Recent development in direct methods for trifluoromethylthiolation

Organic Seminar

Zeren Zhang

Dec 4th, 2013

Outline

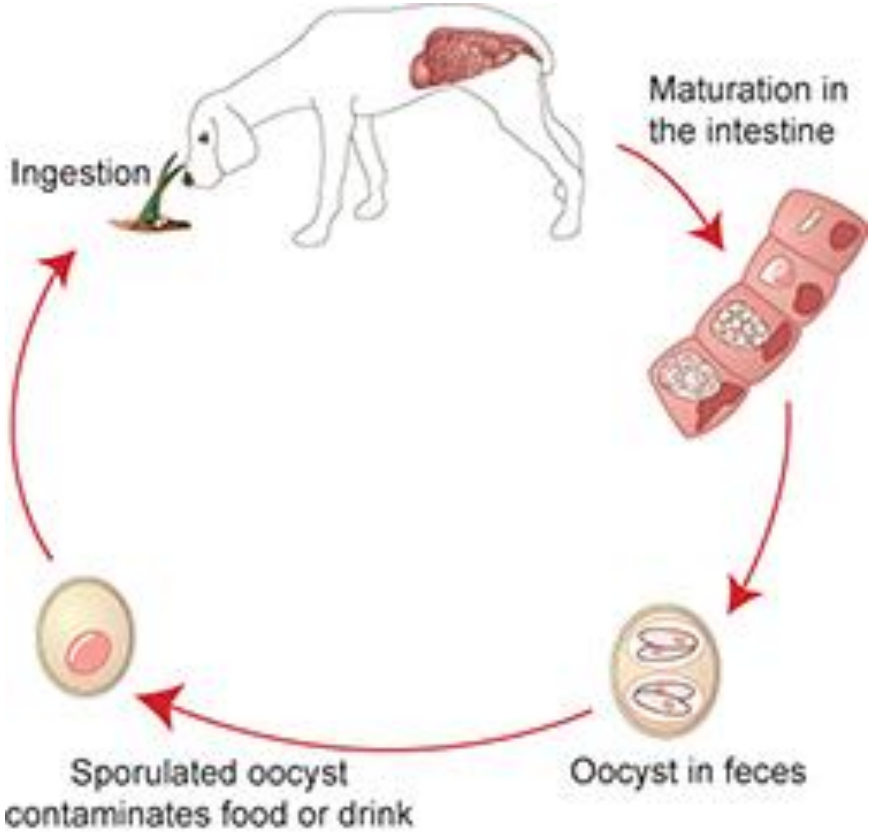
1. Introduction

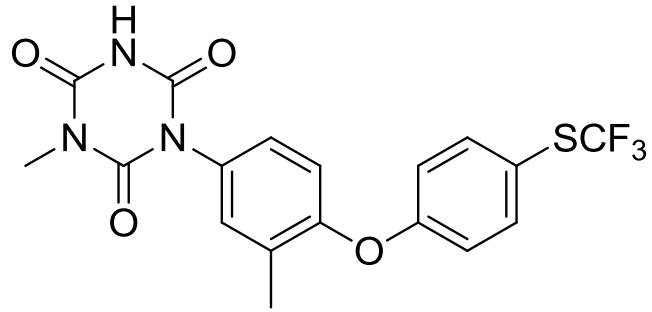
2. Direct trifluoromethylthiolation
   - Electrophilic trifluoromethylthiolation
   - Transition metal-catalyzed nucleophilic trifluoromethylthiolation

3. Summary

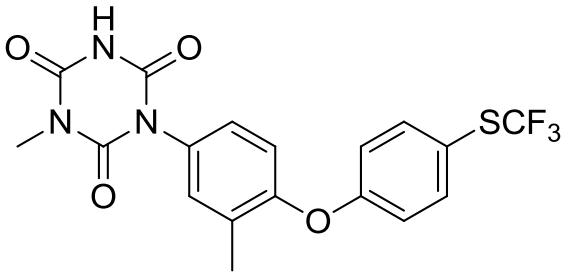
Introduction

Coccidiosis

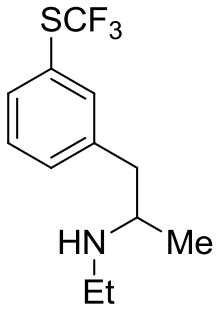




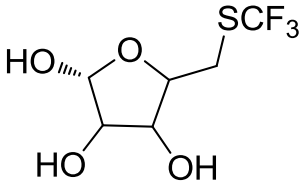
Toltrazuril



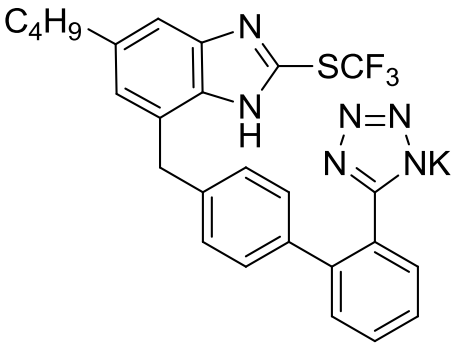
coccidiostatics
Toltrazuril



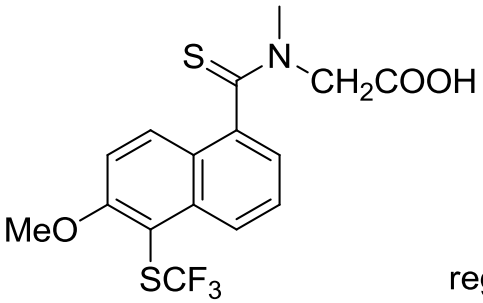
nervous anorexia treatment



antimalarial
antipneumonia

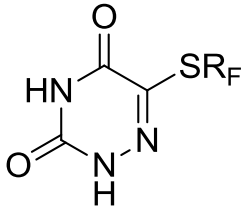


losartan analogues
treatment of cardiovascular diseases

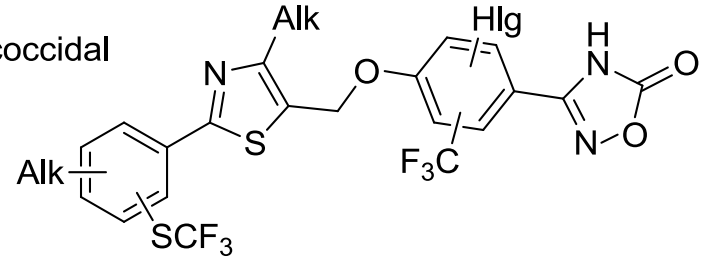


diabetes melitus treatment

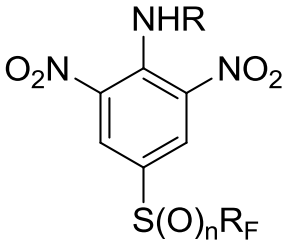
R_F = CF_3, C_3F_7
regulators of plants growth,
fugicides, berbicides



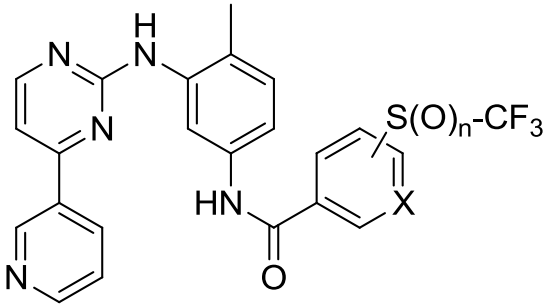
anticoccidal



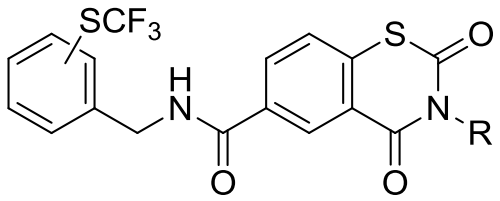
agonists of proxisoma receptor



n = 0-2
RF = CH_2F, CHF_2, CF_3
potential fungicides



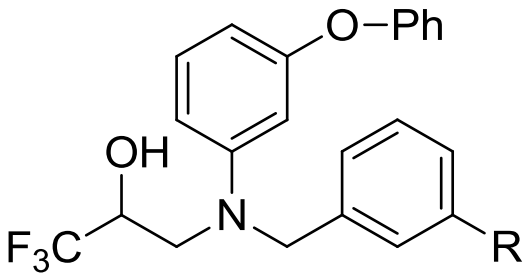
n = 0-2
X = CH, N
therapy of chronic myelodi leukemia



arthritis treatment

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

Introduction

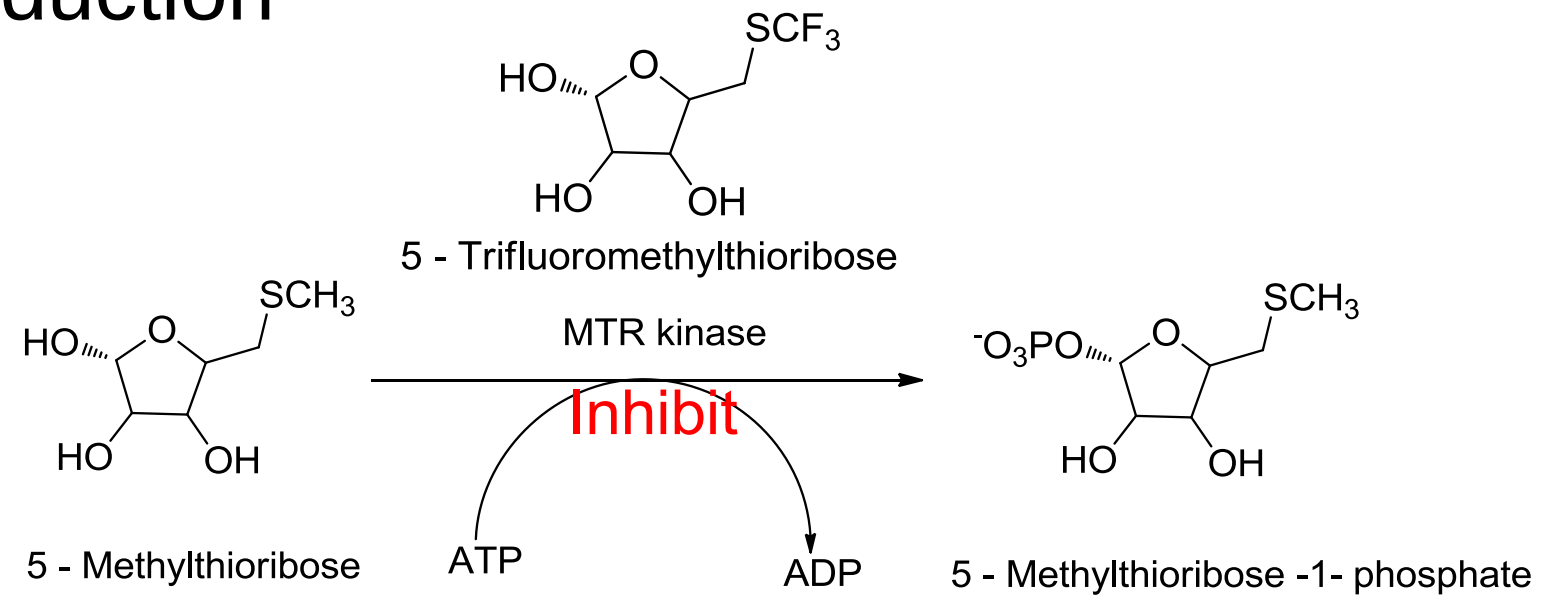


Potential Inhibitor of
Cholesteryl Ester Transfer Protein

Inhibitor	R	IC_{50} (μM) in buffer
1	OMe	15
2	OEt	1.6
3	OPh	5.2
4	OCF_3	1.0
5	SCF_3	**0.39**

Durley , R.C., et al, *J. Med. Chem.*, **2002**, *45*, 3891-3904

Introduction



Element	H	Be	B	C	N	F	Cl	Br
Radius (pm)	29.9	83.0	76.7	70.2	65.9	61.9	102.3	119.9

Gianotti., A,J; Tower, P.A. Sheley, J.H, Conte, P.A, Spiro,C, Ferro, A.J., Fitchen, J.H, Riscoe, M.K; *J Biol Chem,* **1990**, *265*, 831-837.

Introduction

Hansch constant (π), a number to present lipophilic properties .

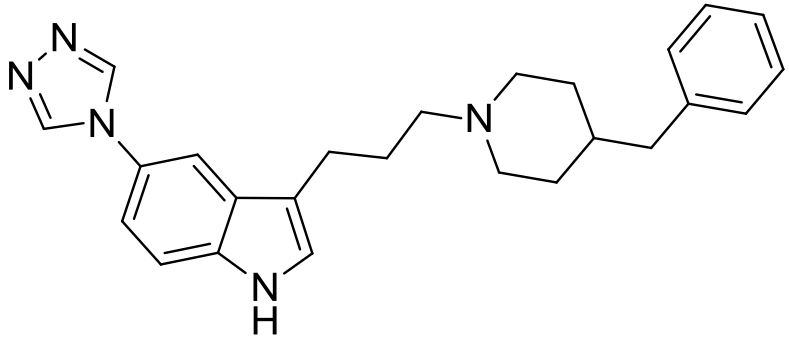
substituent	π	substituent	π
X = H	0.00	X= CH_3	0.56
X = F	0.14	X= CF_3	0.88
X = Cl	0.71	X= OCF_3	1.04
X = Br	0.86	X= SCF_3	1.44
X = I	1.12	X= $CH(CH_3)_2$	1.53

Lipophilicity Increments π as Assessed for Monosubstituted Benzenes H_5C_6 -X

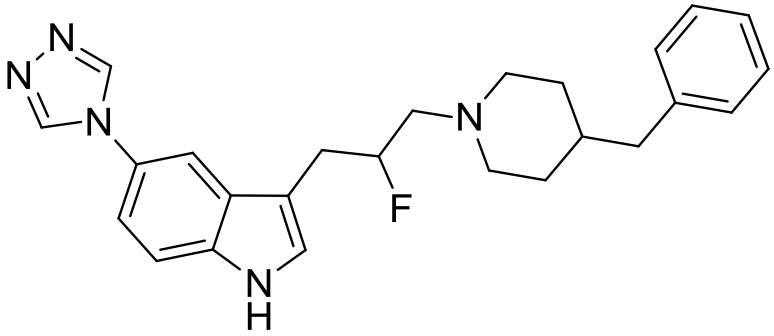
Lipophilic compounds have a tendency to be oxidized by liver enzymes.

