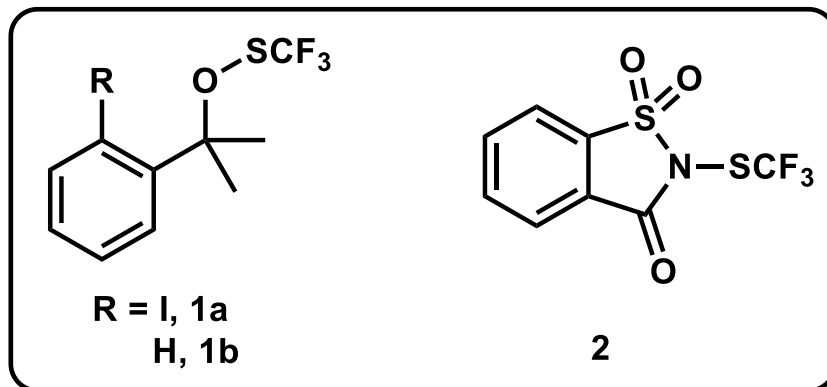


# Self-stable Electrophilic Reagents for Trifluoromethylthiolation



*Reporter: Linrui Zhang*

*Supervisor: Prof. Yong Huang*

*Date: 2017-12-25*



# Content

- Introduction
- Trifluoromethanesulfenates: *Preparation and reactivity*
- N-trifluoromethylthiosaccharin: *Preparation and reactivity*
- Compararison of the reactivities of Trifluoromethanesulfenates 1a and 1b and N-trifluoromethylthiosaccharin 2
- Summary



# Content

## ➤ Introduction

➤ Trifluoromethanesulfenates: *Preparation and reactivity*

➤ N-trifluoromethylthiosaccharin: *Preparation and reactivity*

➤ Compararison of the reactivities of Trifluoromethanesulfenates 1a and 1b and N-trifluoromethylthiosaccharin 2

➤ Summary

# Introduction of Author

## Research Areas

- Organofluorine Chemistry: Electrophilic fluoroalkylation reagents and their reactions
- Organometallics: transition metal-catalyzed reaction, mechanistic study including isolation of the key intermediate, kinetics
- Material Science: living-polymerization of fluorinated monomer

## Education

1992-1996, Department of Environmental Science and Engineering, Nanjing University, China, Bachelor  
1996-1999, Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Master  
2000-2002, Chemistry Department, University of Massachusetts, Dartmouth, Master  
2002-2007, Chemistry Department, Yale University, PhD

## Honors & Distinctions

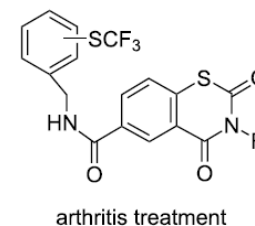
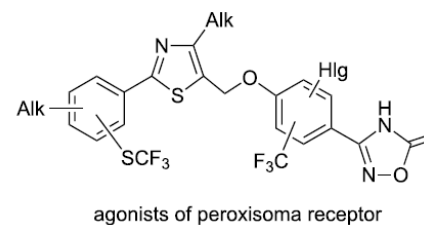
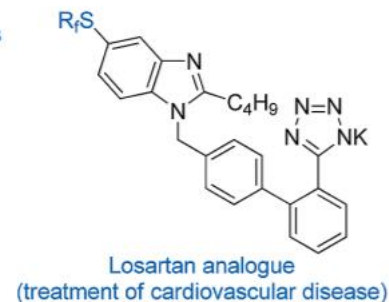
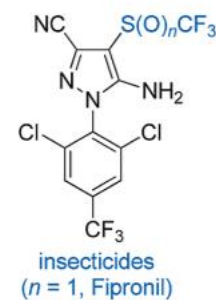
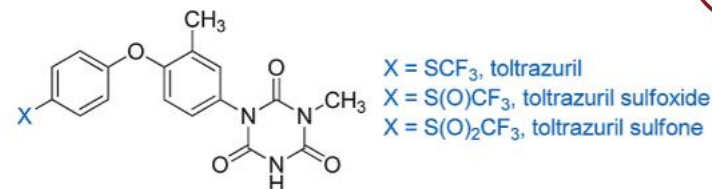
2010, Hundreds Talens Program of SIOC  
2011, Pujiang Program of Shanghai  
2013, Thieme Chemistry Journal Award  
2015, Asia Core Program Lectureship Award  
2016, The National Science Fund for Distinguished Young Scholars



**Prof. Qilong Shen**

*Key Laboratory of Organofluorine  
Chemistry Shanghai Institute of  
Organic Chemistry*

# Introduction



- $\pi = 1.44$ : high Hansch lipophilicity parameter
- The privileged structural motifs in drug design: improving the drug's pharmacokinetics and efficacy

Boiko, V. N. *J. Org. Chem.* **2010**, 6, 880–921.

Purser, S.; Moore, P. R.; Swallow, S.; *Chem. Soc. Rev.* **2008**, 37, 320–330.

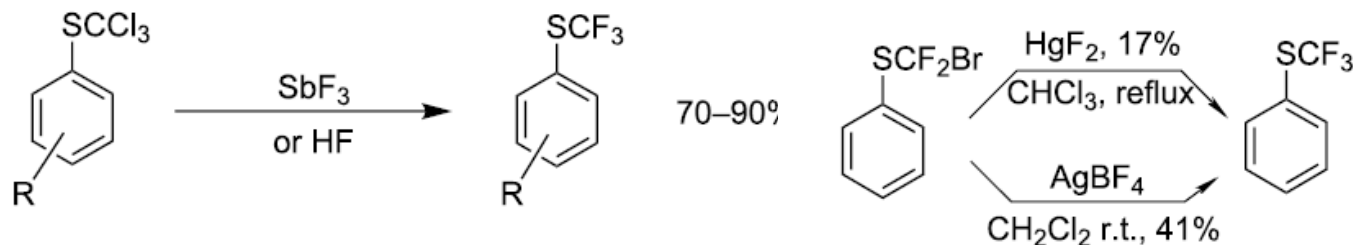
Wang, J.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, 114, 2432–2506.

# Methods for Trifluoromethylthiolation

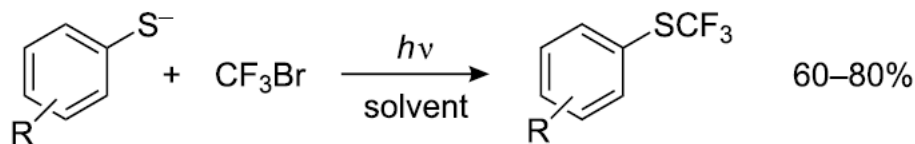
## ➤ Indirect strategies

- require preformation of the thiolated precursors
- suffer from harsh conditions
- limited substrate scope

Halogen–fluorine exchange of polyhalogenomethyl thioethers



Trifluoromethylation of sulfur-containing compounds



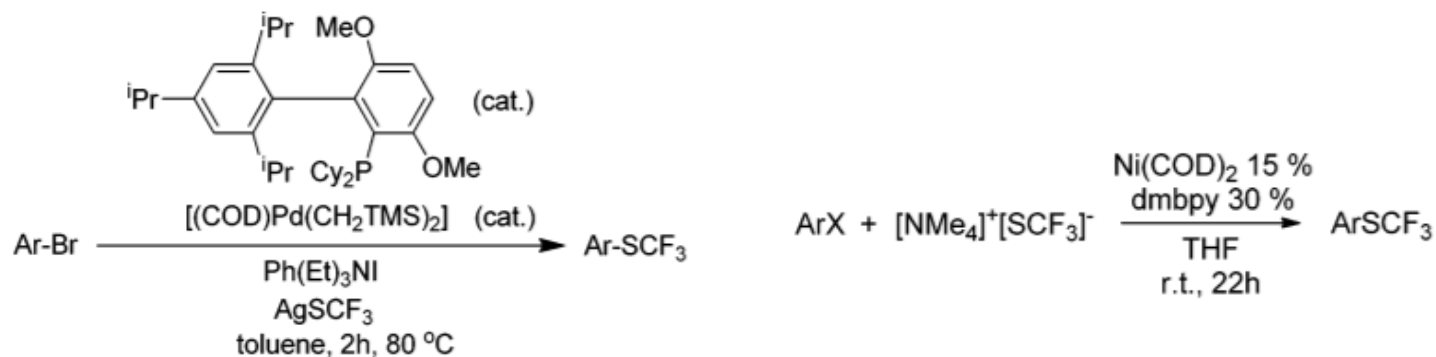
Buchanan, J. B.; Gregory, W. *Chem. Abstr.* **1963**, 58, 10127.

