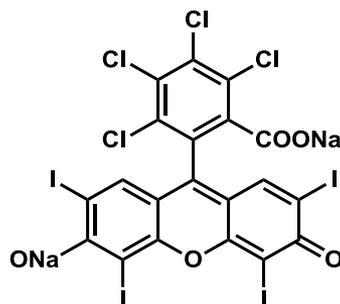


## *Sp<sup>3</sup> C-H :*

### *Oxidative C-H Functionalisation of Tertiary Amines*

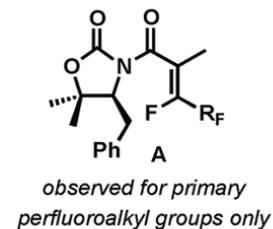
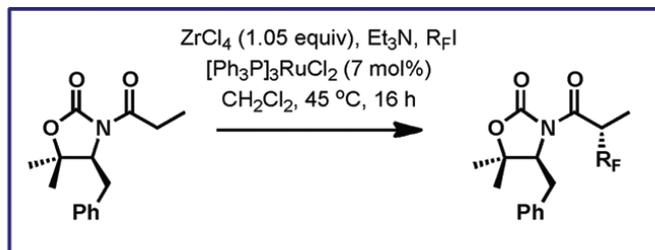


Rose Bengal =

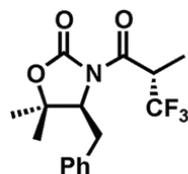


# *Sp<sup>3</sup> C-H :*

## *Ru-Catalyzed Asymmetric Trifluoromethylation of N-Acyl Oxazolidinones*

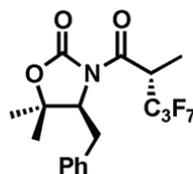


1



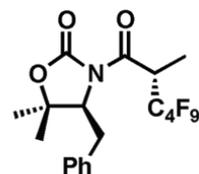
74% yield<sup>b</sup>  
dr 9:1

2



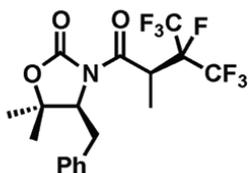
74% yield (12%)  
dr 24:1

3



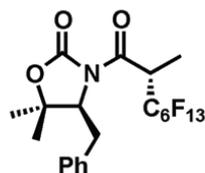
71% yield, (16%)  
dr 24:1

4



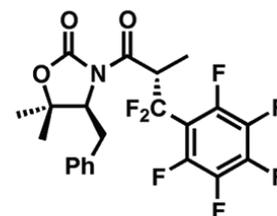
75% yield  
91 % brsm<sup>c</sup>  
dr >98:2