Hansch, C,. Leo, A,. Unger, S.H,. Kim, K.H, Xikaitani, D and Lien, EJ, *J. Med. Chem.*, **1973**, *16 (11),* 1207

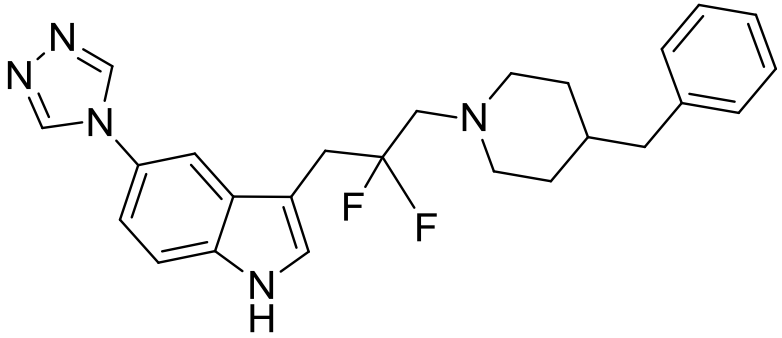
Introduction



IC_{50} = 0.3 nM
pK_a = 9.7
very low bioavailability



IC_{50} = 0.9 nM
pK_a = 8.7
medium bioavailability

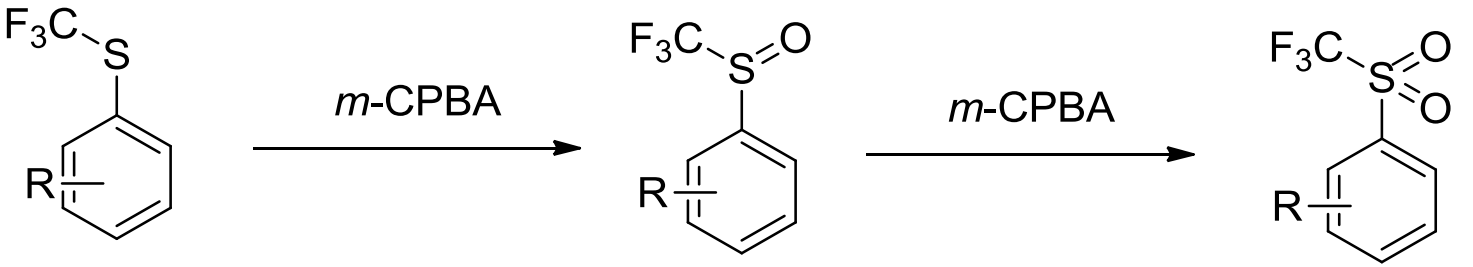


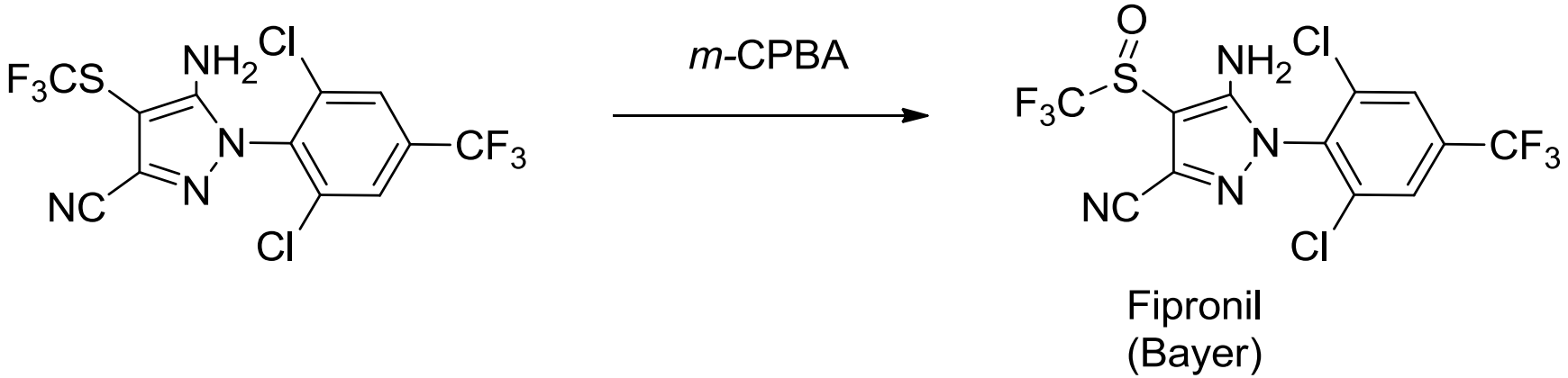
IC_{50} = 78 nM
pK_a= 6.7

Bohm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M., *Chembiochem* **2004**, *5*, 637-643.

Introduction

Important intermediate for the synthesis of trifluoromethyl sulfones and sulfoxides



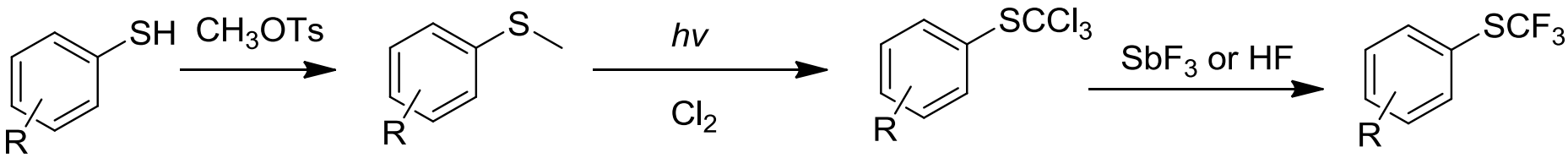


Fipronil
(Bayer)

Ancel, JE., Vidal, J., US patent 7323574 B2, Jan. 29, 2008

Previous Indirect methods

Substitution of halogen atoms by fluorine

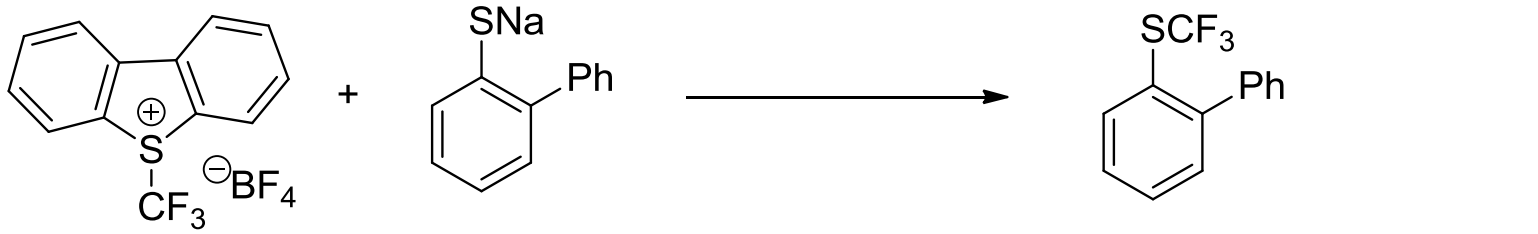


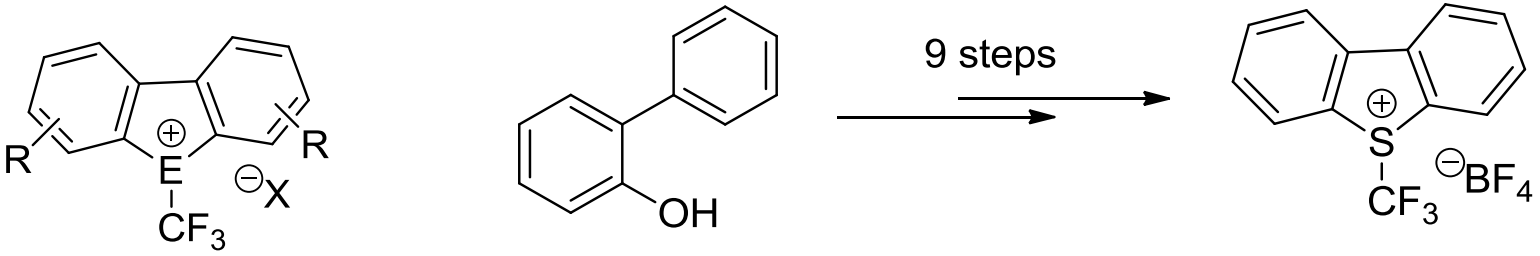
- Corrosive
- Low boiling point of HF (19.4℃)
- Pre-purification of SbF_3 - sublimation

Scherer, B., *Angew. Chem,* **1939,** *52*. 457-459

Previous Indirect methods

Trifluoromethylation





E = S, Se, Te
X = BF_4, OTf

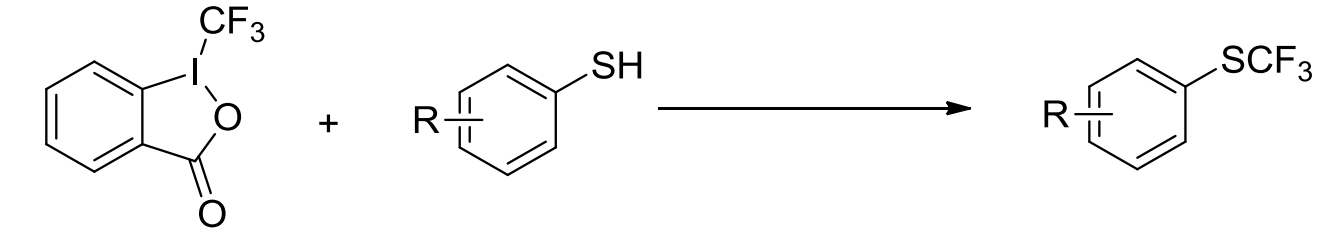
Umemoto reagent

Long synthesis steps

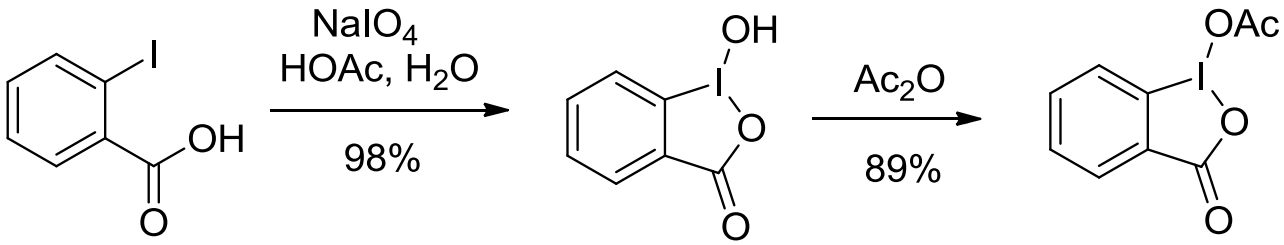
Umemoto, T., Ishihara , S., *J. Am. Chem. Soc*. **1993**, *115*, 2156-2164

Previous Indirect methods

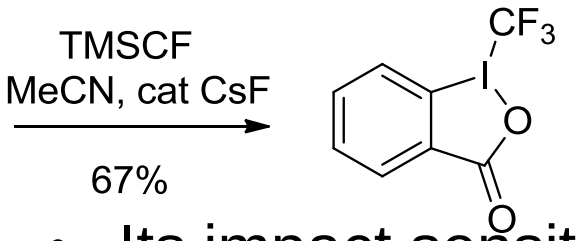
Trifluoromethylation



Togni reagent II



R	Yield (%)
m-Br	82
p-NO_2	88
o-NH_2	82
m-NH_2	72

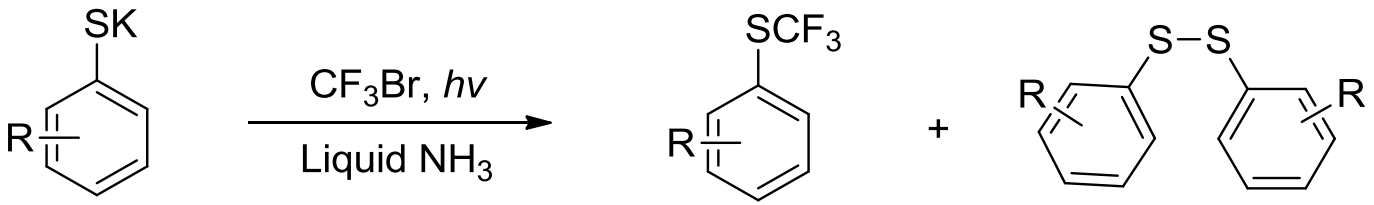


- Its impact sensitiveness is similar to that of TNT.
- And highly explosive to heat.

Eisenerger, P., Gischig, S., Togni, A., *Chem. Eur. J*, **2006**, *12*, 2579-2586
Fiederling, N., Haller , J., Schramm, H., *Org. Process Res. Dev*. **2013**, *17*, 318-319

Previous Indirect methods

Radical reaction



4-$NHCO_2CH_3$	70%	9%
2-NH_2	66%	7%
4-NO_2	24%	

- Disulfide bond formation
- Must be performed in Liquid NH_3
- Low yield for some substituents

Wakselman, C ., Tordeux, M., *Chem. Comm.*, **1984**, 793-794

Outline

1. Introduction

2. Direct trifluoromethylthiolation
   - Electrophilic trifluoromethylthiolation
   - Transition metal-catalyzed nucleophilic trifluoromethylthiolation

3. Summary

Direct trifluoromethylthiolation

$Cl\text{-}SCF_3$

Electrophilic method

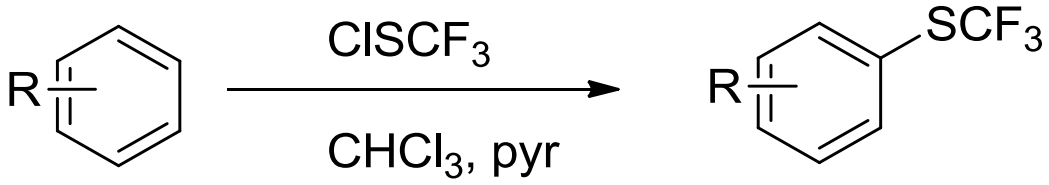
$$SCF_3^+ + Nuc \longrightarrow Nuc\text{-}SCF_3$$

$Ag\text{-}SCF_3$

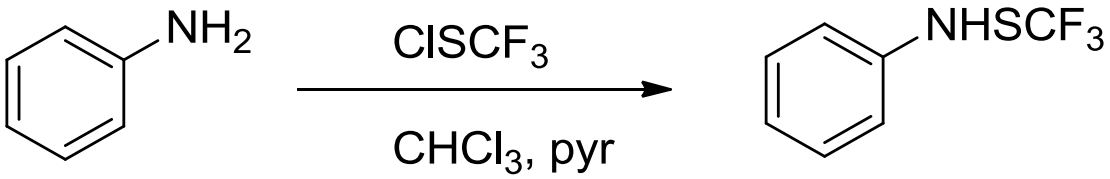
Nucleophilic method

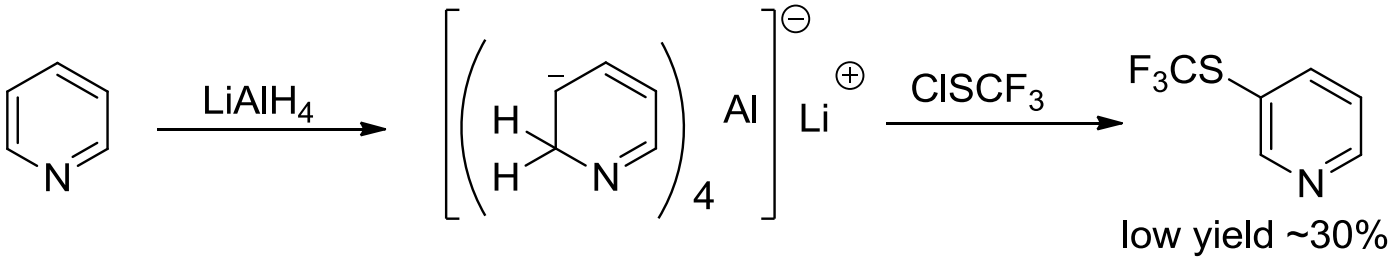
$$SCF_3^- + E \longrightarrow E\text{-}SCF_3$$

Electrophilic methods

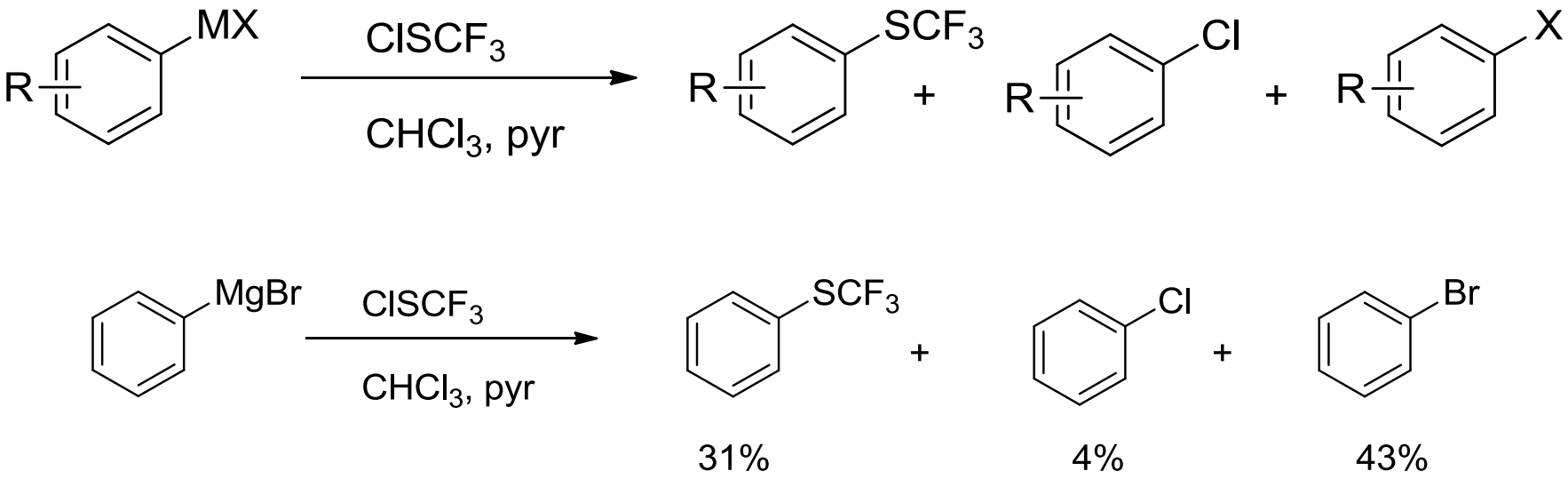


R must be an electron-donating group





Croft, T,S., *Phosphorus Sulfur Relat. Elem*, **1976***, 2*, 133-139.
Gerstenberger, M, R,C., Hass, A, J., *J. Fluorine. Chem*. **1983**, *23*, 525-540