Suda, M.; Hino, C. *Tetrahedron Lett.* **1981**, 22, 1997–2000.

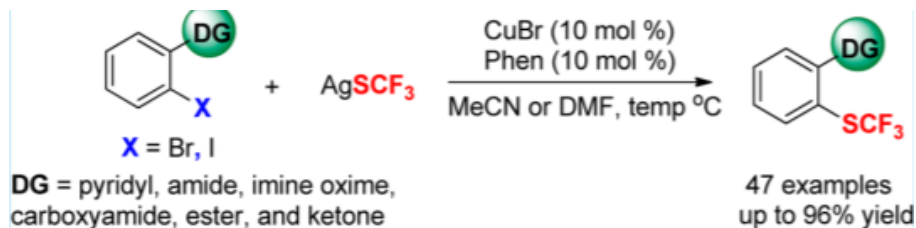
## ➤ Direct Trifluoromethylthiolation

### I. Transition-metal catalyzed direct trifluoromethylthiolation

- Pd, Ni-Catalyzed Trifluoromethylthiolation*



- Cu-Catalyzed of Aryl Halides with Diverse Directing Groups*



mild conditions  
good functional group tolerance

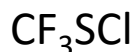
Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, 50, 7312–7314.

Zhang, C. P.; Vicic, D. A. Nickel, *J. Am. Chem. Soc.* **2012**, 134, 183–185.

Xu, J.-B.; Mu, X.; Chen, P.-H.; Ye, J.-X.; Liu, G.-S. *Org. Lett.* **2014**, 16, 3942–3945.

## ➤ Direct Trifluoromethylthiolation

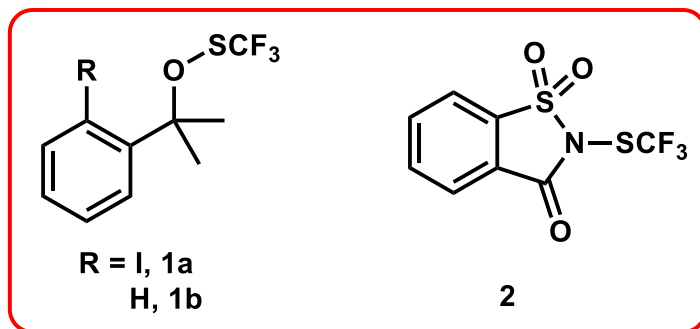
II. Using electrophilic trifluoromethylthiolating reagents *more efficient and straightforward*



*toxic gas*



*Effective of alkenes, alkynes, indoles, et. al,  
Need a strong Lewis acid or Brønsted acid.*



*Shelf-stable, highly reactive,  
Ease in preparation, broad scope,  
and mild reaction conditions.*

Very attractive as general reagents that allow rapid installation of the trifluoromethylthiol group into small molecules.

Ferry, A. L.; Billard, T.; Langlois, B. R.; Bacque, E. *J. Org. Chem.* **2008**, *73*, 9362–9365.

Ferry, A.; Billard, T.; Langlois, B. R.; Bacque, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8551–8555.

Ferry, A.; Billard, T.; Bacque, E.; Langlois, B. R. *J. Fluorine Chem.* **2012**, *134*, 160–163.



# Content

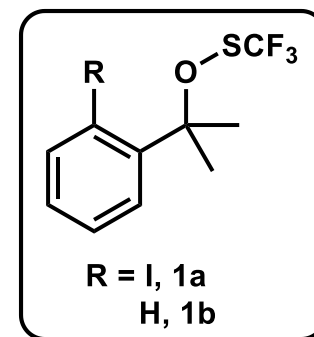
➤ Introduction

➤ **Trifluoromethanesulfenates: *Preparation and reactivity***

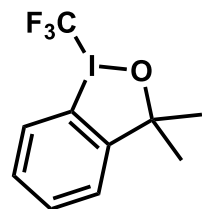
➤ N-trifluoromethylthiosaccharin: *Preparation and reactivity*

➤ Comparison of the reactivities of Trifluoromethanesulfenates 1a and 1b and N-trifluoromethylthiosaccharin 2

➤ Summary

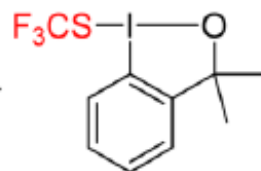
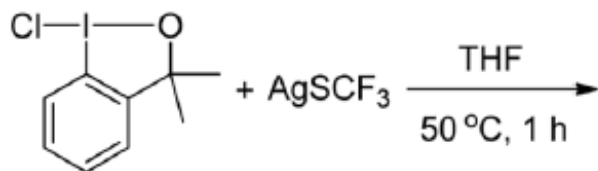
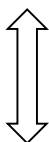


## 2.1. Synthesis of Trifluoromethanesulfenate 1a and Structure Revision



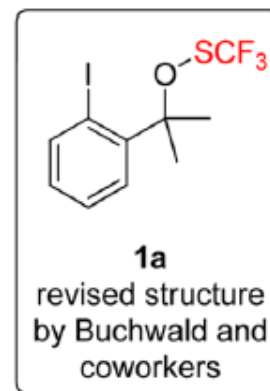
Togni reagent I

- Inspired by Togni's reagent
- hypervalent iodine skeleton is an excellent platform to transfer a trifluoromethyl group to other molecules.



**1a'**  
initially proposed  
structure

*spectroscopic techniques,  
derivatization experiments,  
crystal sponge technology.*



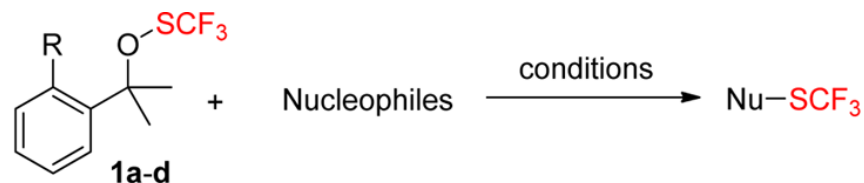
DSC and TGA analysis: colorless stable liquid; boiling point: 151–153 °C

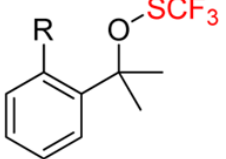
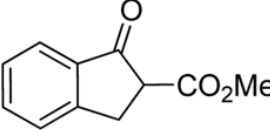
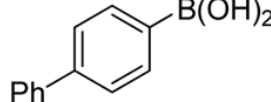
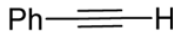
Shao, X.-X.; Wang, X.-Q.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, 52, 3457–3460.

Ma, B.-Q.; Shao, X.-X.; Shen, Q. *J. Fluorine Chem.* **2015**, 171, 73–77.

Vinogradova, E. V.; Müller, P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2014**, 53, 3125. 3128.

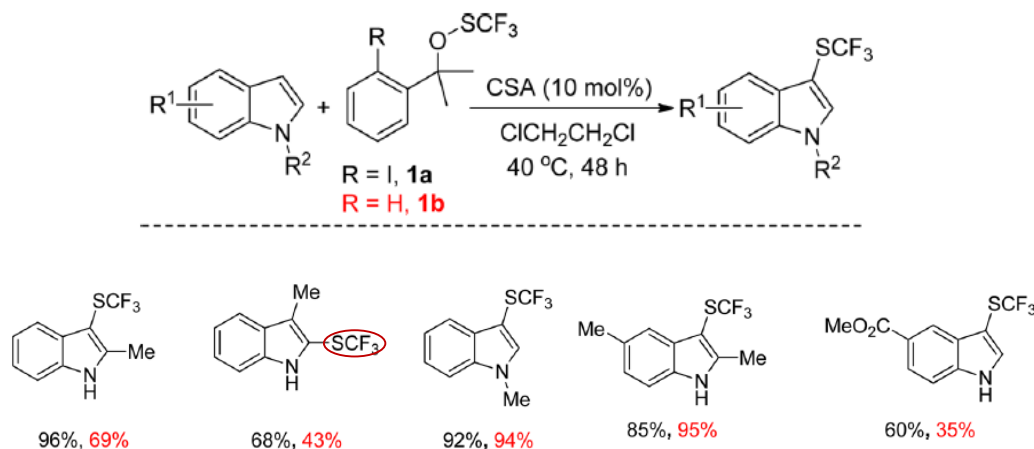
## 2.2. Structure–Reactivity Relationship Study of Trifluoromethanesulfenate 1a and 1b