5



63% yield, (17%)  
dr >98:2

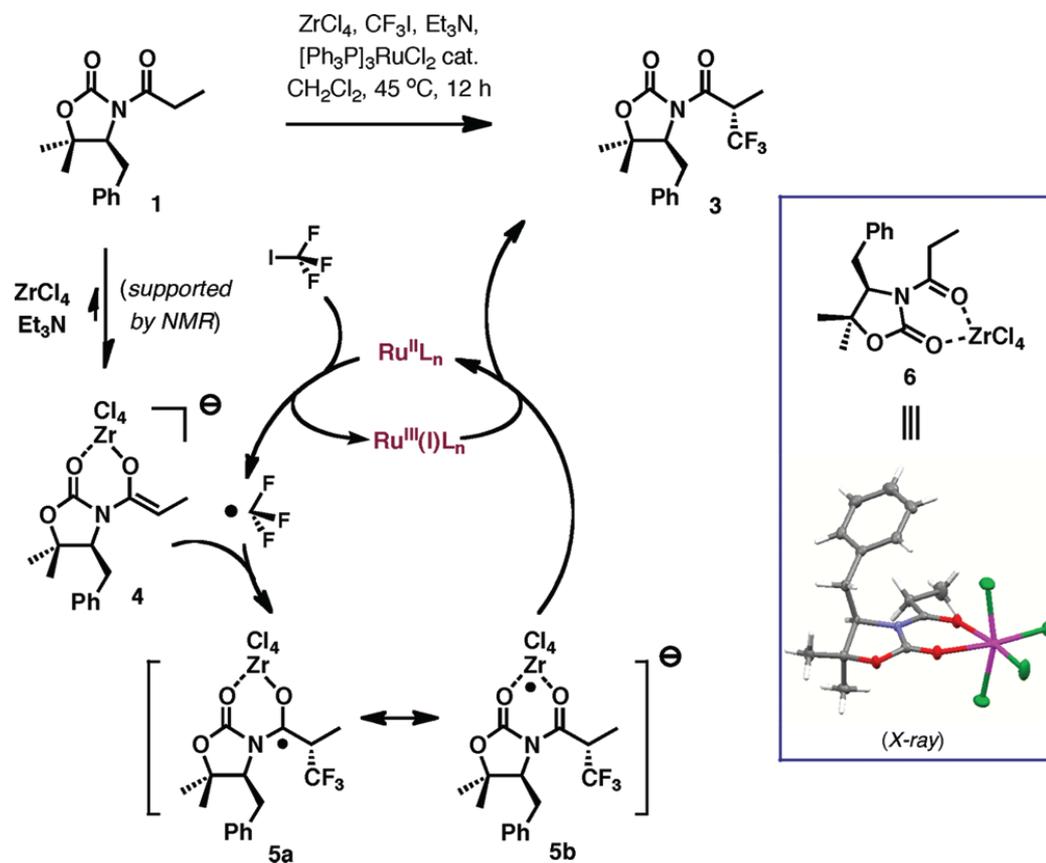
6



73% yield, (9%)  
dr >98:2

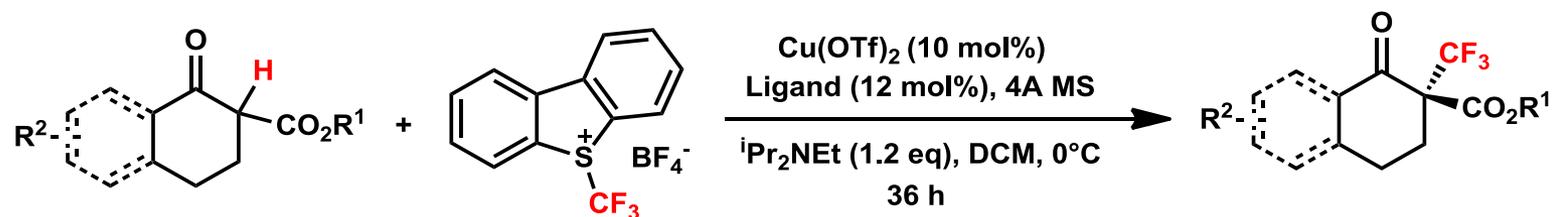
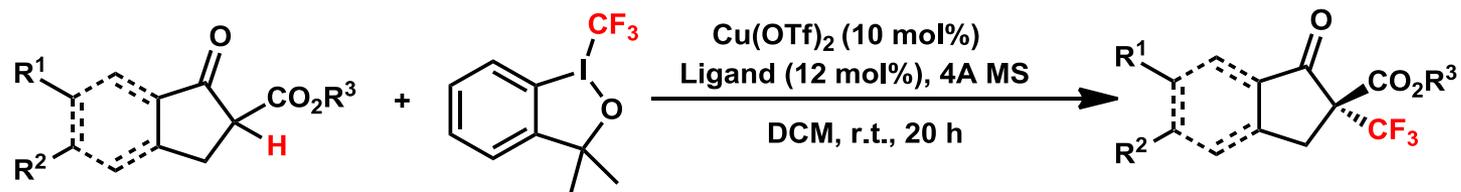
*Sp*<sup>3</sup> C-H :