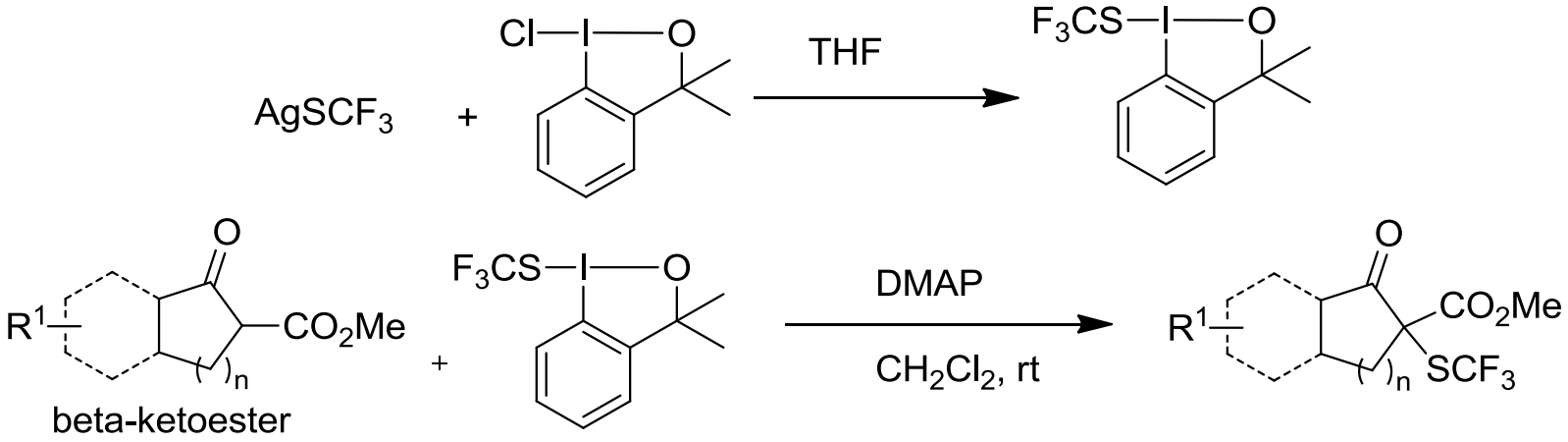


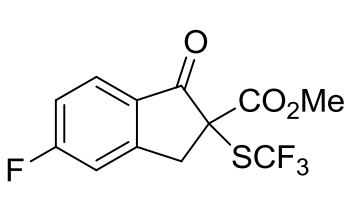
Sheppard, W.A., *J. Org, Chem*, **1964***, 29*, 895-898

Electrophilic methods

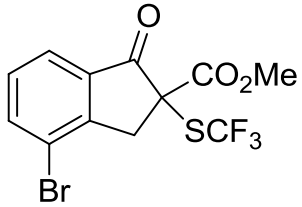
- Hypervalent Iodine reagent
- Trifluoromethanesulfenamide
- Trifluoromethanesulfonyl hypervalent iodonium ylide (iodonium ylide)

Hypervalent Iodine reagent

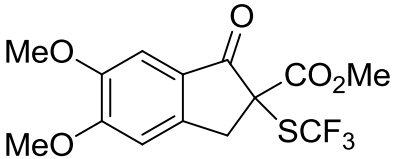




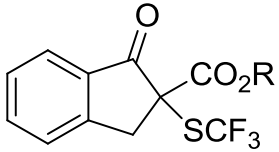
96%



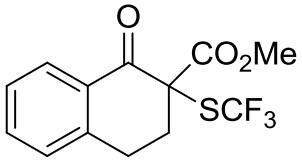
84%



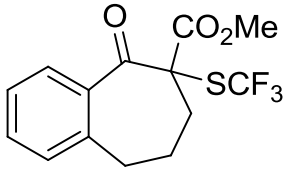
96%



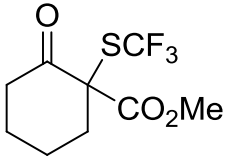
R = Me 93%
Et 90%
*i*Pr 98%



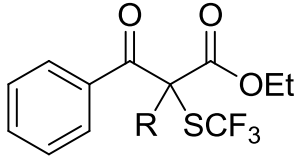
97%



91%



85%

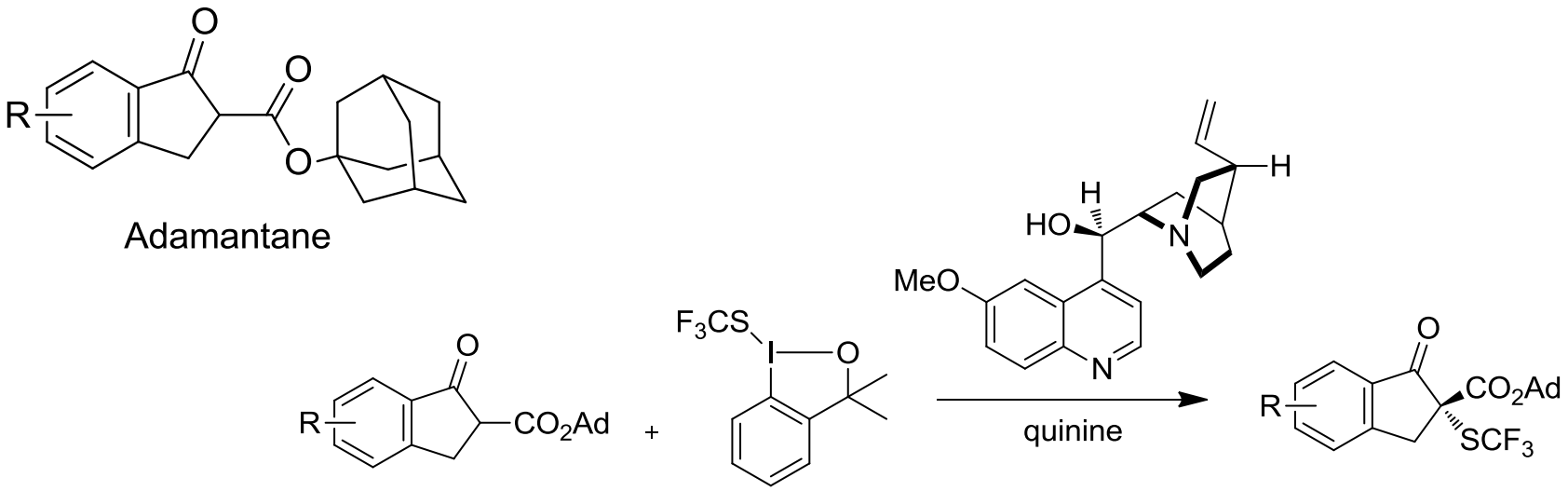


R = H 0%
Me 90%

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

Hypervalent Iodine reagent

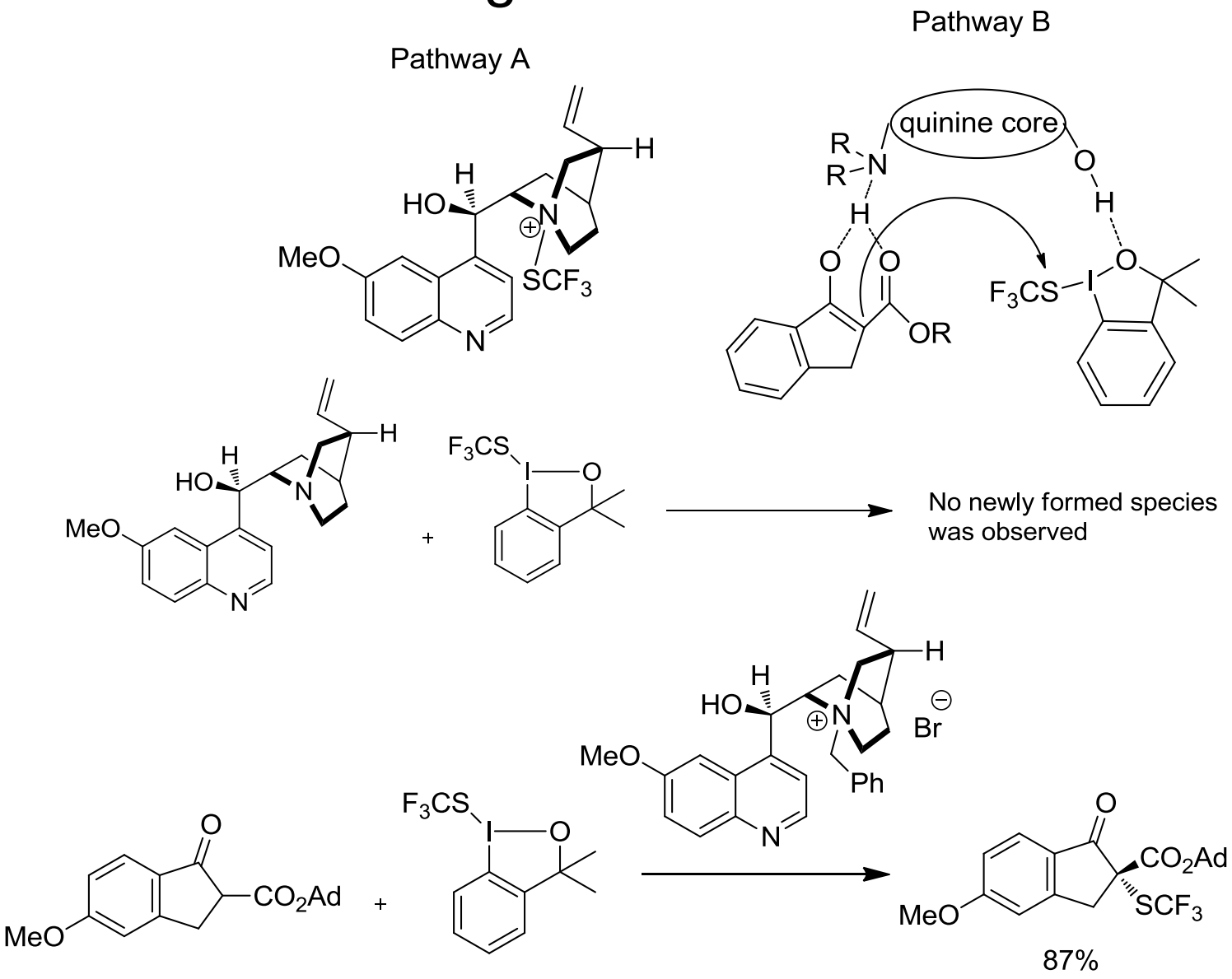
Stereoselective introduction of SCF_3 groups to generate chiral centers to beta-ketoesters



Substitution (R)	H	2-Me	4-OMe	2,3-diOMe	3-Cl	2-Br	3-Br	4-Br
Yield (%)	90	97	95	91	87	83	81	82
ee (%)	92	86	94	94	92	93	92	89

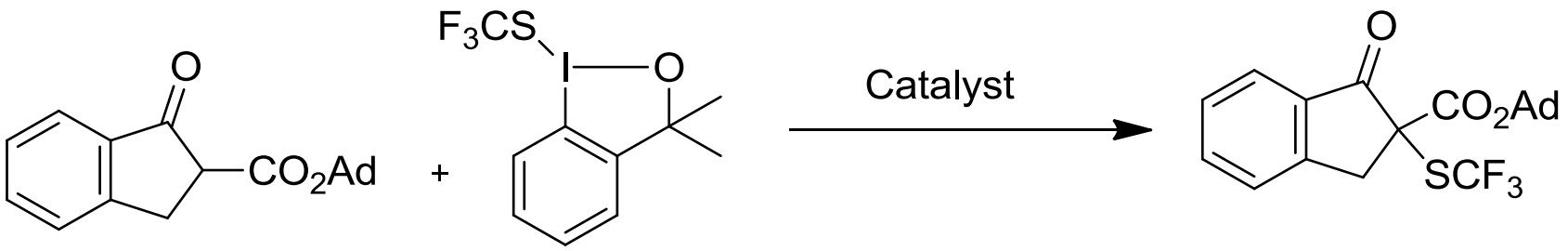
Wang, X.; Yang, T.; Cheng, X.; Shen, Q., *Angew. Chem. Int. Ed* , **2013**, *52*. 12860-12864

Hypervalent Iodine reagent

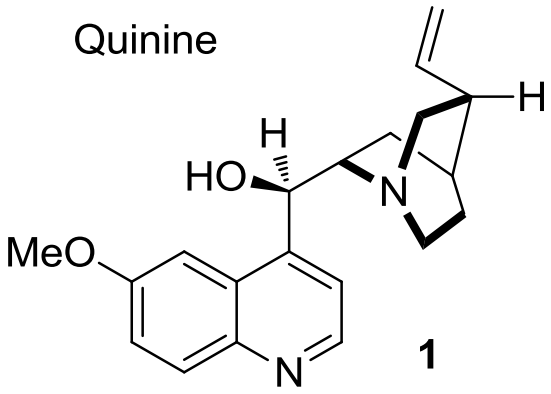


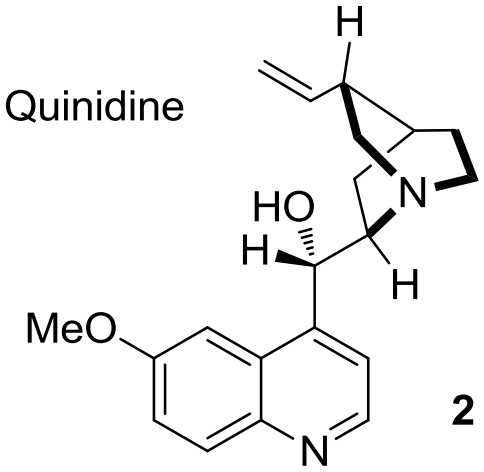
Wang, X.; Yang, T.; Cheng, X.; Shen, Q., *Angew. Chem. Int. Ed* , **2013**, *52*. 12860-12864