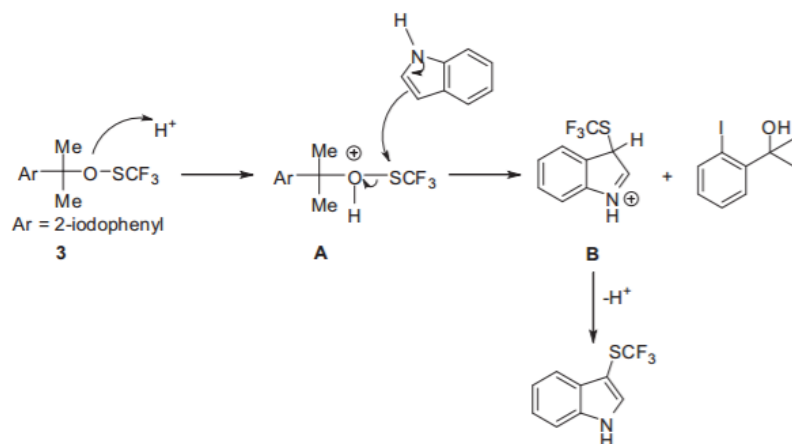
			
R = I, <b>1a</b>	98%	99%	99%
R = H, <b>1b</b>	95%	57%	98%
R = Br, <b>1c</b>	92%	57%	73%
R = Me, <b>1d</b>	99%	54%	90%

Reagent 1b is **less effective** but **much cheaper** compared with 1a.

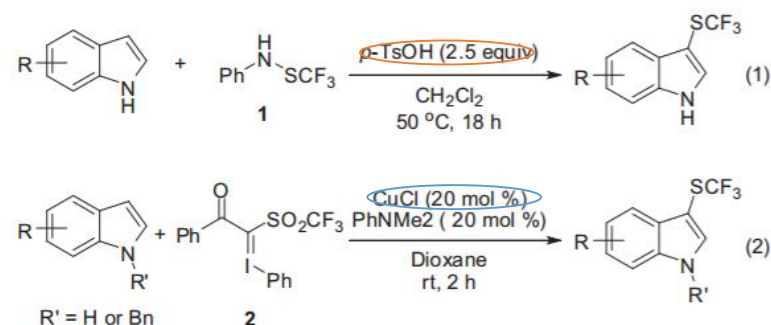
## 2.3. Reactions of Reagents 1a and 1b with Indoles



### Proposed mechanism



### Other similar methods

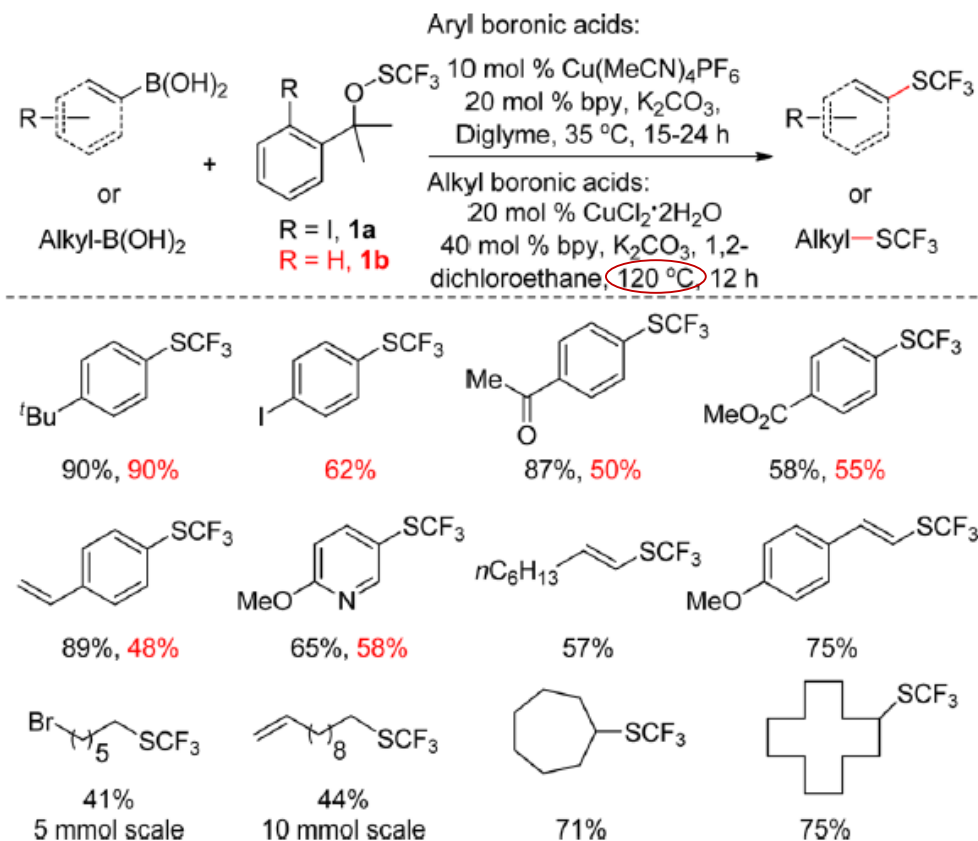


Ma, B.-Q.; Shao, X.-X.; Shen, Q. *J. Fluorine Chem.* **2015**, 171, 73–77.

Ferry, A.; Billard, T.; Bacque, E.; Langlois, B. R. *J. Fluorine Chem.* **2012**, 134, 160–163.

Yang, Y. D.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, 135, 8782–8785.

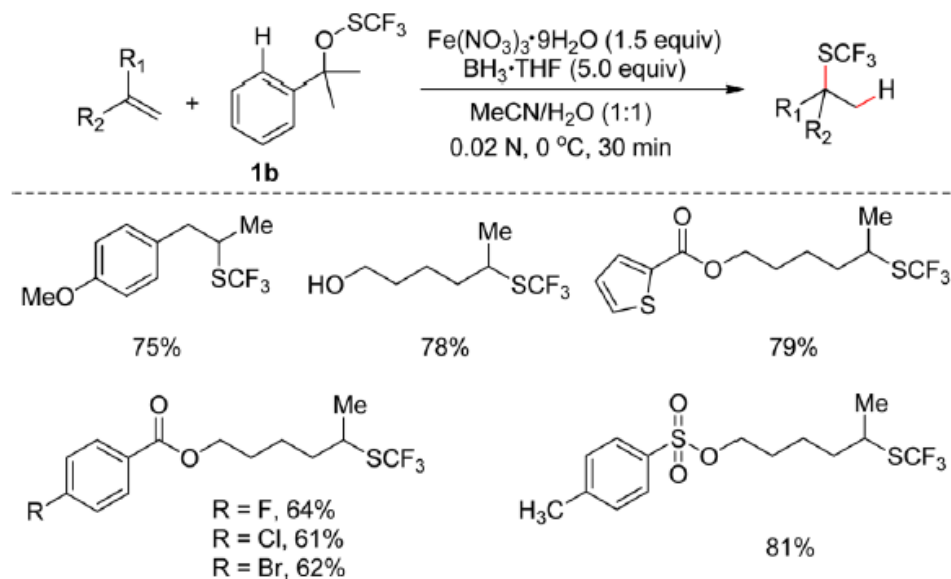
## 2.4. Reactions of Reagents 1a and 1b with Aryl-, Vinyl-, and Alkylboronic Acids



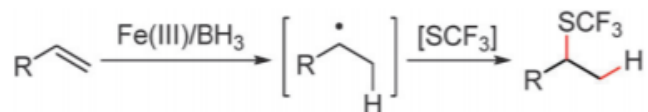
Shao, X.-X.; Wang, X.-Q.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, 52, 3457–3460.

Shao, X.-X.; Liu, T.-F.; Lu, L.; Shen, Q. *Org. Lett.* **2014**, 16, 4738–4741.