## *Ru*-Catalyzed Asymmetric Trifluoromethylation of *N*-Acyl Oxazolidinones

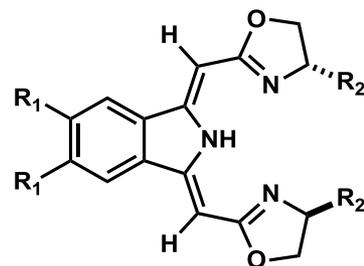


# *Sp<sup>3</sup> C-H :*

## *Enantioselective Copper-Catalyzed Electrophilic Trifluoromethylation of $\beta$ -Ketoesters*



Ligand =



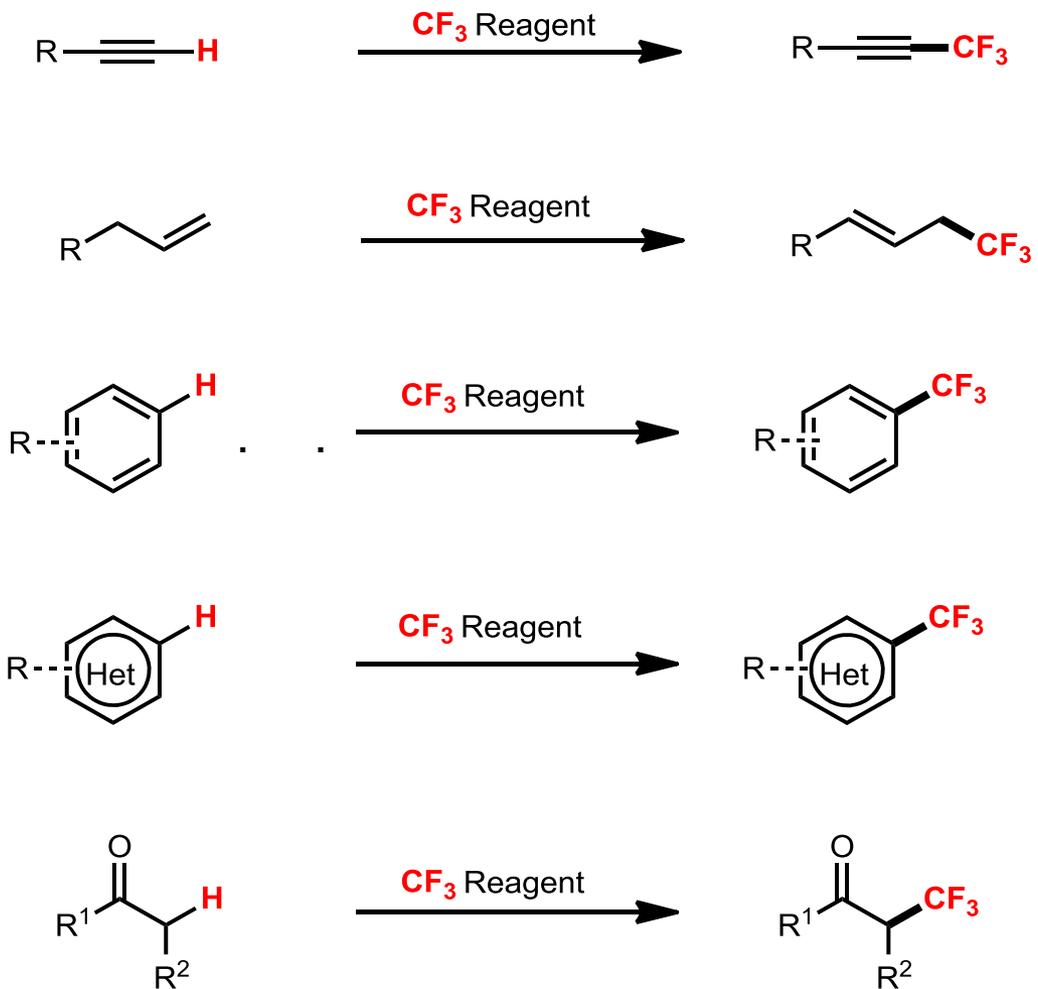
$R_1 = \text{Me}, R_2 = \text{Ph}$

# *Contents*

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- *Background*
- *Trifluoromethylation of  $sp$ -Hybridized C-H Bonds*
- *Trifluoromethylation of  $sp^2$ -Hybridized C-H Bonds*
- *Trifluoromethylation of  $sp^3$ -Hybridized C-H Bonds*
- ***Summary & Acknowledgement***

# Summary:



New Catalyst

Regioselectivity

Enantioselectivity



WHAT CAN WE DO NEXT?

# *Acknowledgement:*

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- **Prof. Yong Huang**
- **All members of E201**
- **All of you Here**

*Thank you for your attention !*