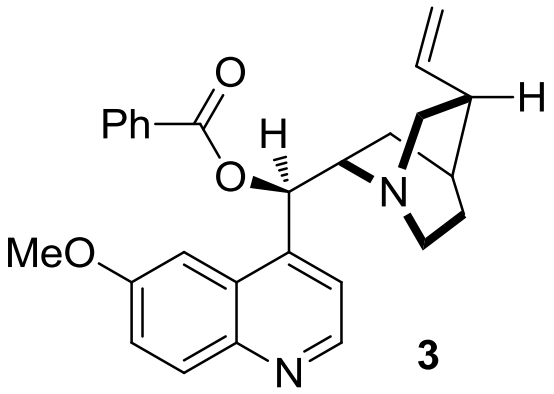
Hypervalent Iodine reagent



Catalyst	Yield (%)	ee (%)
1	91	92 (R)
2	83	88 (S)
3	<5	N/A

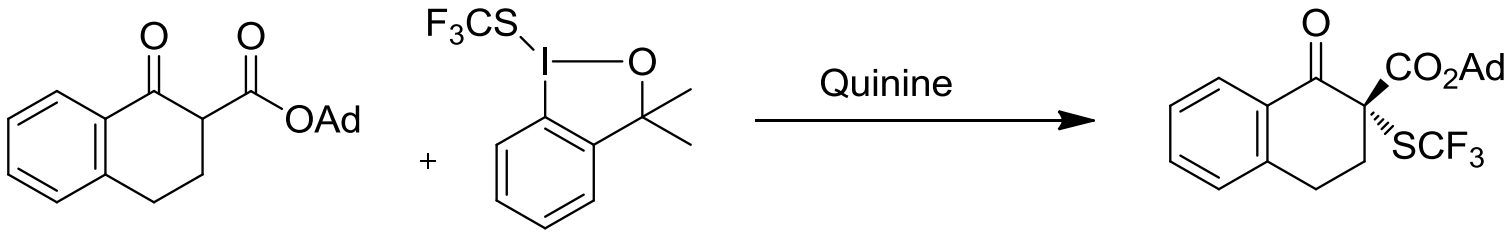


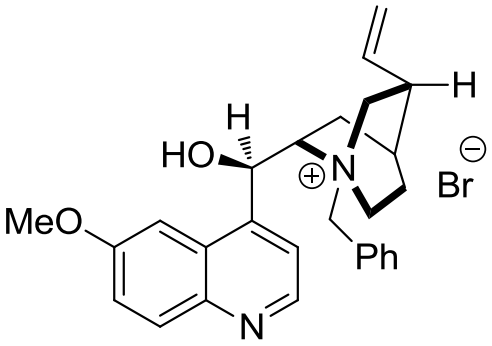




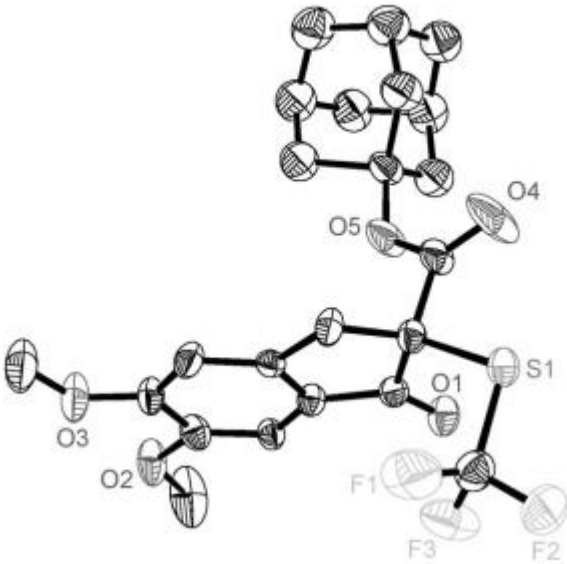
Wang, X.; Yang, T.; Cheng, X.; Shen, Q., *Angew. Chem. Int. Ed* , **2013**, *52*. 12860-12864

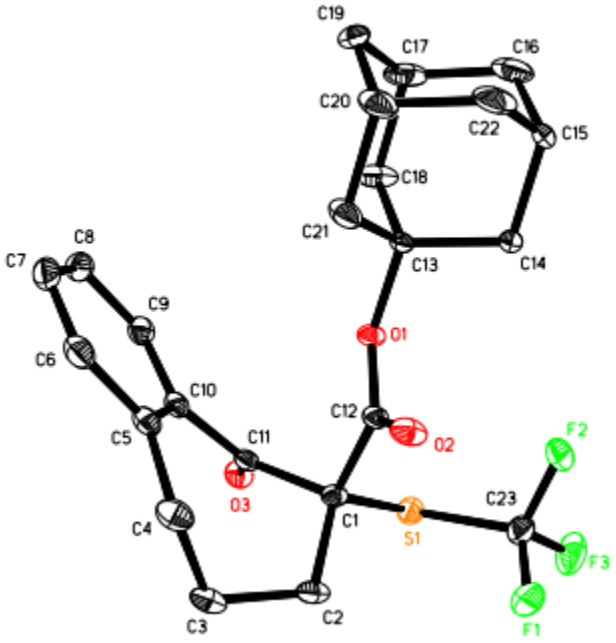
Hypervalent Iodine reagent





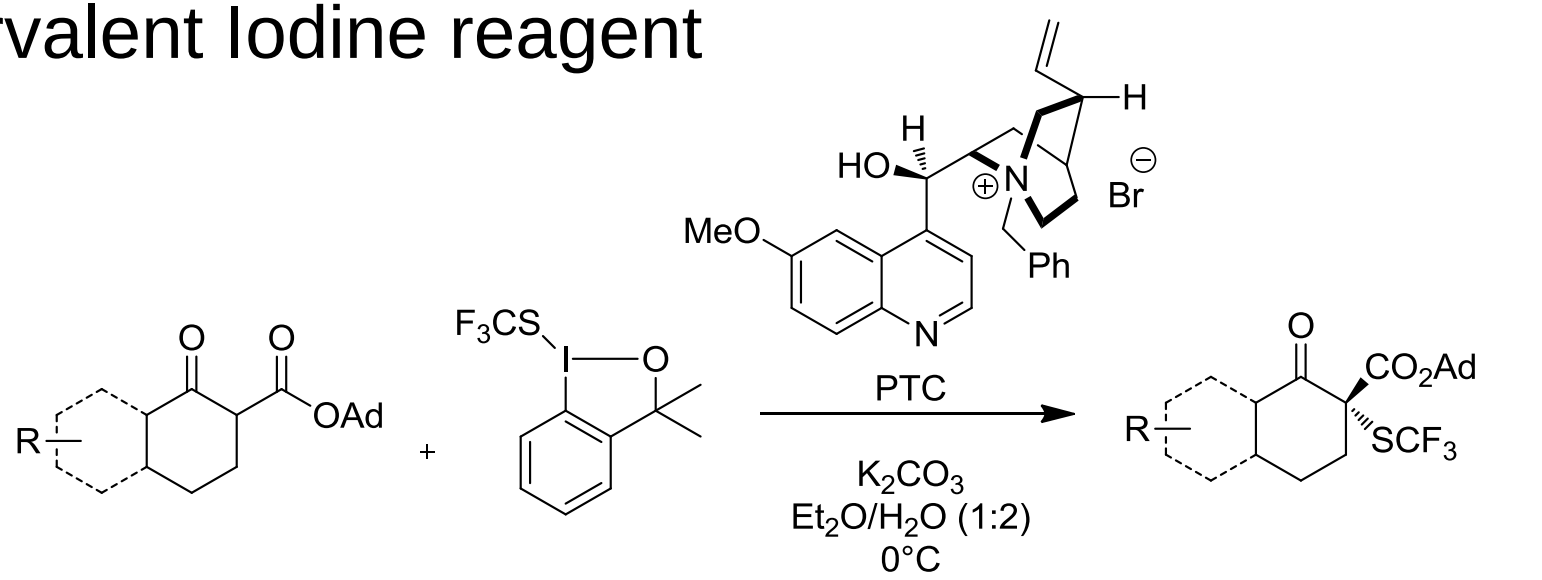
Phase-transfer catalyst

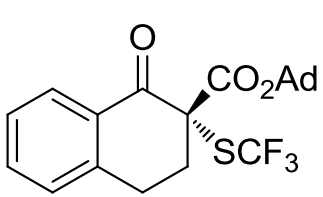




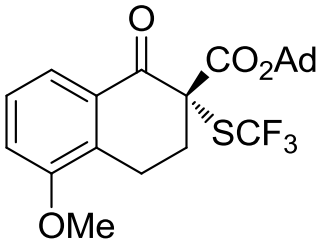
Lee, J.-H.; Yoo, M.-S.; Jung, J.-H.; Jew, S.-s.; Park, H.-g.; Jeong, B.-S., *Tetrahedron* **2007**, *63* , 7906-7915.
Wang, X.; Yang, T.; Cheng, X.; Shen, Q., *Angew. Chem. Int. Ed* , **2013**, *52*. 12860-12864

Hypervalent Iodine reagent

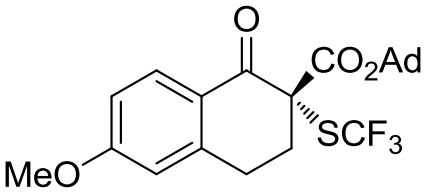




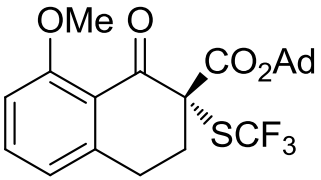
93%, 80% *ee*



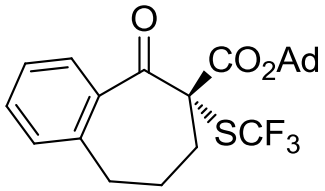
90%, 77% *ee*



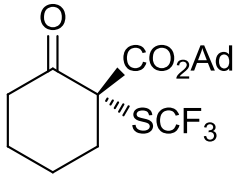
91%, 66% *ee*



91%, 73% *ee*



88%, 96% *ee*



49%, 64% *ee*

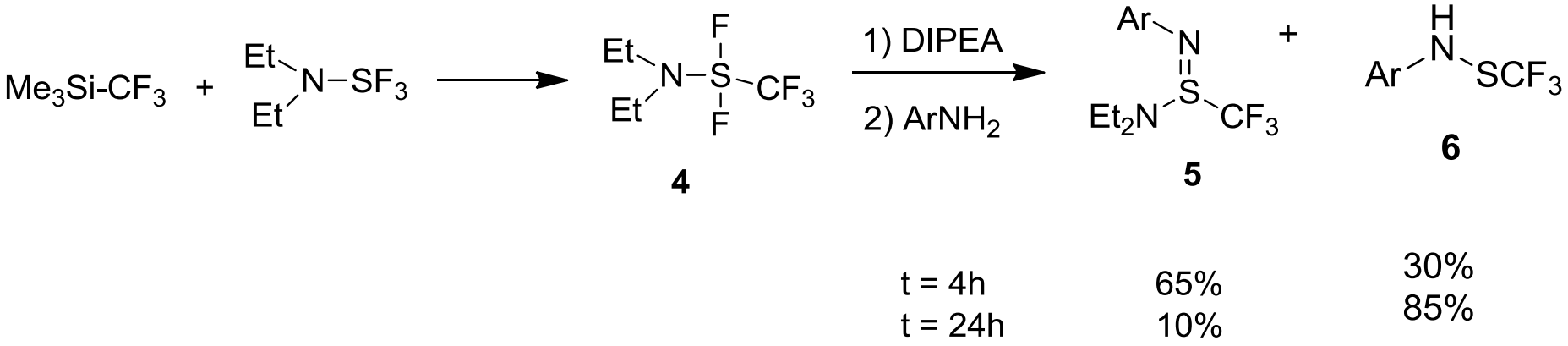
Wang, X.; Yang, T.; Cheng, X.; Shen, Q., *Angew. Chem. Int. Ed* , **2013**, *52*. 12860-12864

Electrophilic methods

- Hypervalent Iodine reagent
- Trifluoromethanesulfenamide
- Trifluoromethanesulfonyl hypervalent iodonium ylide

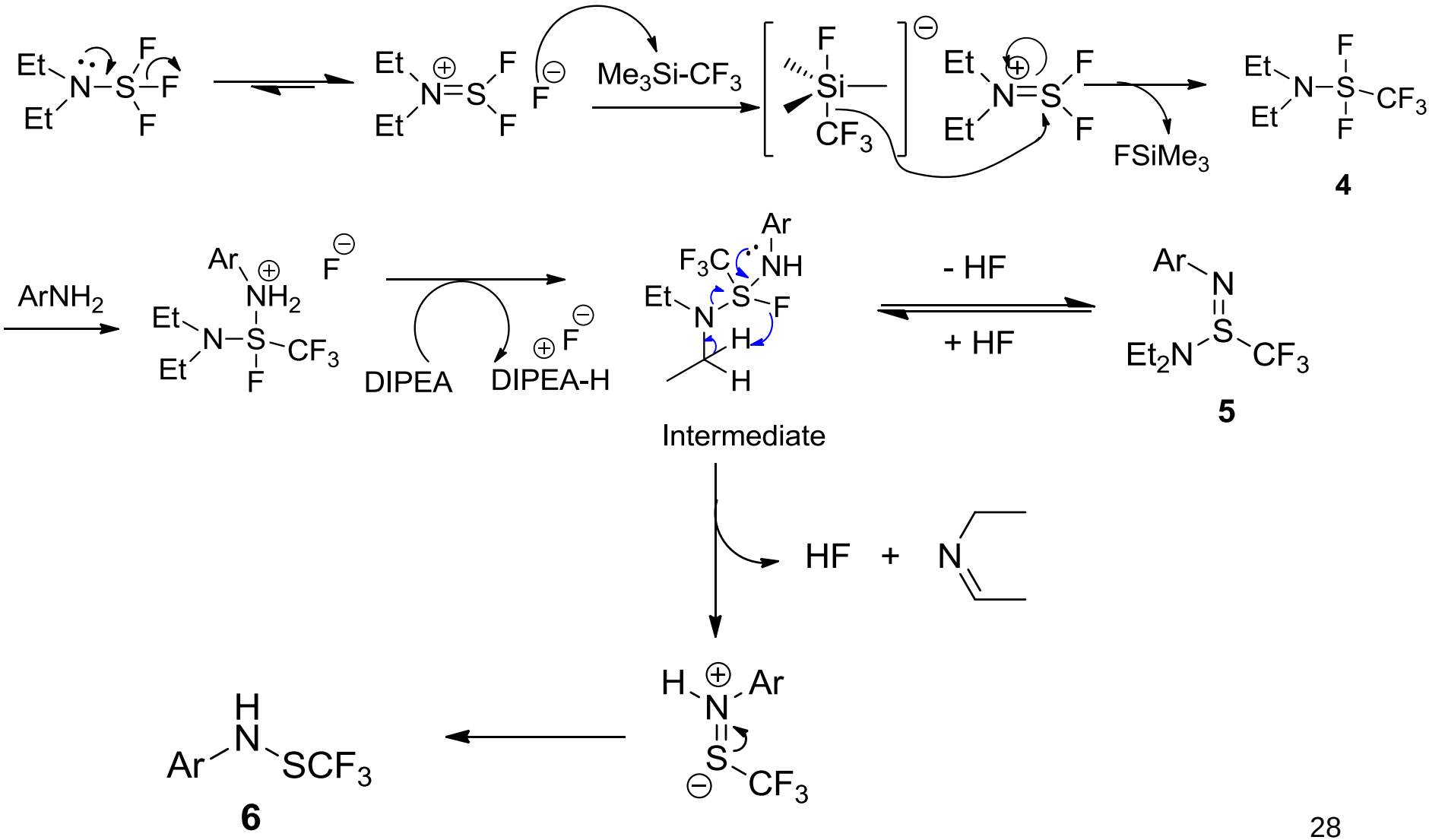
Trifluoromethanesulfenamide

A New SCF_3 source: Found as a sideproduct of prepareing Trifluoromethanesulfinamidines



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

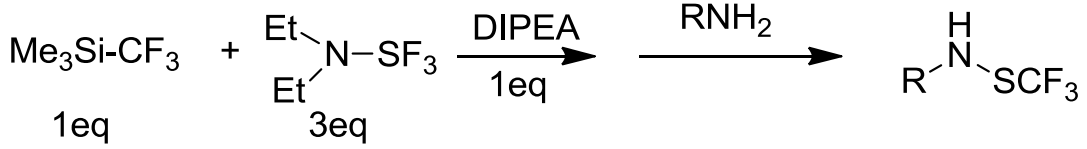
Trifluoromethanesulfenamide

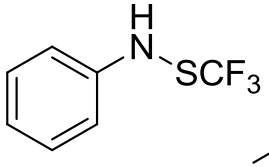


Ferry,A.; Billard, T.; Langlois, B. R.; Bacque, E.;. *J. Org. Chem*. **2008**, *73*, 9362–9365

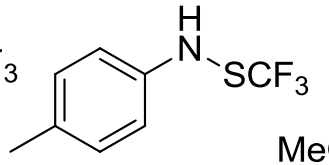
Trifluoromethanesulfenamide

Apply to various primary and secondary amines

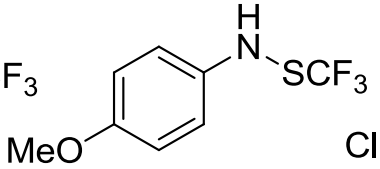




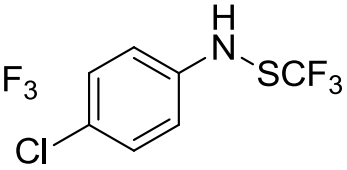
81% (95%)



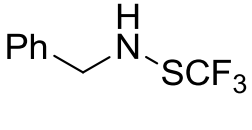
68% (90%)