## 2.5. Iron-Catalyzed Hydrotrifluoromethylthiolation of Alkenes with Reagent 1b



A free radical process:

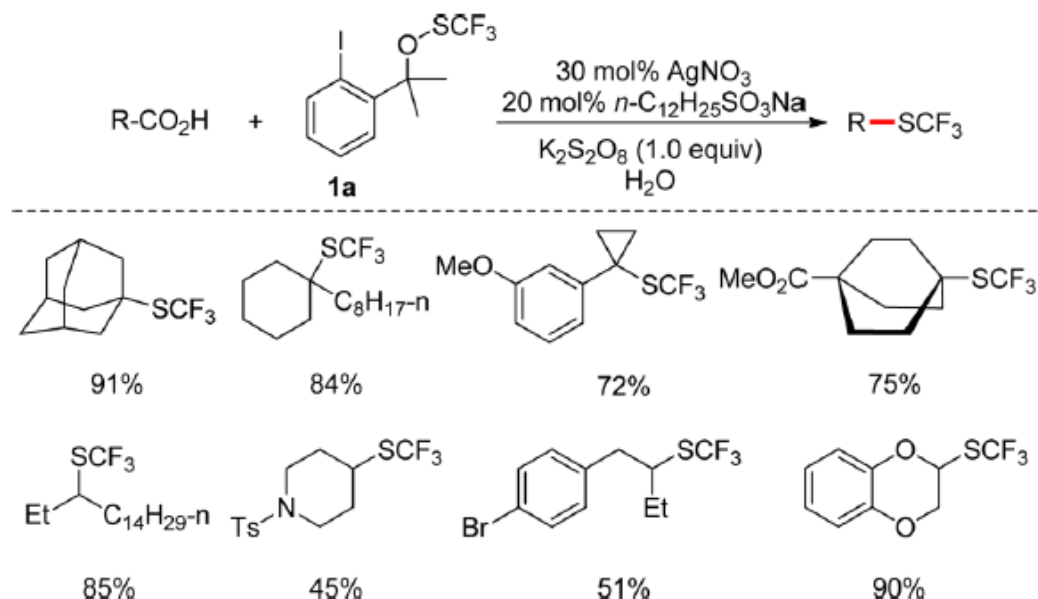


Markovnikov's rule

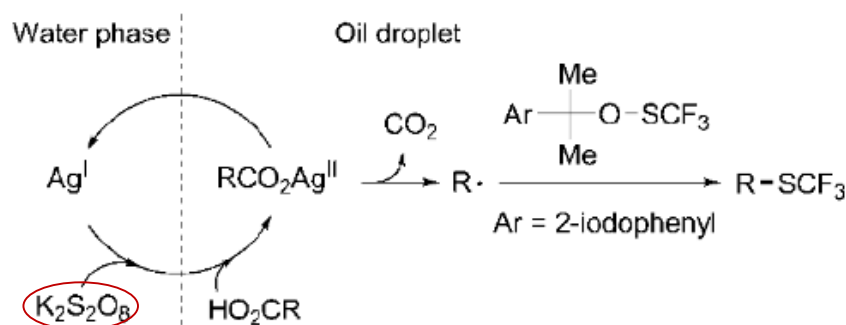
Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13588–13591.

Yang, T.; Lu, L.; Shen, Q. *Chem. Commun.* **2015**, *51*, 5479–5481.

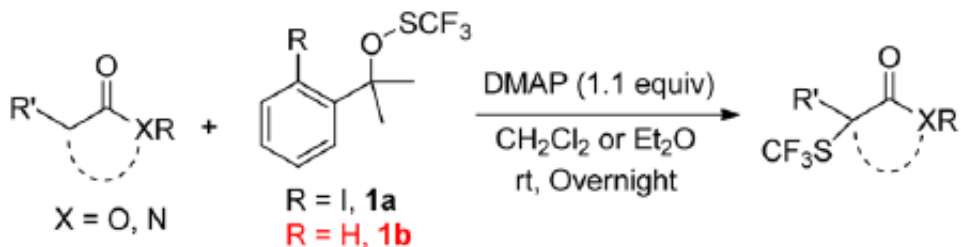
## 2.6. Silver-Catalyzed Decarboxylative Trifluoromethylthiolation of Alkyl Carboxylic Acids with Reagent 1a in Aqueous Emulsion



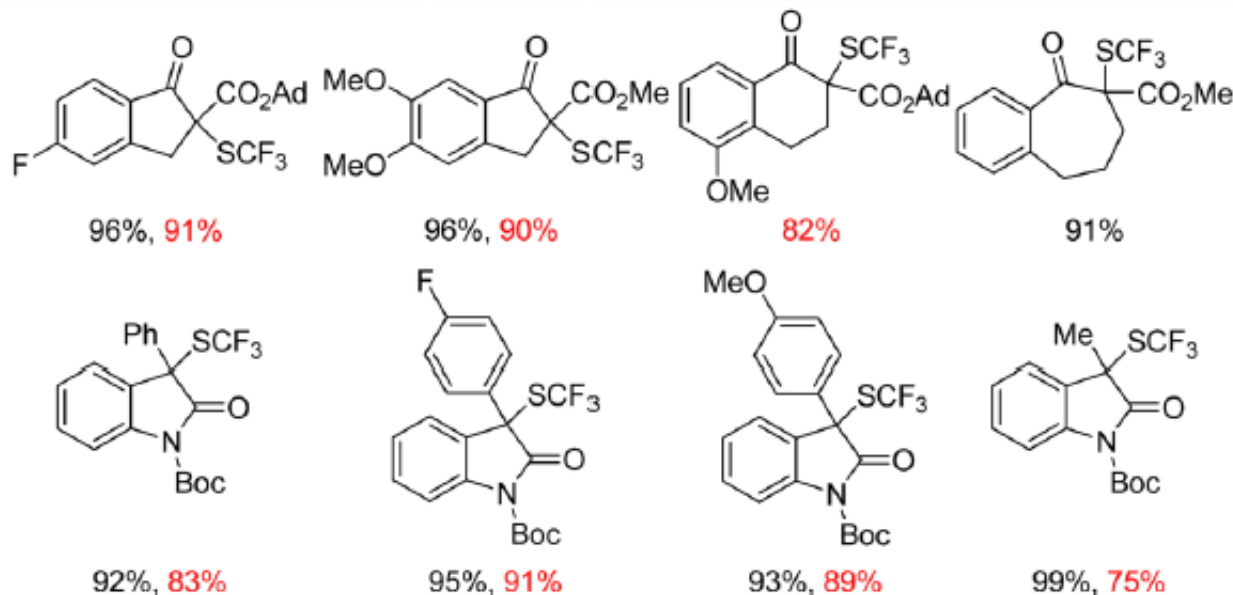
Proposed mechanism:



## 2.7. Reactions of Reagents 1a and 1b with $\beta$ -Keto Esters and Oxindoles

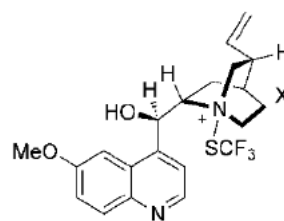


- Soft nucleophile
- No transition metal

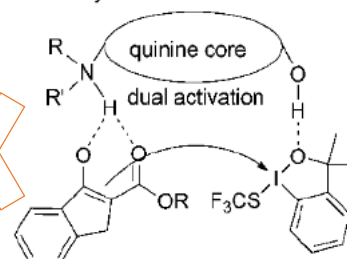
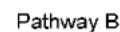