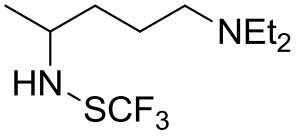
43% (75%)



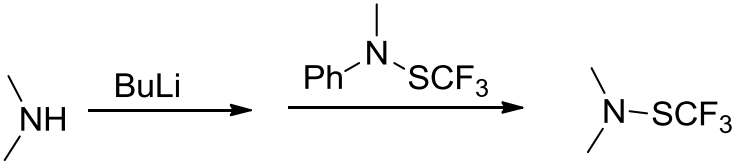
66% (80%)

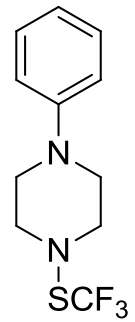


64% (75%)

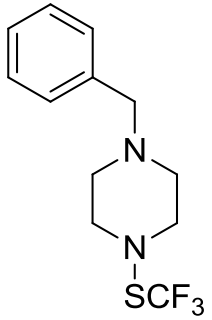


50% (74%)

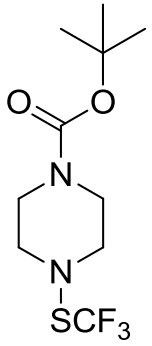




69% (86%)

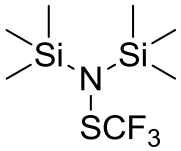


52% (64%)

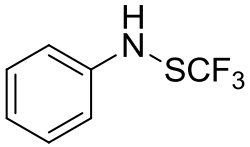


45% (76%)

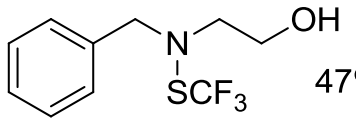
85%(95%)



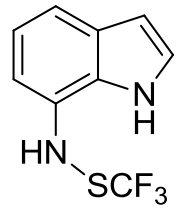
(quant)



68%



47% (61%)

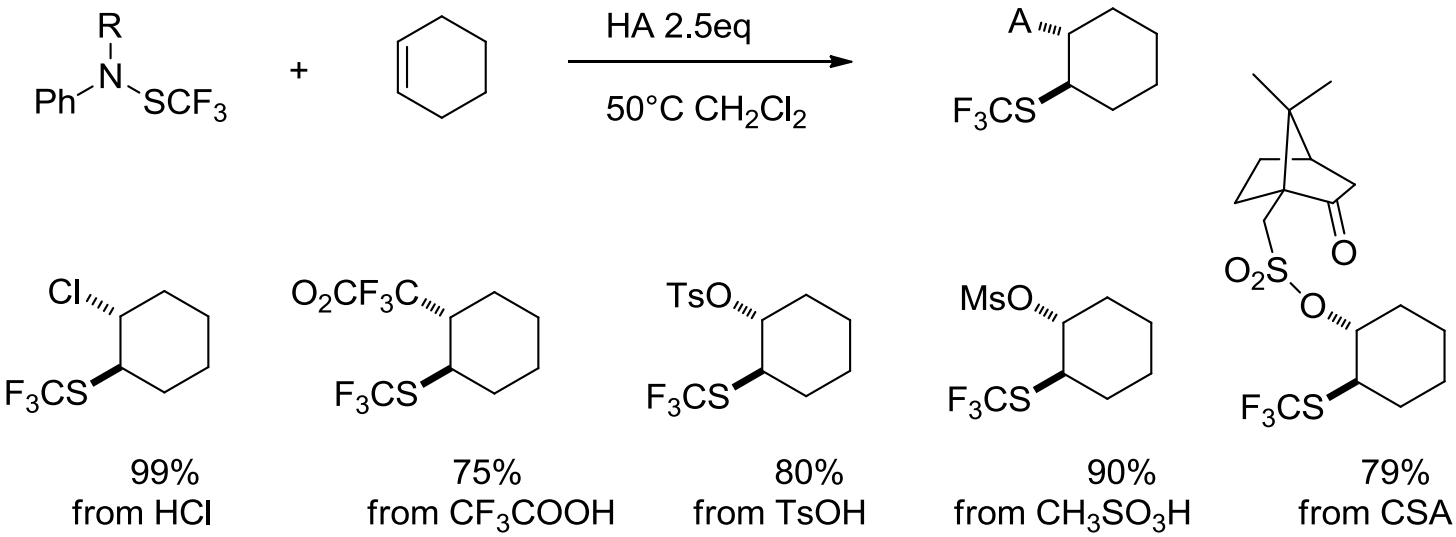


35%(59%)

Ferry,A.; Billard, T.; Langlois, B. R.; Bacque, E, *J. Org. Chem*. **2008***, 73*, 9362–9365
Ferry, A.; Billard, T.; Bacqué, E.; Langlois, B. R., *J Fluorine Chem* **2012**, *134*, 160-163

Trifluoromethanesulfenamide

Then apply to alkenes and alkynes



99% from HCl

75% from CF_3COOH

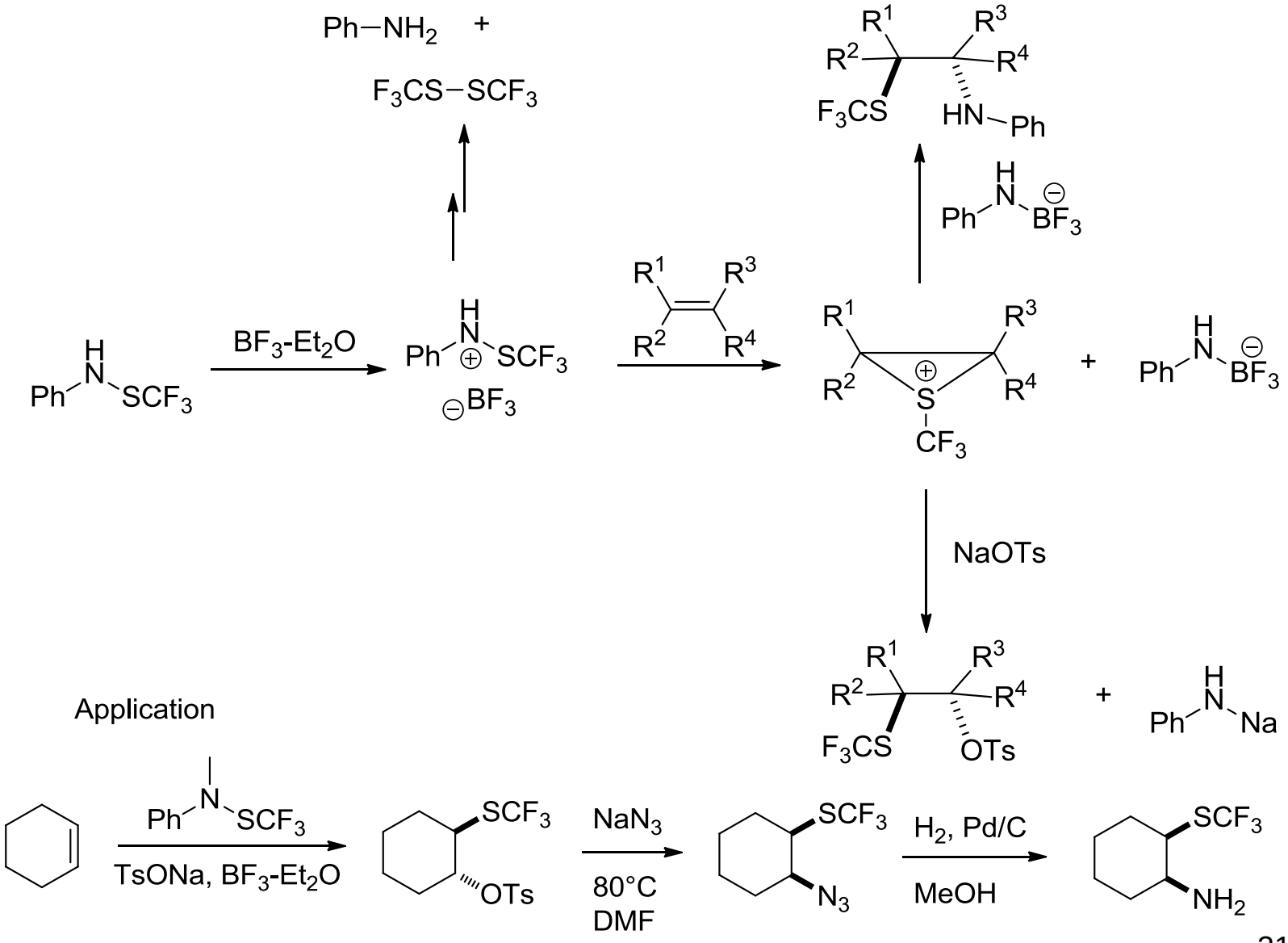
80% from TsOH

90% from CH_3SO_3H

79% from CSA

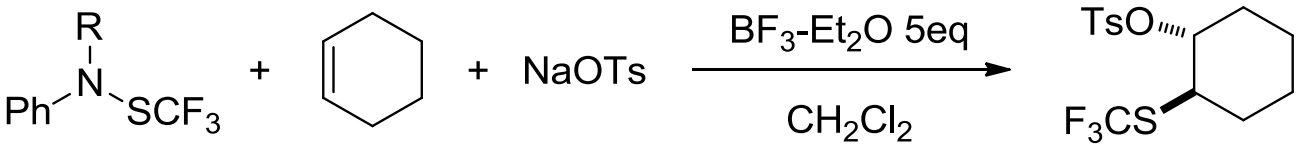
Ferry, A.; Billard, T.; Langlois, B. R.; Bacque, E. *Angew. Chem. Int. Ed* **2009**, *48* , 8551-8555.

Trifluoromethanesulfenamide

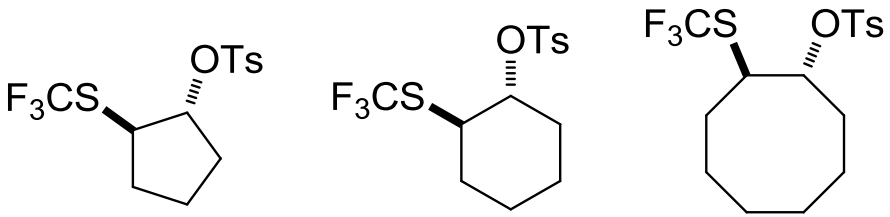


Ferry, A.; Billard, T.; Langlois, B. R.; Bacque, E. *Angew. Chem. Int. Ed* **2009**, *48* , 8551-8555.

Trifluoromethanesulfenamide



R = H : t = 18h / crude yield: 85%
R = Me: t = 4h / crude yield: 90%



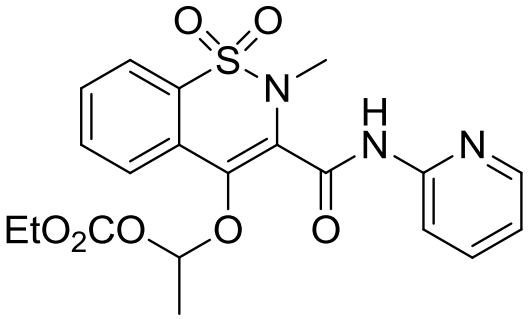
73% 85% 66%

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

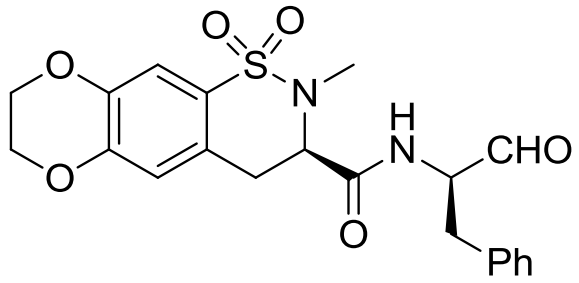
Trifluoromethanesulfenamide

Intramolecular cyclization

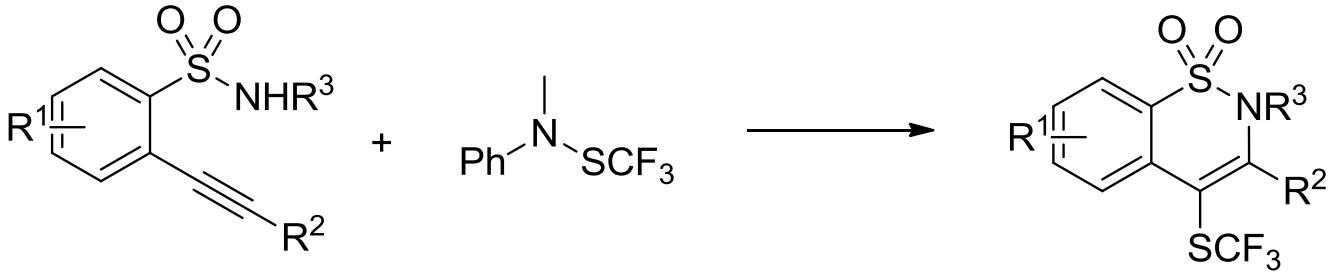
synthesis of a improtant building block for natural products



Ampiroxicam
anti-inflammatory and analgesic drug



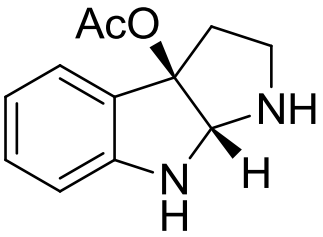
Calpain I inhibitor



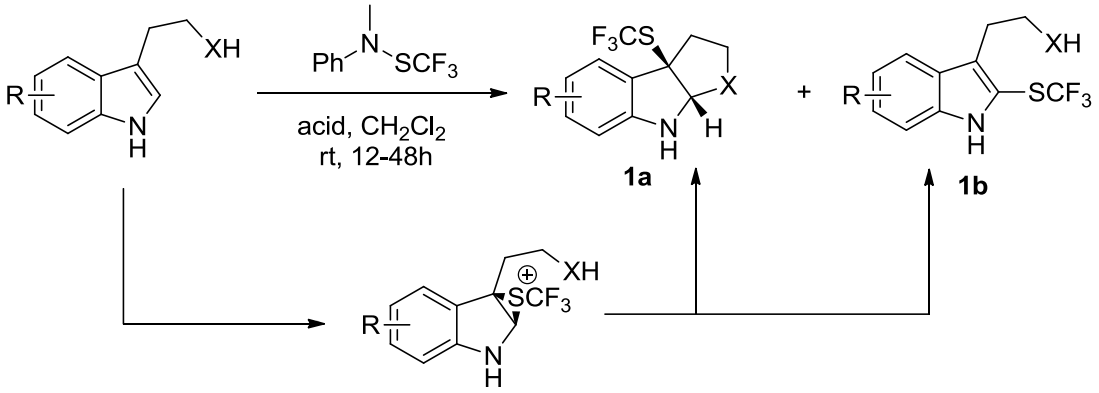
Xiao, Q.; Sheng, J.; Chen, Z.; Wu, J.. *Chem Comm,* **2013**, *49* , 8647-8649.

Trifluoromethanesulfenamide

synthesize SCF_3 contained pyrrolidinoindoline derivates



Alkaloid A

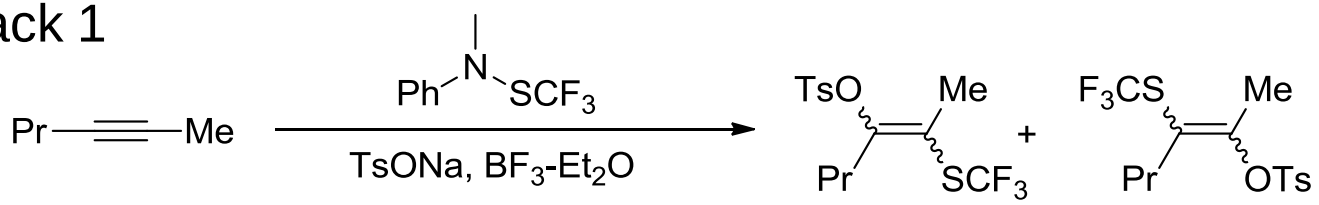


Entry	Acid	Temp (℃)	Time (h)	ratio	Isolated yield
1	TsOH	50	12	1:1	95
2	TsOH	rt	12	>20:1	96
3	(+)-CSA	rt	12	>20:1	94
4	MsOH	rt	12	9:1	95
5	HOAc	rt	24	NR	NR
6	CF_3COOH	rt	24	5.5:1	33
7	BF_3-OEt_2	rt	48	Nearly only **1b**	97

Yang, Y.; Jiang, X.; Qing, F. L., *J. Org. Chem* **2012**, *77 ,* 7538-7547.

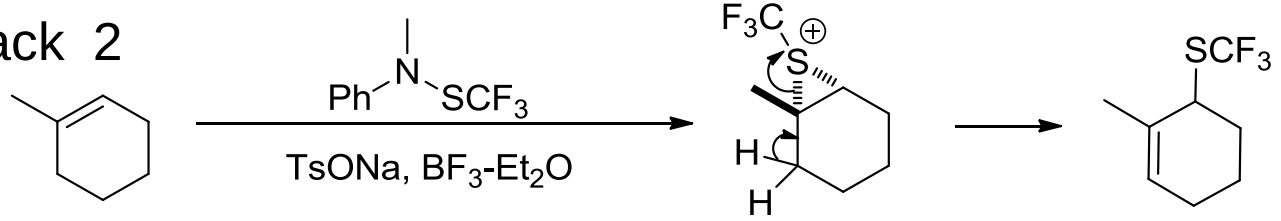
Trifluoromethanesulfenamide

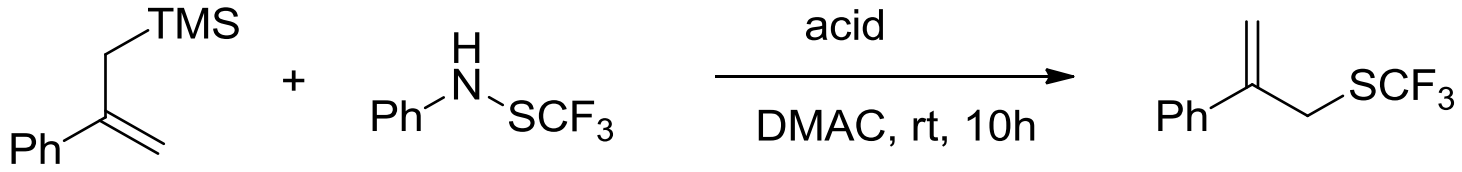
Drawback 1



73% 55:45

Drawback 2

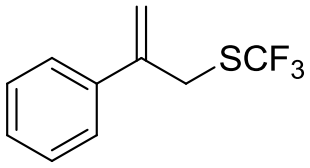




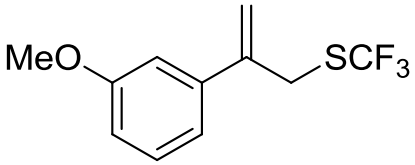
Ferry, A.; Billard, T.; Langlois, B. R.; Bacque, E. *Angew. Chem. Int. Ed* **2009**, *48*, 8551-8555.
Liu, J., Chu, L., and Qing, FL., *Org. Lett*., **2013**, *15*, 894-897

Trifluoromethanesulfenamide

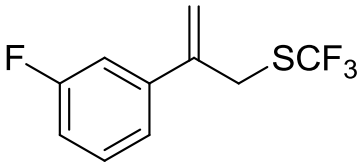
Acid	$BF_3 \cdot Et_2O$	TsOH	CH_3COCl	CH_3COCl	CH_3COCl
Solvent	DCM	DCM	DCM	DMF	DMAC
Yield (%)	26	13	37	78	84



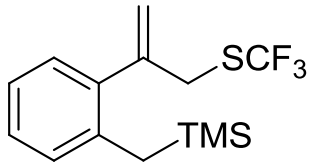
88%



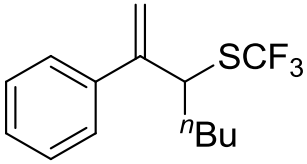
80%



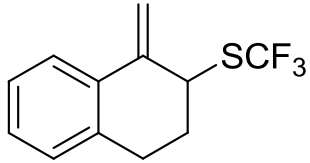
89%



71%



56%

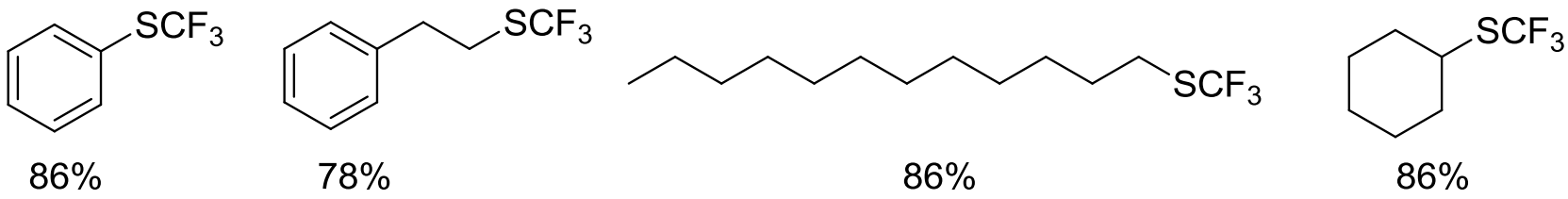


53%

Liu, J., Chu, L., and Qing, FL., *Org. Lett*., **2013**, *15*, 894-897

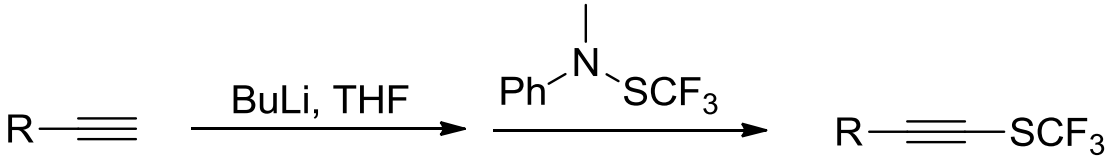
Trifluoromethanesulfenamide

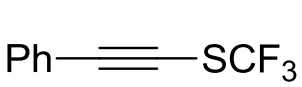
Extension to Grignard reagent & terminal alkynes



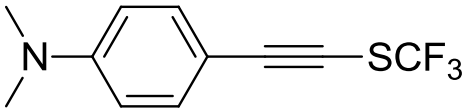
Baert, F.; Colomb, J.; Billard, T., *Angew. Chem. Int. Ed* **2012**, *51* , 10382-10385

Trifluoromethanesulfenamide

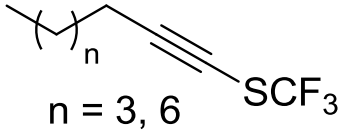




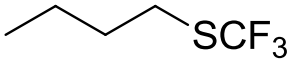
73%



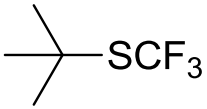
69%



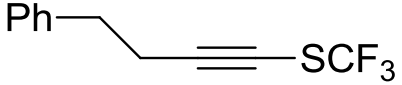
n = 3, 6
60%, 81%



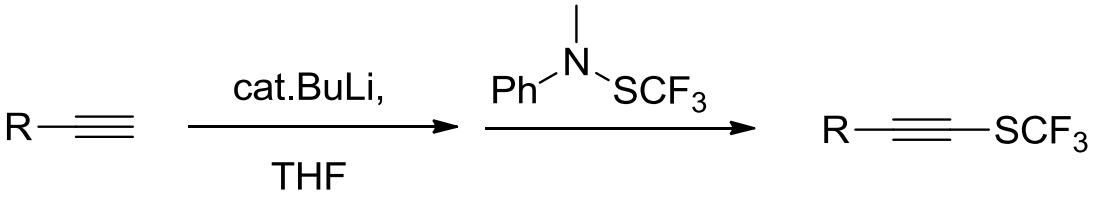
42%

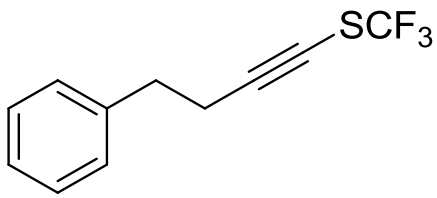


60%



19%





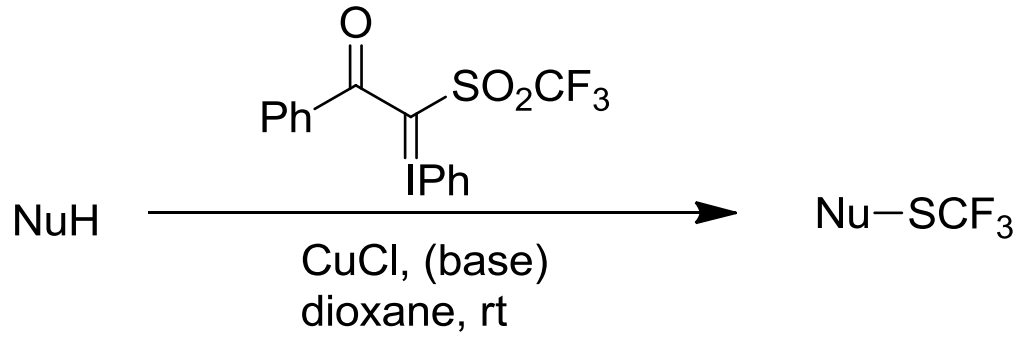
19%--->75%

Alazet, S.; Zimmer, L.; Billard, T., *Angew. Chem. Int. Ed* **2013**. *52*, 10814-10817

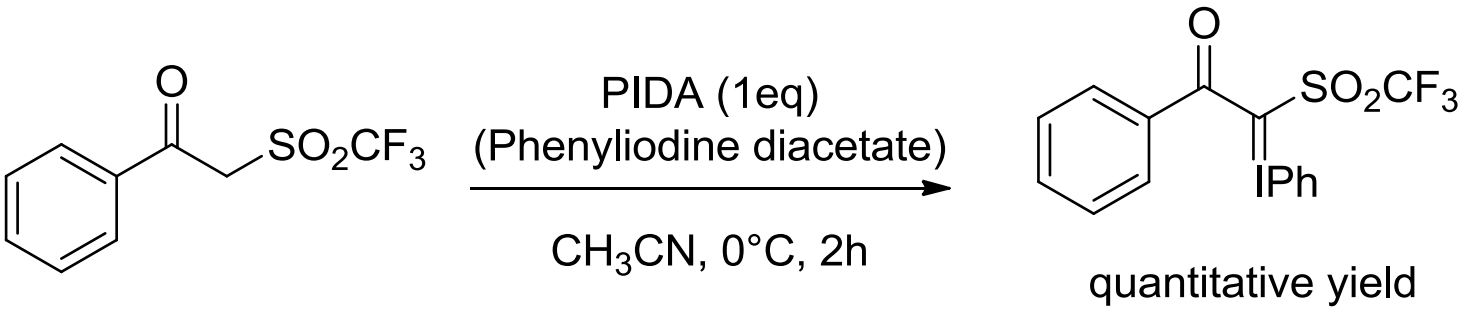
Electrophilic methods

- Hypervalent Iodine reagent
- Trifluoromethanesulfenamide
- Trifluoromethanesulfonyl hypervalent iodonium ylide

Iodonium Ylide



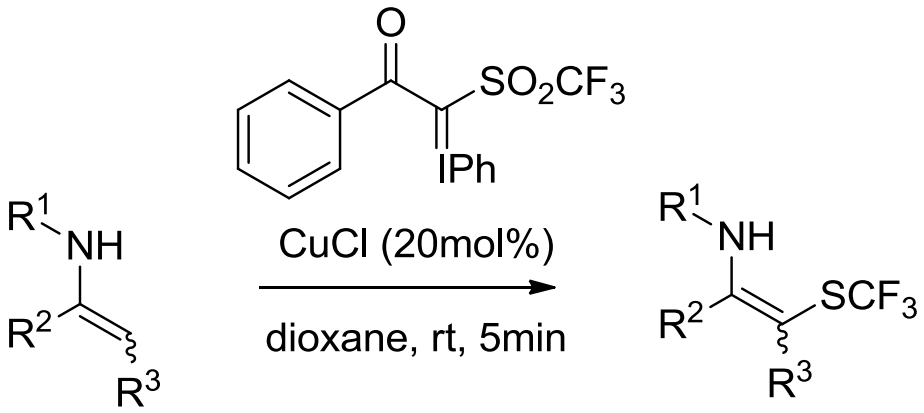
can form enamines, beta-keto esters, indoles

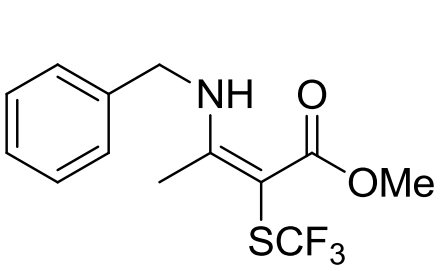


quantitative yield

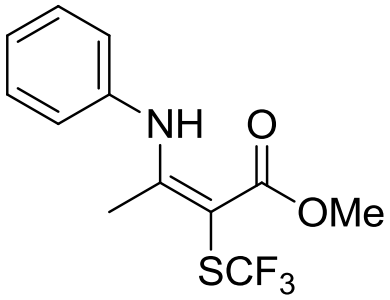
Yang, Y. D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N., *J. Am. Chem. Soc*. **2013**, *135 ,* 8782-8785.