Open-chain  $\beta$ -keto esters give no product



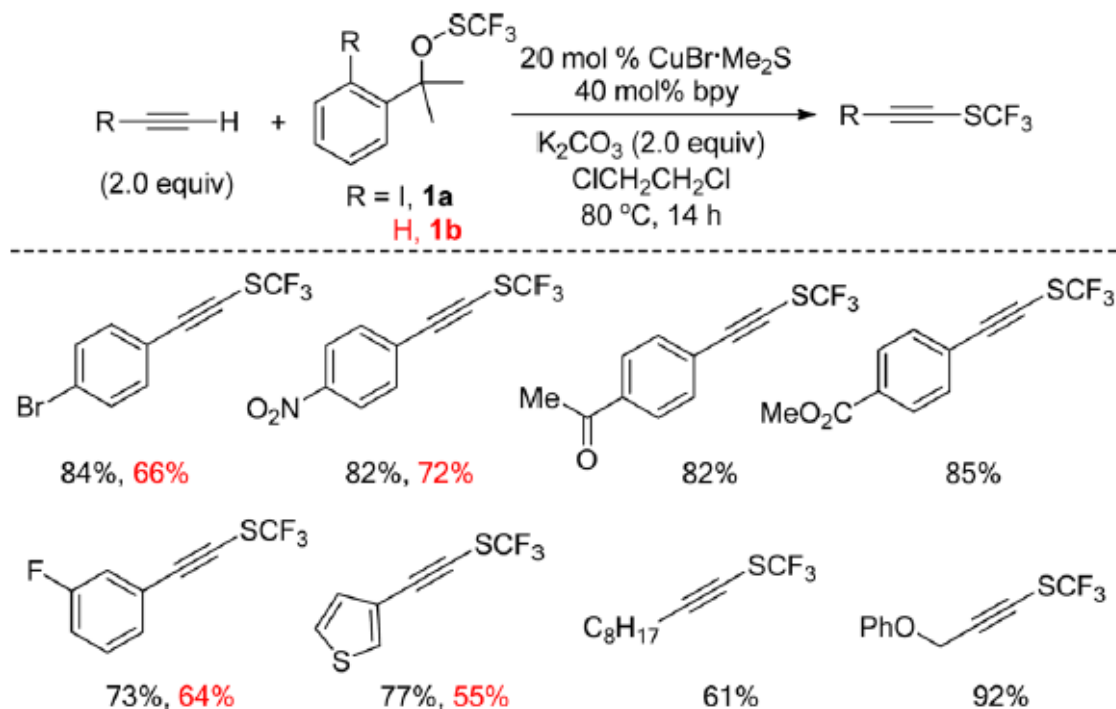


## Two possible pathways rule out



  
**mechanism is in progress**

## 2.9. Reaction of Reagents 1a and 1b with Alkynes

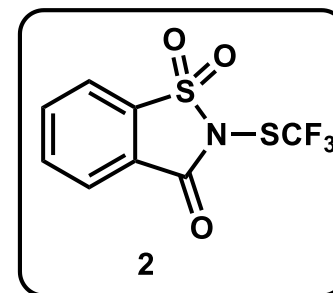


# Content

➤ Introduction

➤ Trifluoromethanesulfenates: *Preparation and reactivity*

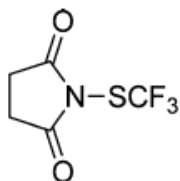
➤ **N-trifluoromethylthiosaccharin: *Preparation and reactivity***



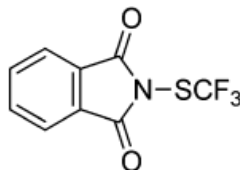
➤ Comparison of the reactivities of Trifluoromethanesulfenates 1a and 1b and N-trifluoromethylthiosaccharin 2

➤ Summary

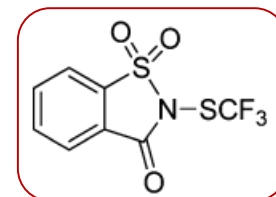
### 3.1. Three Trifluoromethylthiolated NBS Analogues



(1)



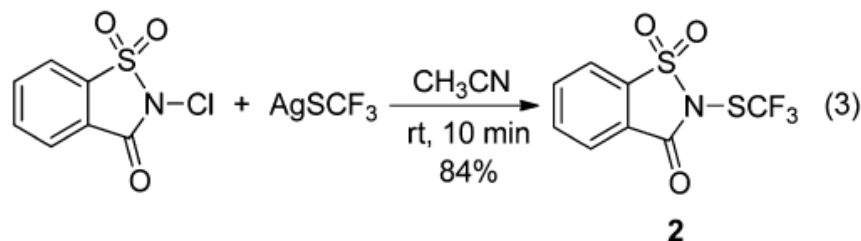
(2)



(3) / **2**

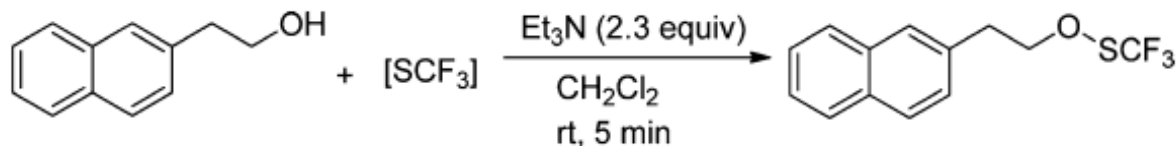
*Higher  
reactivity*

*Preparation :*



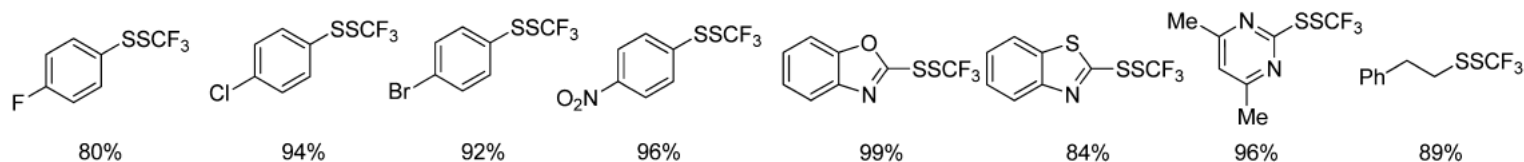
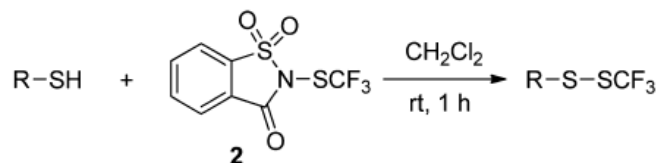
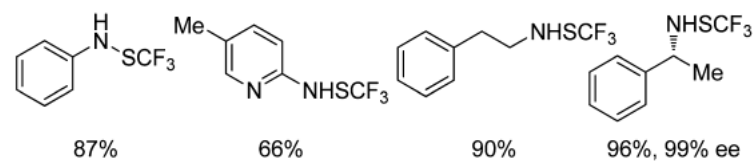
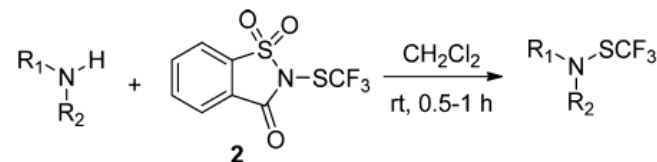
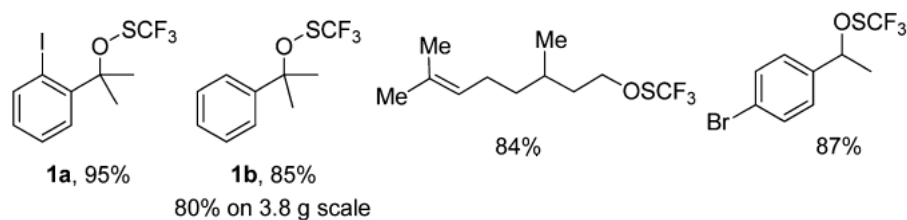
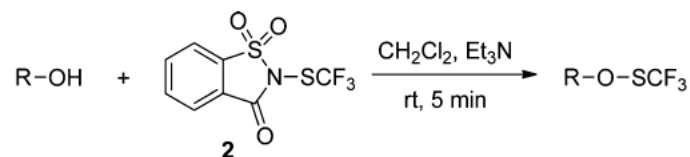
easily scaled up to 20.0 g