Iodonium Ylide

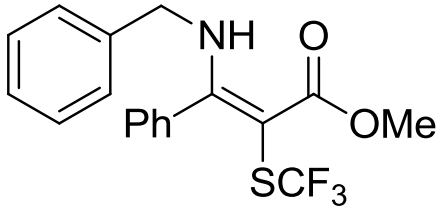




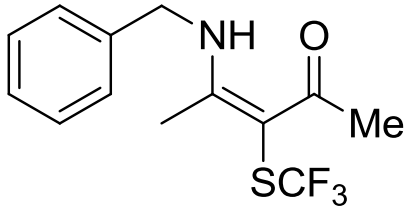
92%



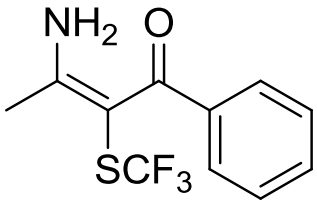
77%



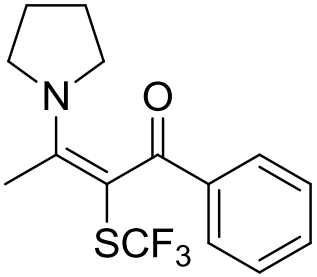
90%



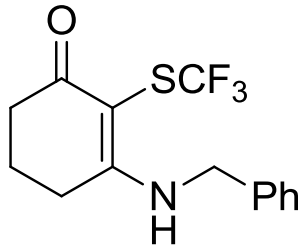
96%



84%



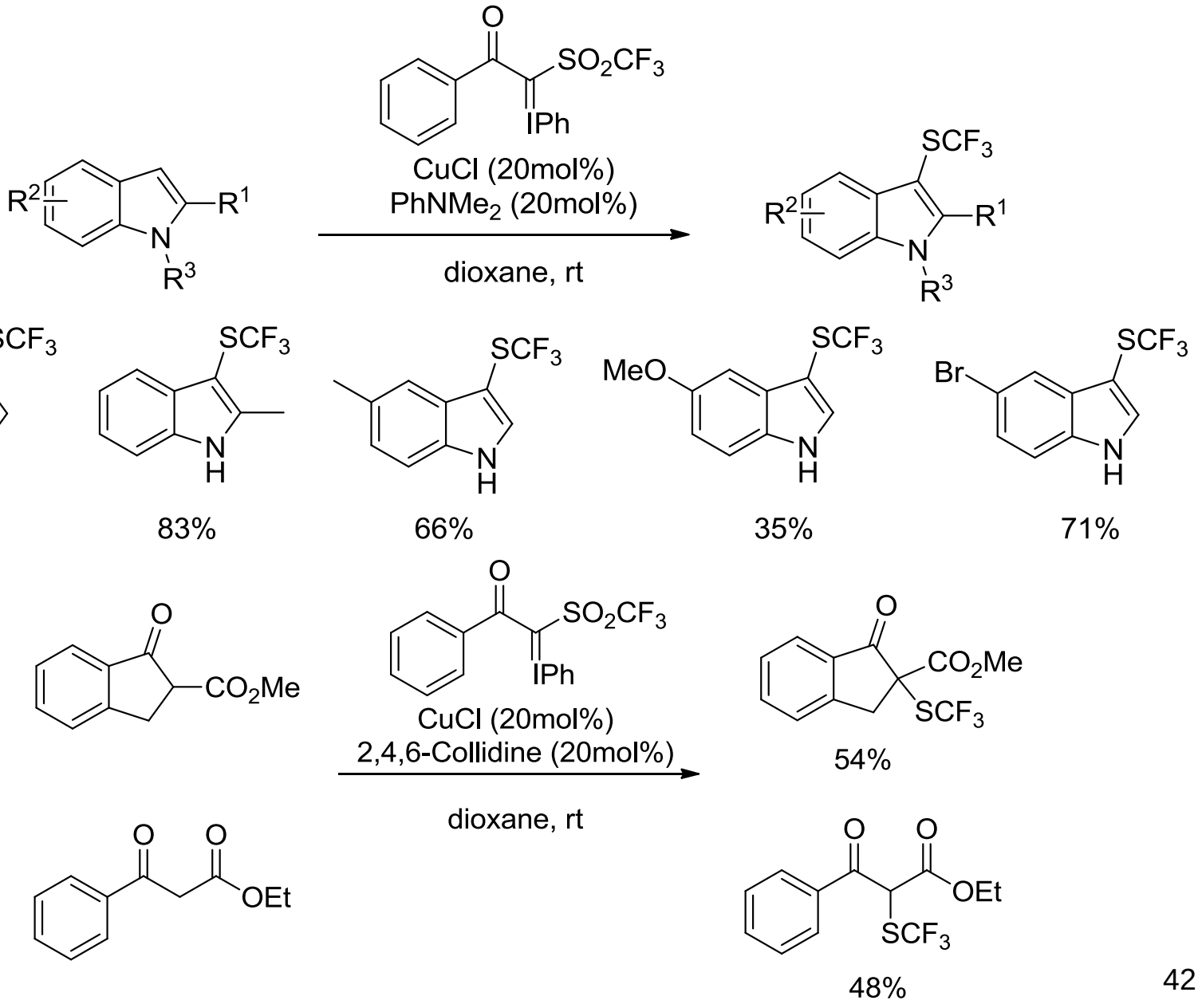
74%



84%

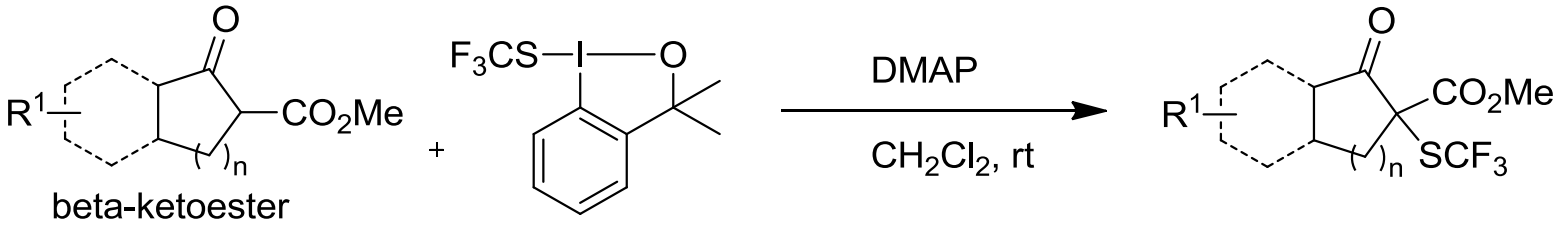
Yang, Y. D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N., *J. Am. Chem. Soc*. **2013**, *135 ,* 8782-8785.

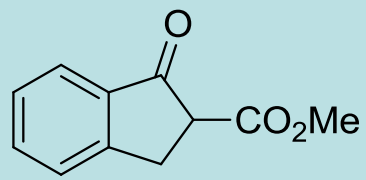
Iodonium Ylide

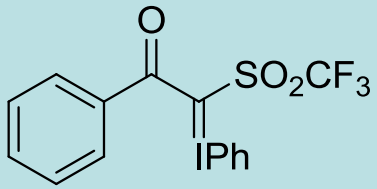


Yang, Y. D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N., *J. Am. Chem. Soc*. **2013**, *135 ,* 8782-8785.

Comparison of 2 Hypervalent Iodine reagent

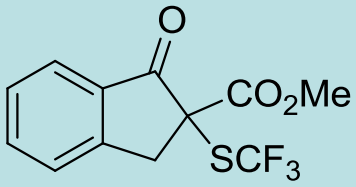




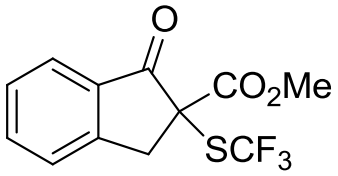


CuCl (20mol%)
2,4,6-Collidine (20mol%)

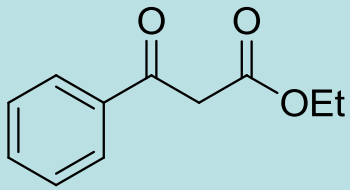
dioxane, rt

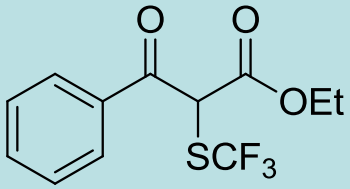


54%

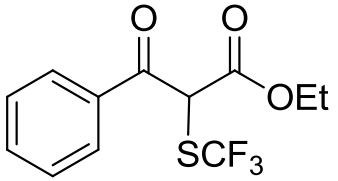


93%





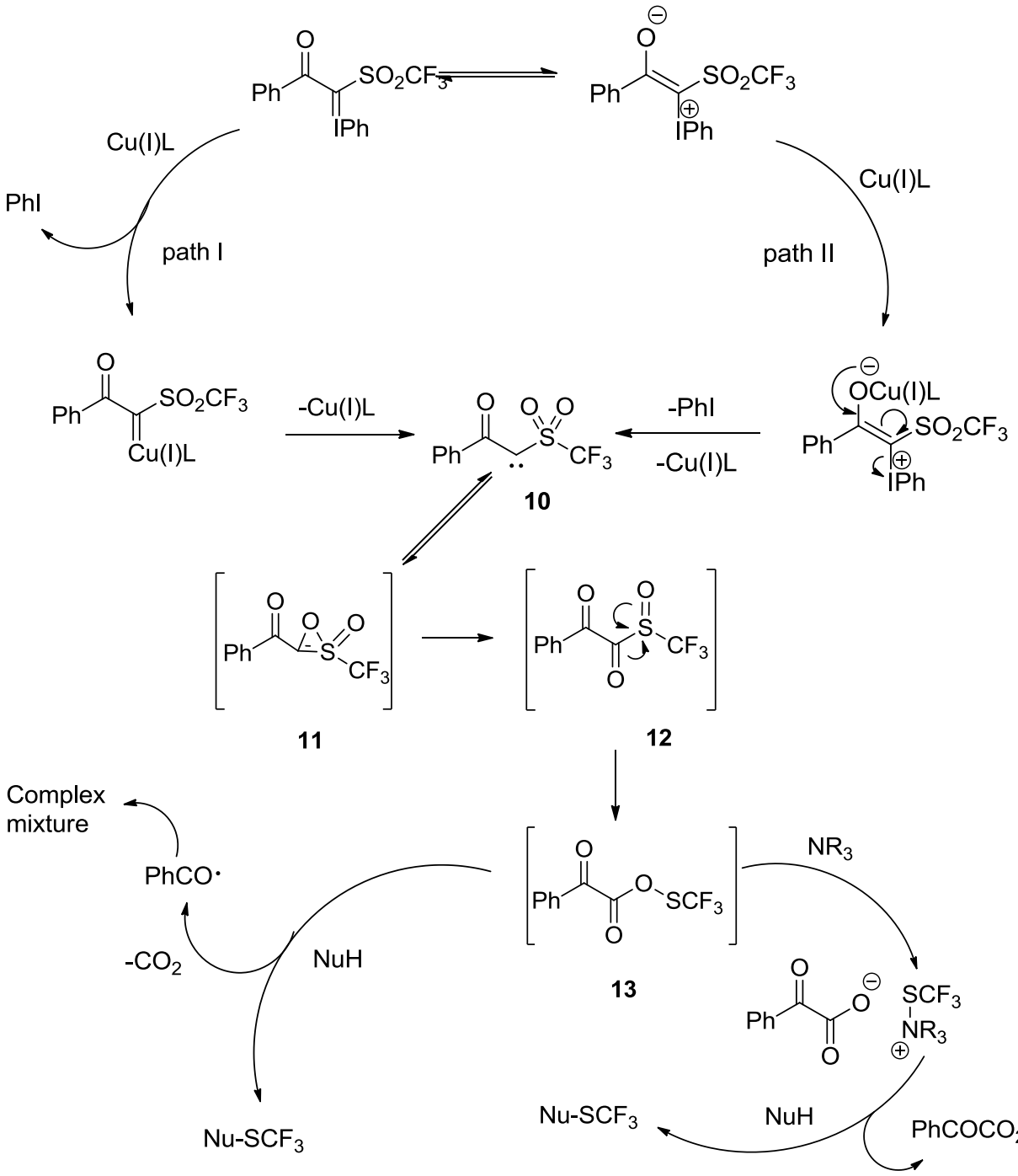
48%



0%

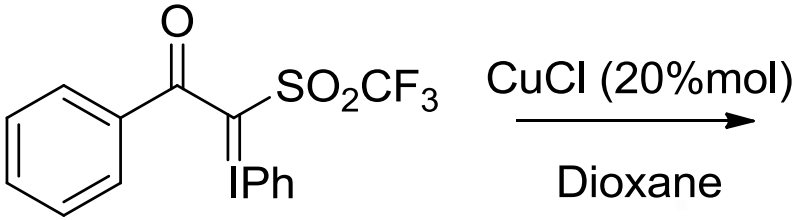
Yang, Y. D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N., *J. Am. Chem. Soc*. **2013**, *135 ,* 8782-8785.
Shao, X.; Wang, X.; Yang, T.; Lu, L.; Shen, Q., *Angew. Chem. Int. Ed,* **2013**, *52 ,* 3457-3460.

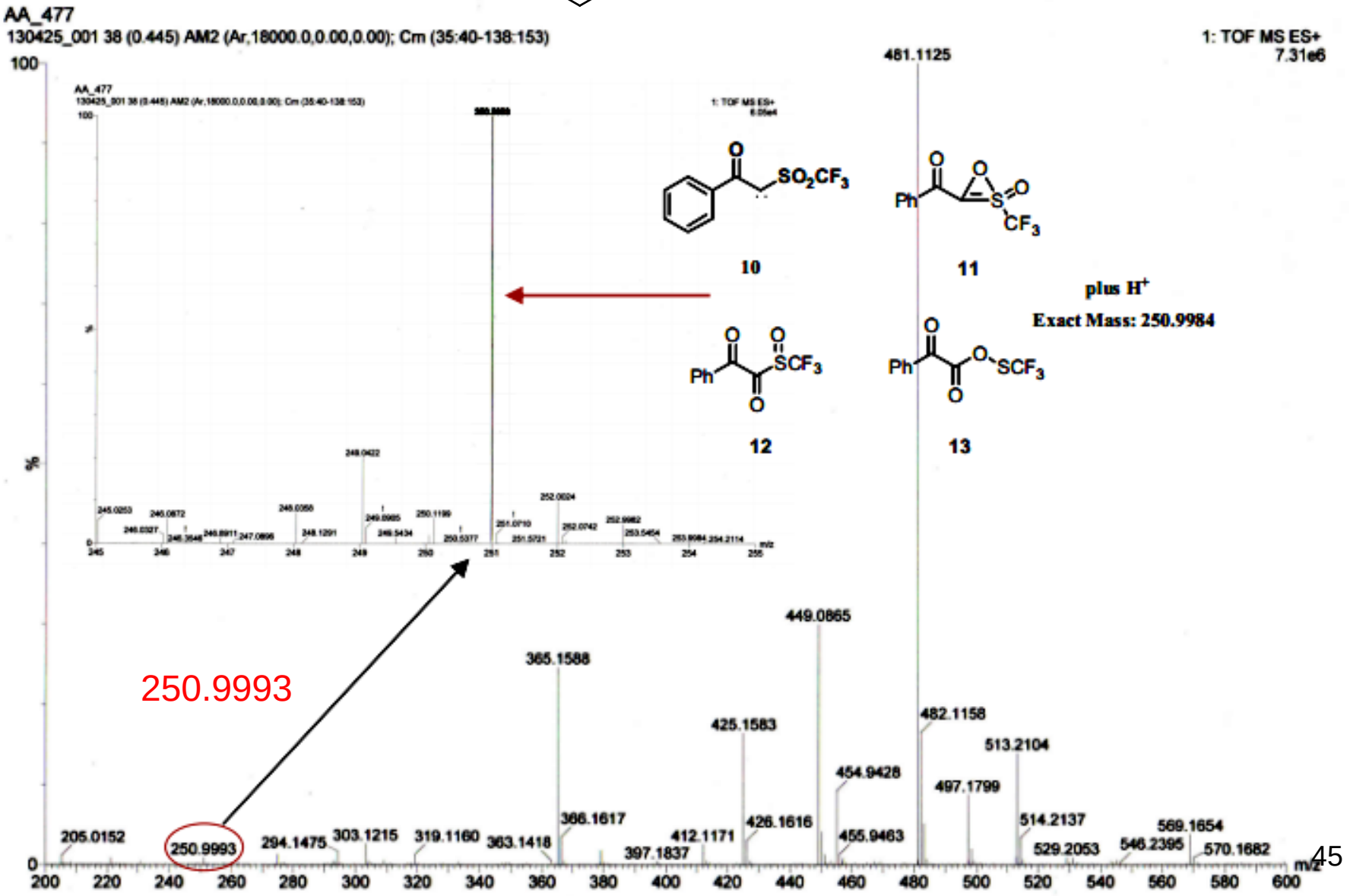
Iodonium Ylide



Yang, Y. D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N., *J. Am. Chem. Soc*. **2013**, *135* , 8782-8785.