*Reactivity :*



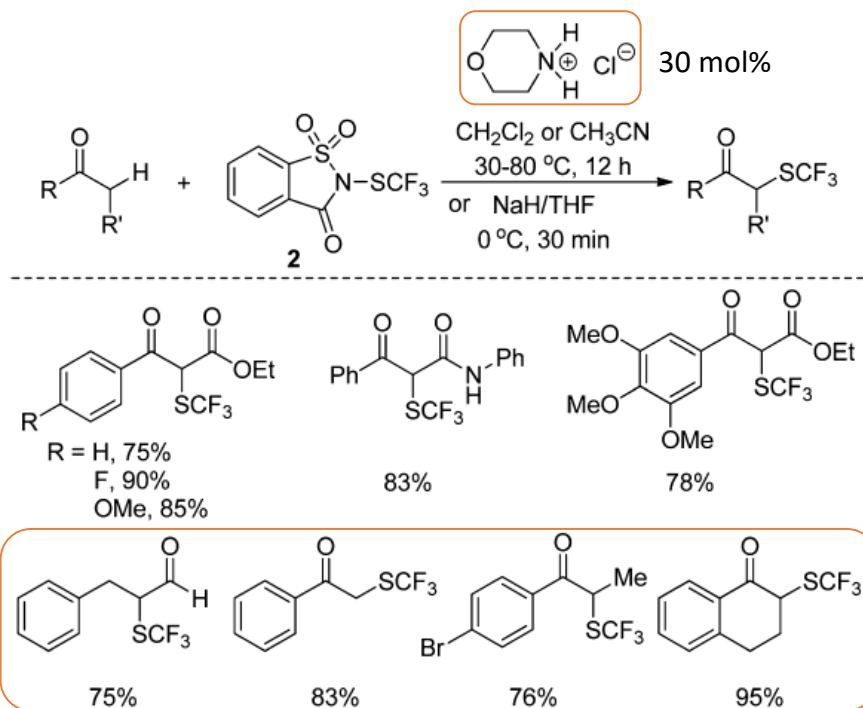
Yield : (1) 16%; (2) 12%; (3) **99%.**

## 3.2. Reaction of Reagent 2 with Alcohols, Amines and Thiols

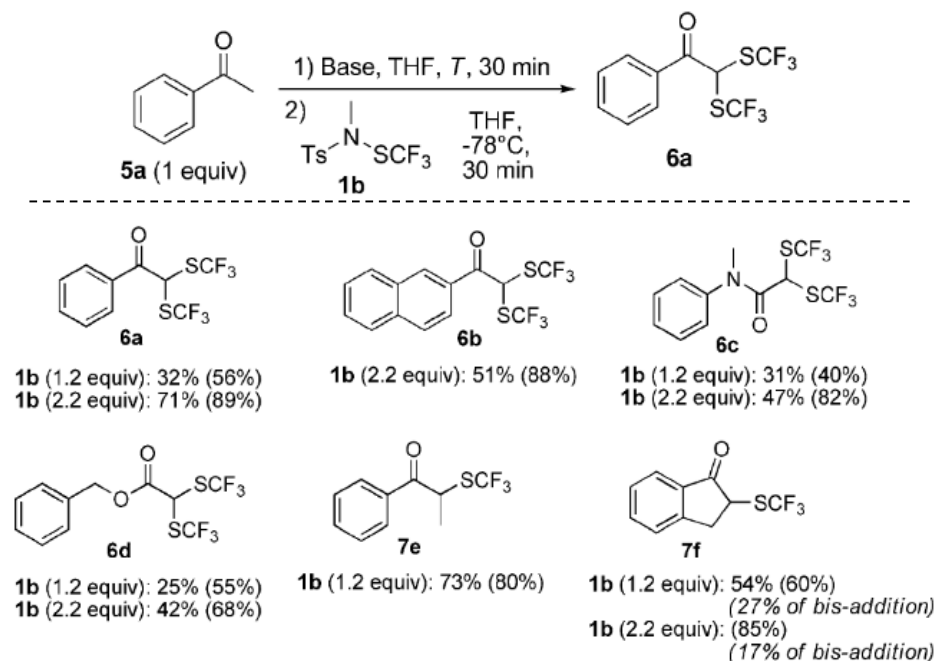


# 3.3. Monotrifluoromethylthiolation of Carbonyl Nucleophiles Using Reagent 2

## Selective $\alpha$ -monotrifluoromethylthiolation



## Di-trifluoromethylthiolation

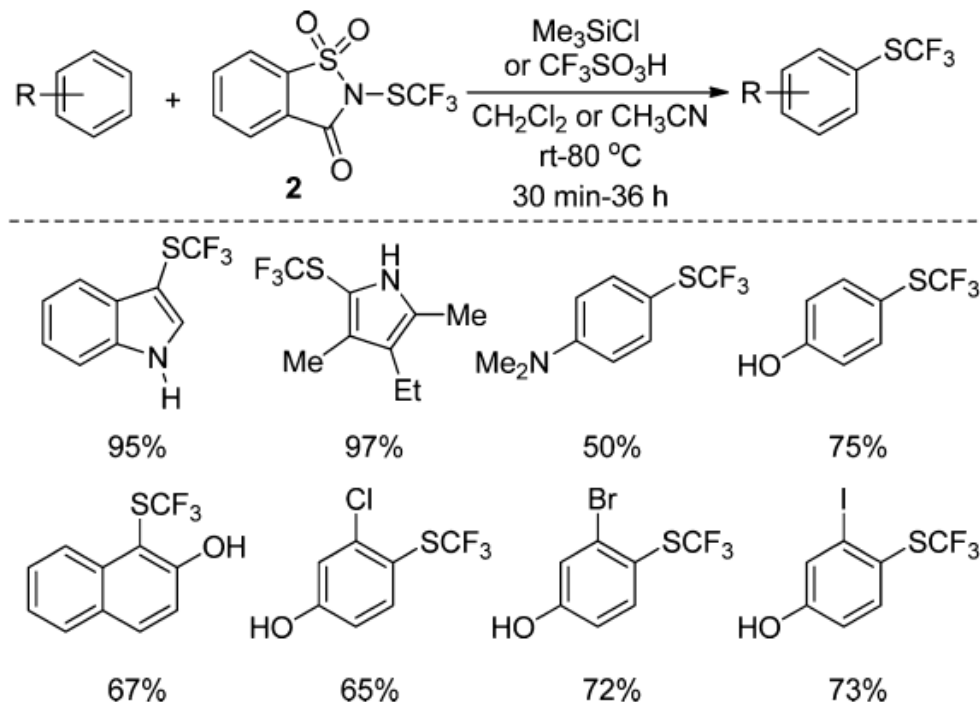


Shao, X.-X.; Wang, X.-Q.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, 52, 3457-3460.

Xu, C.-F.; Ma, B.-Q.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, 53, 9316-9320.

Alazet, S.; Zimmer, L.; Billard, T. *Chem. Eur. J.* **2014**, 20, 8589-8593.

### 3.4. Electrophilic Aromatic Trifluoromethylthiolation of Electron-Rich Arenes Using Reagent 2





# Content

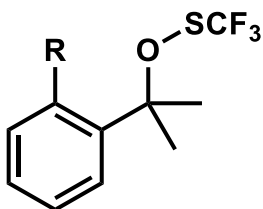
- Introduction
- Trifluoromethanesulfenates: *Preparation and reactivity*
- N-trifluoromethylthiosaccharin: *Preparation and reactivity*
- **Compararison of the reactivities of Trifluoromethanesulfenates 1a and 1b and N-trifluoromethylthiosaccharin 2**
- Summary



## 4. Comparison of the reactivities of trifluoromethanesulfenates 1a and 1b and N-trifluoromethylthiosaccharin 2

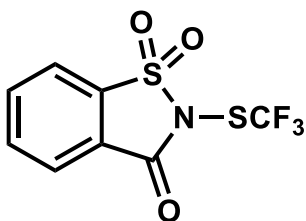
shelf-stable, highly reactive, ease in preparation, broad scope, and mild reaction conditions

**Difference:** *two different families; substrates scope complementary.*



R = I, 1a  
H, 1b

More reliable in **transition-metal-catalyzed** reactions:  
copper-catalyzed: **aryl/vinyl/alkylboronic acids**;  
silver-catalyzed: **aliphatic carboxylic acids**.



2

More electrophilic and more efficient for **direct trifluoromethylthiolation** of nucleophiles :  
**amines, alcohols, thiols, and electron-rich arenes**.



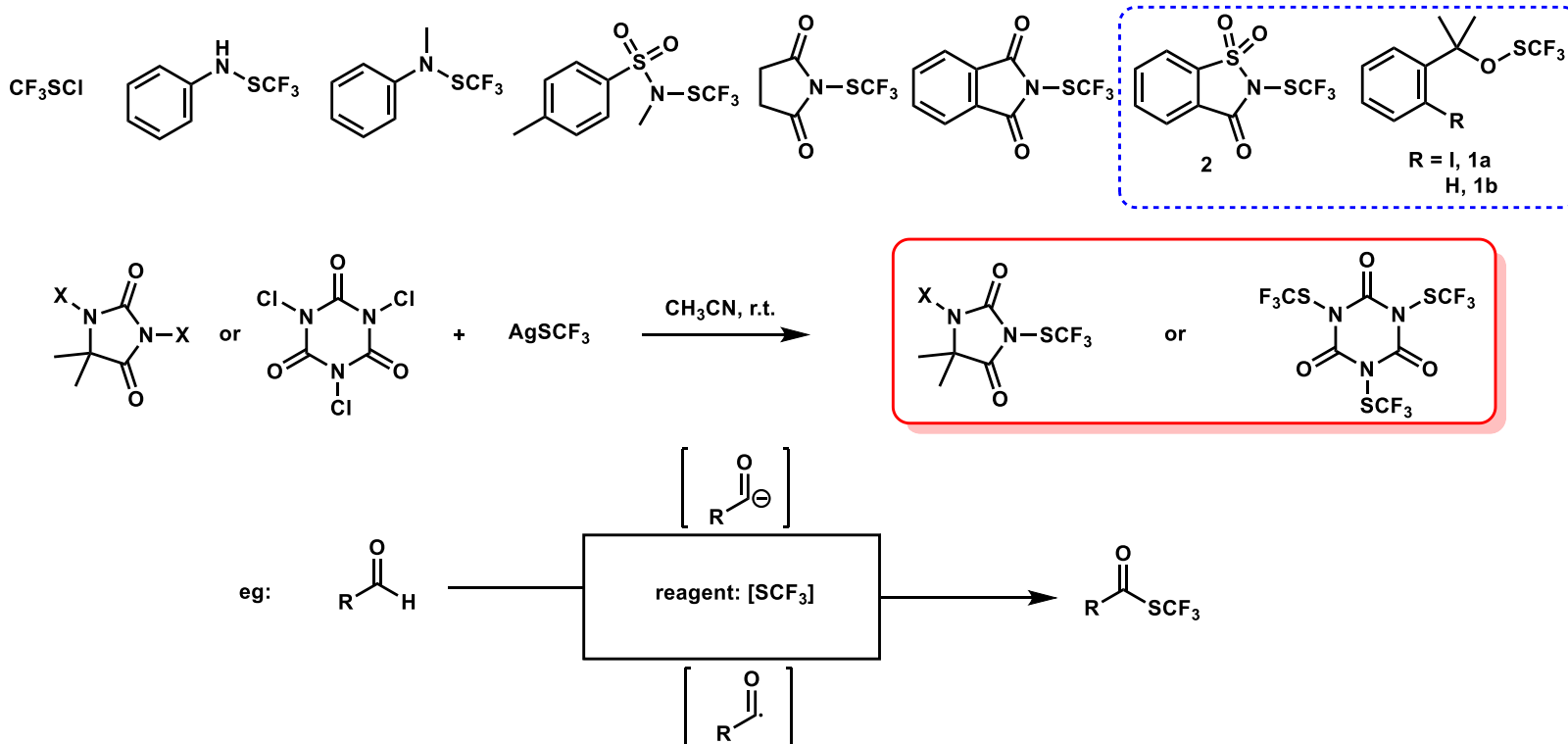
# Content

- Introduction
- Trifluoromethanesulfenates: *Preparation and reactivity*
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- Compararison of the reactivities of Trifluoromethanesulfenates 1a and 1b and N-trifluoromethylthiosaccharin 2
- **Summary**

# Summary



- ◆ Three shelf-stable, highly reactive trifluoromethylthiolation reagents have been developed
- ◆ Various other trifluoromethylthiolation reagents have also been introduced
- ◆ Designing two new reagents and proposing their preparation and application

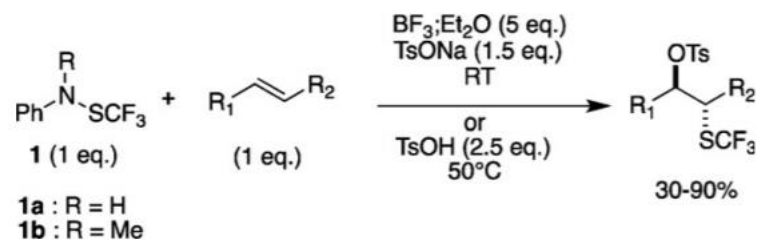


# Acknowledgement

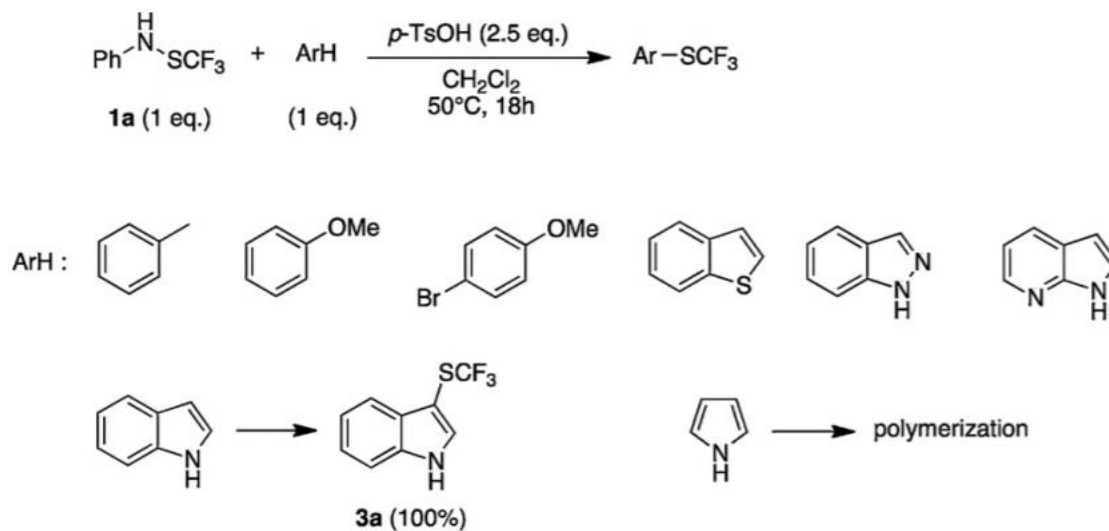
---

- Prof. Huang
- Dr. Chen
- All group members in E201

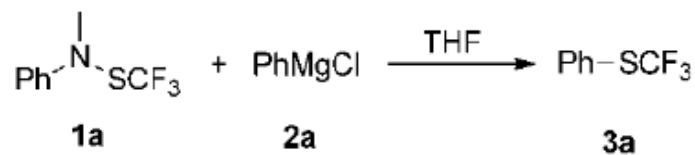
***Thanks for your attention !***

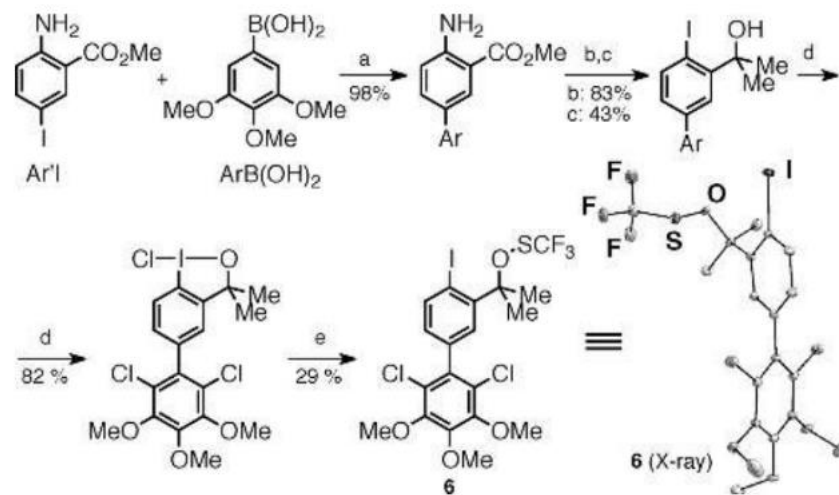
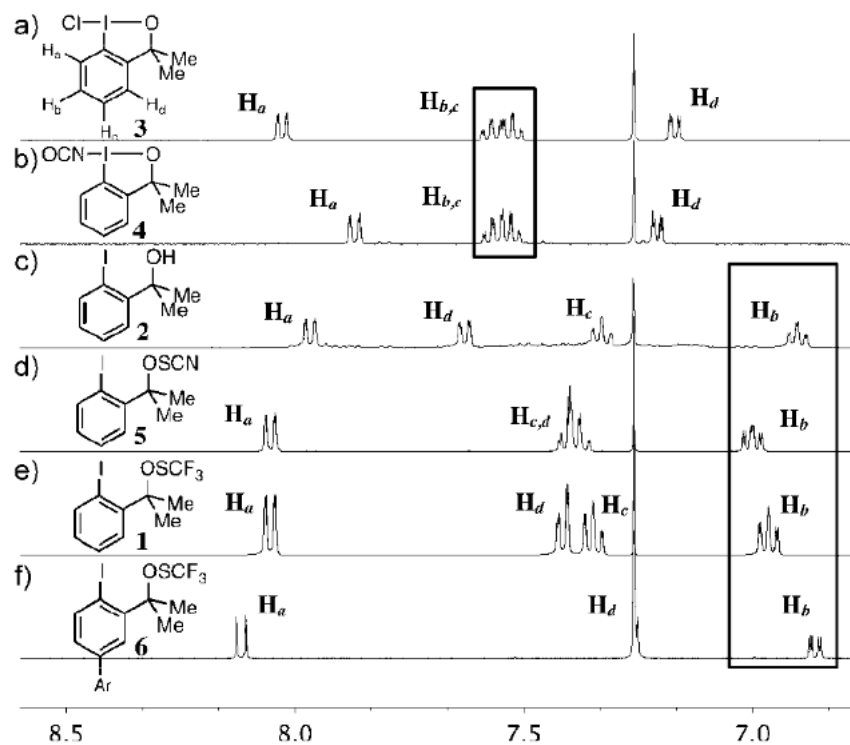


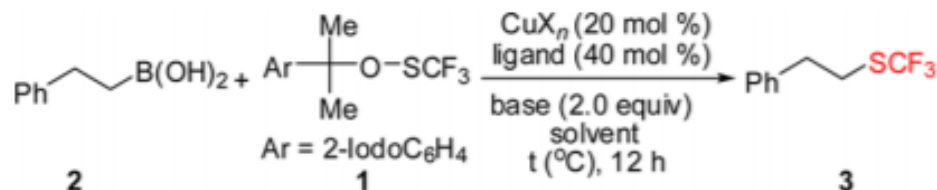
**Scheme 1.** Trifluoromethanesulfonylation of alkenes with trifluoromethanesulfanylamides.



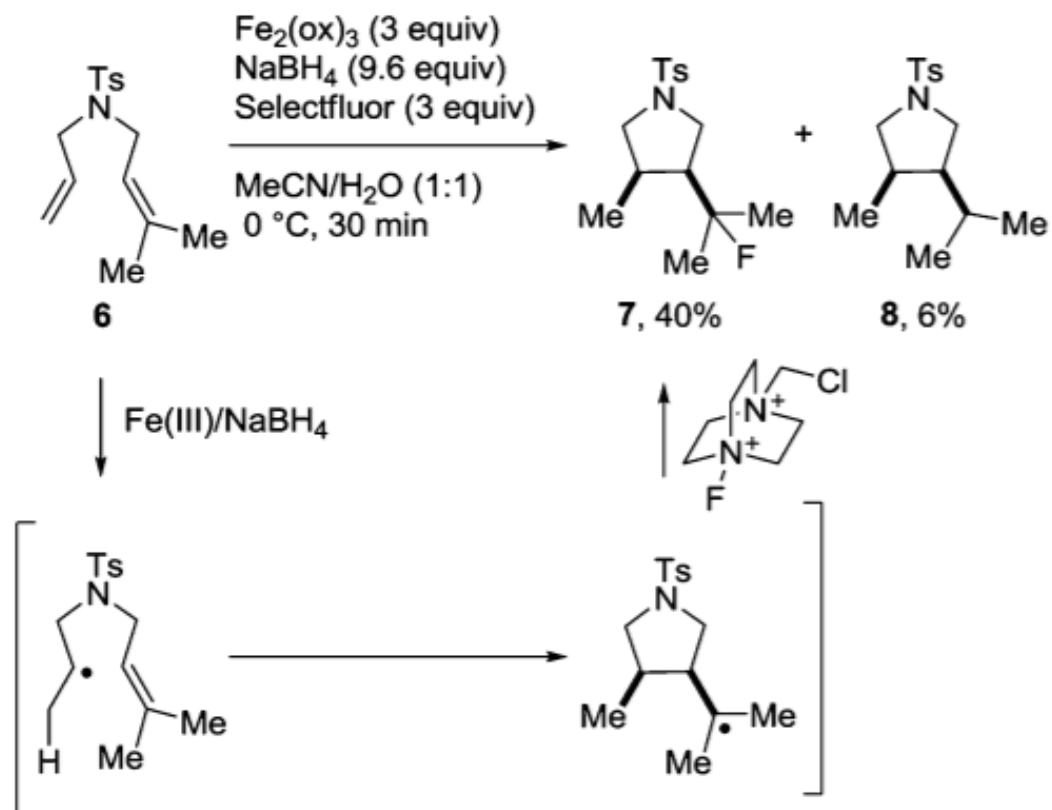
**Scheme 2.** Trifluoromethanesulfonylation of various aromatic compounds.





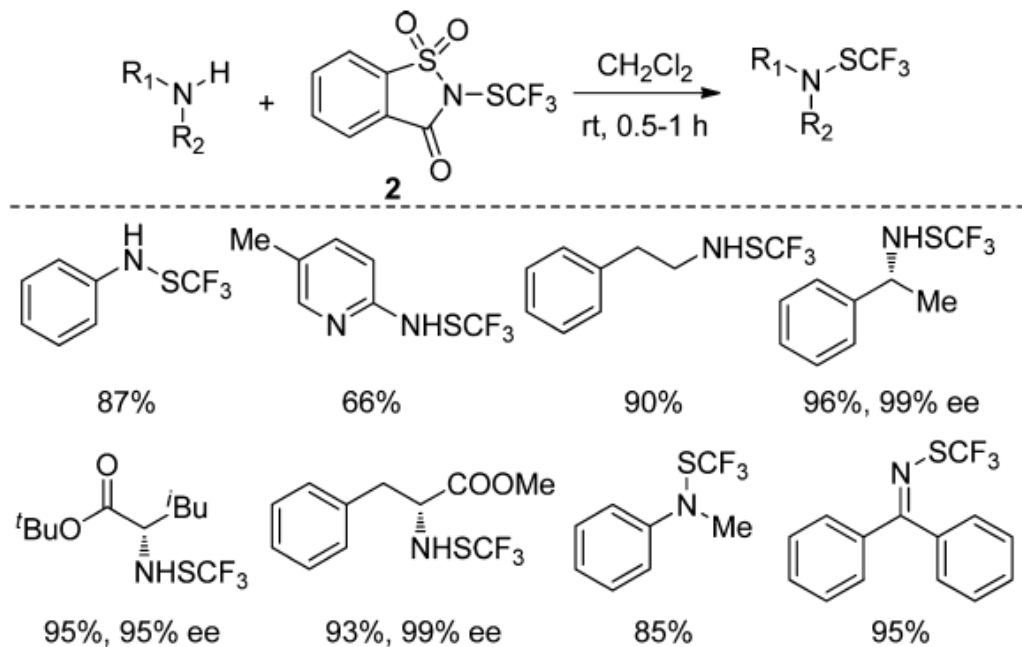


entry	CuX <sub>n</sub>	ligand	base	solvent	temp (°C)	yield (%) <sup>b</sup>
1	Cu(MeCN) <sub>4</sub> PF <sub>6</sub>	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	Diglyme	35	- <sup>c</sup>
2	Cu(MeCN) <sub>4</sub> PF <sub>6</sub>	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	Diglyme	80	35 <sup>b</sup>
3	Cu(MeCN) <sub>4</sub> PF <sub>6</sub>	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	80	60 <sup>c</sup>
4	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	80	58 <sup>c</sup>
5	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	90	73 <sup>c</sup>
6	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	100	73 <sup>c</sup>
7	<b>CuCl<sub>2</sub>·2H<sub>2</sub>O</b>	<b>L1</b>	<b>K<sub>2</sub>CO<sub>3</sub></b>	<b>DCE</b>	<b>120</b>	<b>80</b>
8	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	120	71 <sup>d</sup>
9	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	120	60 <sup>e</sup>
10	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L2</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	120	59
11	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L3</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	120	66
12	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L4</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	120	54
13	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	KOAc	DCE	120	39
14	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>3</sub> PO <sub>4</sub>	DCE	120	45
15	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	Na <sub>3</sub> PO <sub>4</sub>	DCE	120	69
16	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	Na <sub>2</sub> CO <sub>3</sub>	DCE	120	35
17	Cu(OAc) <sub>2</sub>	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	120	49
18	CuBr <sub>2</sub>	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	120	79
19	CuBr·SMe <sub>2</sub>	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	120	72
20	CuTc	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	120	74
21	CuCl <sub>2</sub> ·2H <sub>2</sub> O	-	K <sub>2</sub> CO <sub>3</sub>	DCE	120	30
22	-	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	DCE	120	-
23	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	Toluene	120	72
24	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	NMP	120	trace
25	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	Acetone	120	trace
26	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	120	31
27	CuCl <sub>2</sub> ·2H <sub>2</sub> O	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	THF	120	25





### 3.2. Reaction of Reagent 2 with Amines



### 3.3. Reaction of Reagent 2 with Thiols