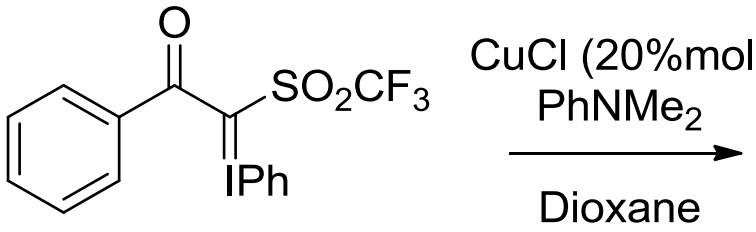
Iodonium Ylide

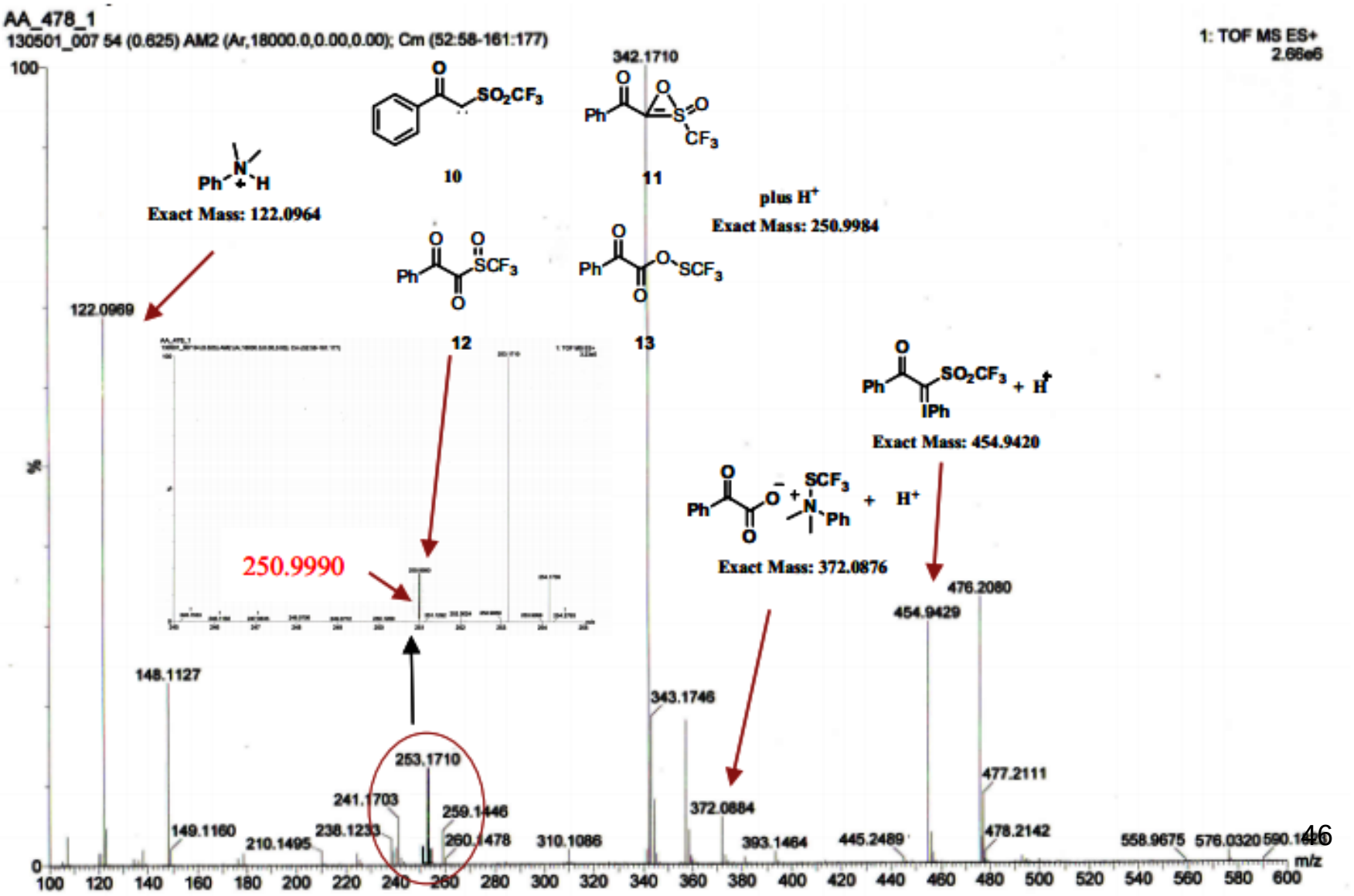




Yang, Y. D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N., *J. Am. Chem. Soc*. **2013**, *135* , 8782-8785.

Iodonium Ylide





Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782-8785.

Electrophilic methods

- Hypervalent iodine reagent can selective introduce SCF_3, but it is potential explosive chemicals.
- Trifluoromethanesulfenamide, a stable SCF_3 source.
- Trifluoromethanesulfonyl hypervalent iodonium ylide, can be effectivly applied to enamines, beta-keto esters, indoles.

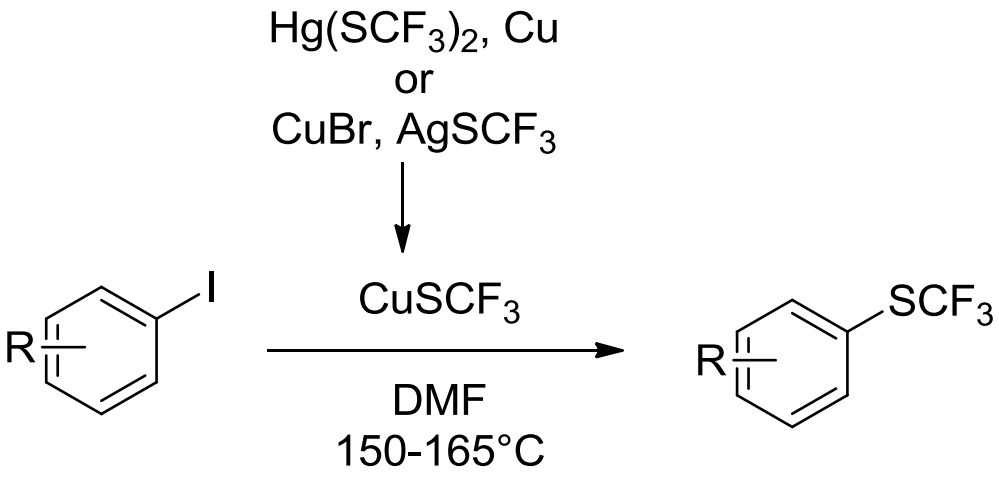
Outline

1. Introduction

2. Direct trifluoromethylthiolation
   - Electrophilic trifluoromethylthiolation
   - Transition metal-catalyzed nucleophilic trifluoromethylthiolation

3. Summary

Transition metal-catalyzed nucleophilic trifluoromethylthiolation



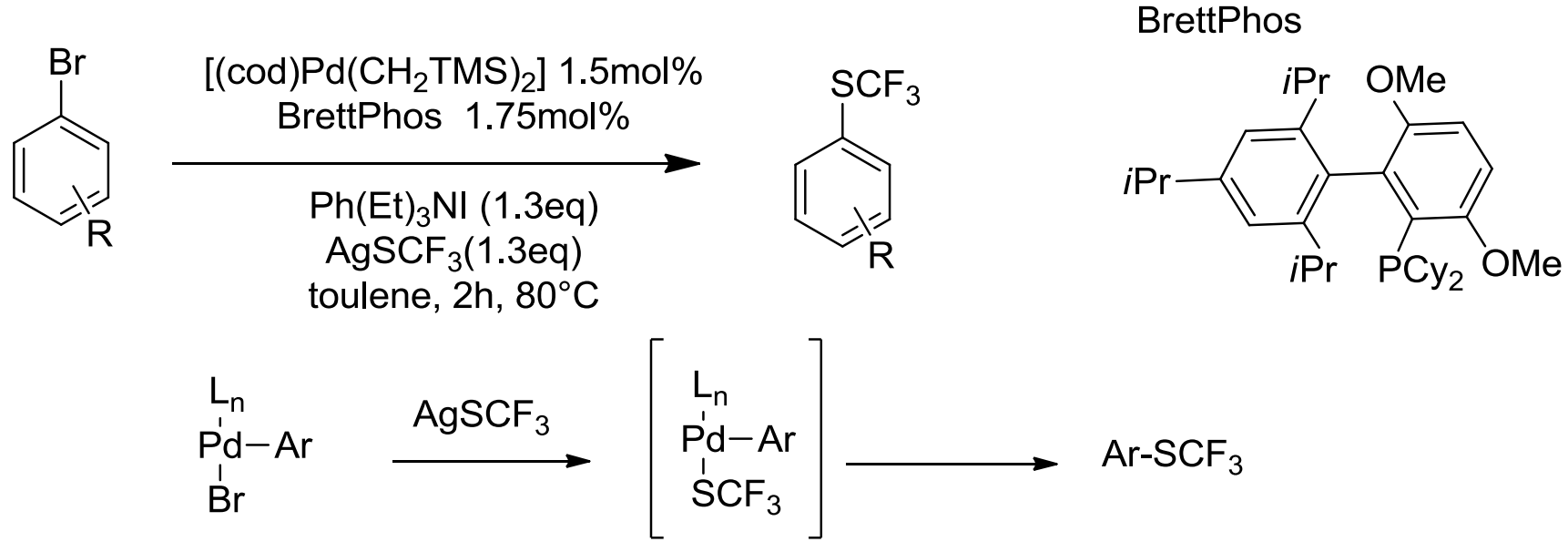
R	Yield (%)
H	55
4-Me	30
4-NO_2	75

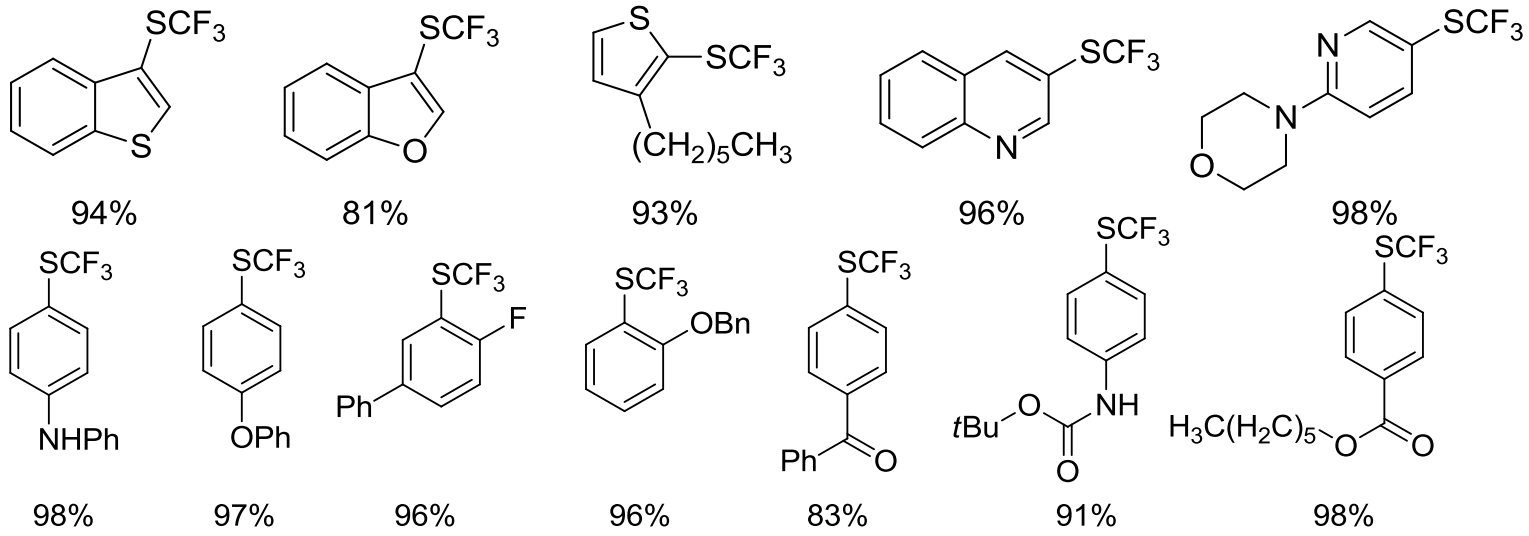
- Cheap and efficient metal catalyst
- Stable SCF_3 source

Yagupolskii, L, M, Kondratenko, N, V, Sambur, V, P., *Synthesis,* **1975**, 721-723.

Nucleophilic trifluoromethylthiolation

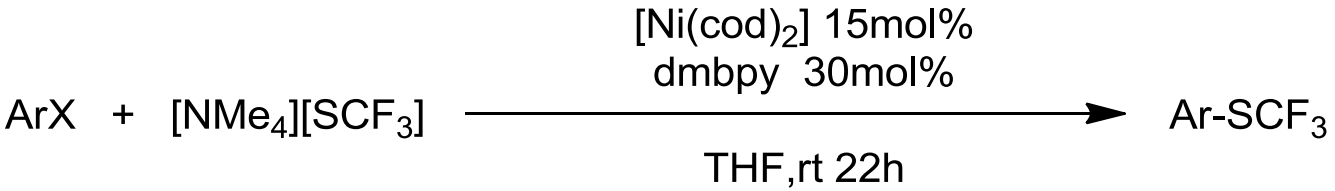
Palladium catalyzed nucleophilic method



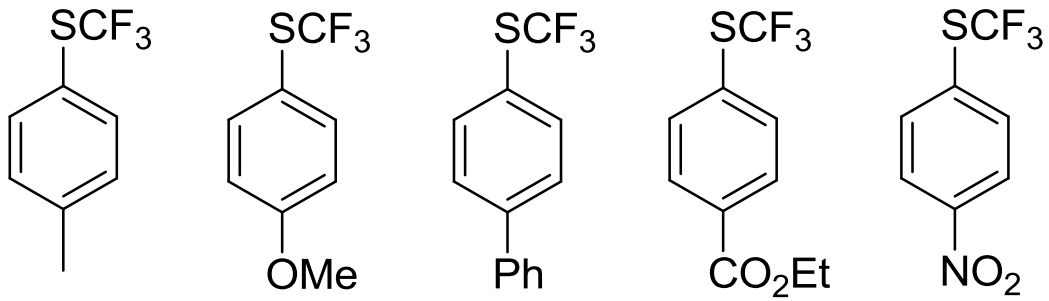


Teverovskiy, G.; Surry, D. S.; Buchwald, S. L., *Angew. Chem. Int. Ed* **2011**, *50* , 7312-7314.

Nucleophilic trifluoromethylthiolation

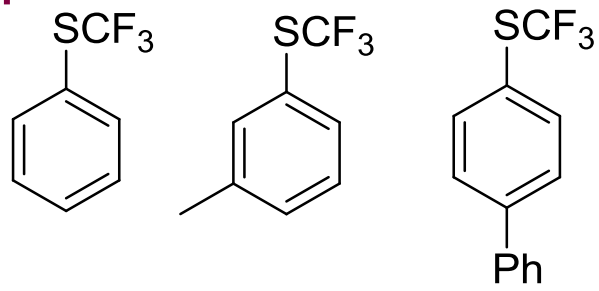


X=I



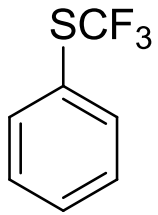
90% 90% 92% 45% 47%

X=Br



65% 37% 64%

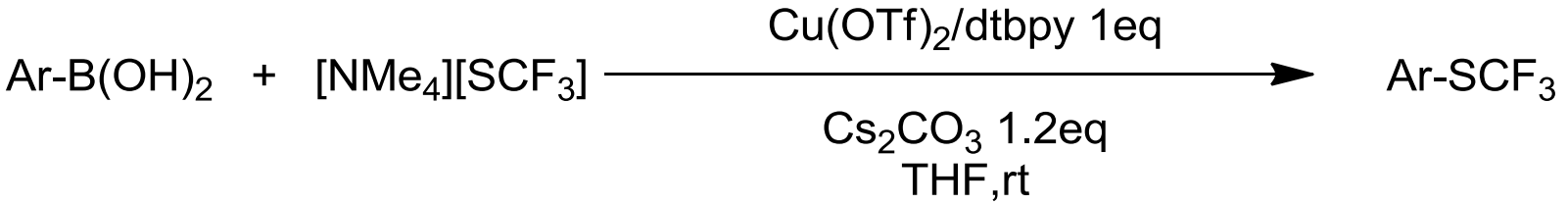
X=Cl

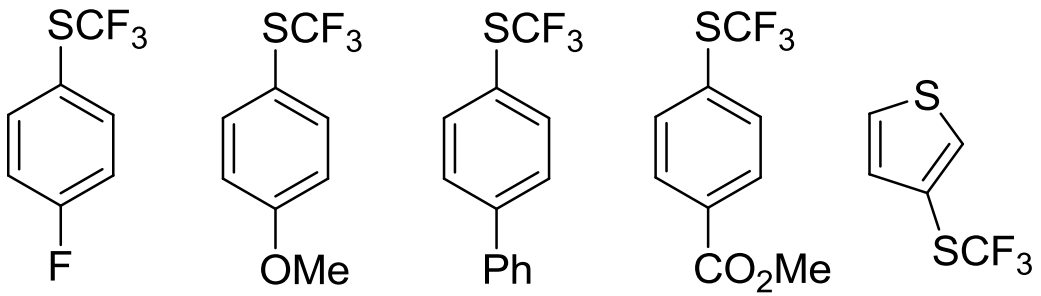


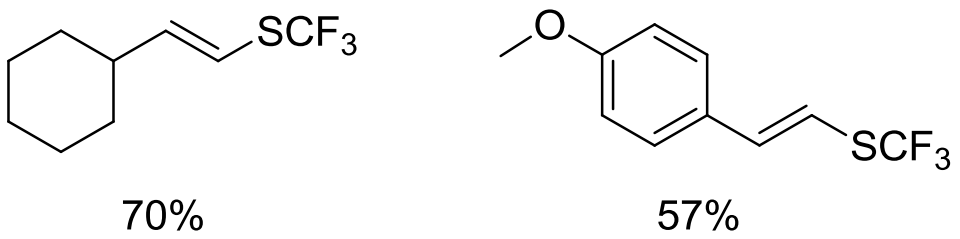
0%

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

Nucleophilic trifluoromethylthiolation



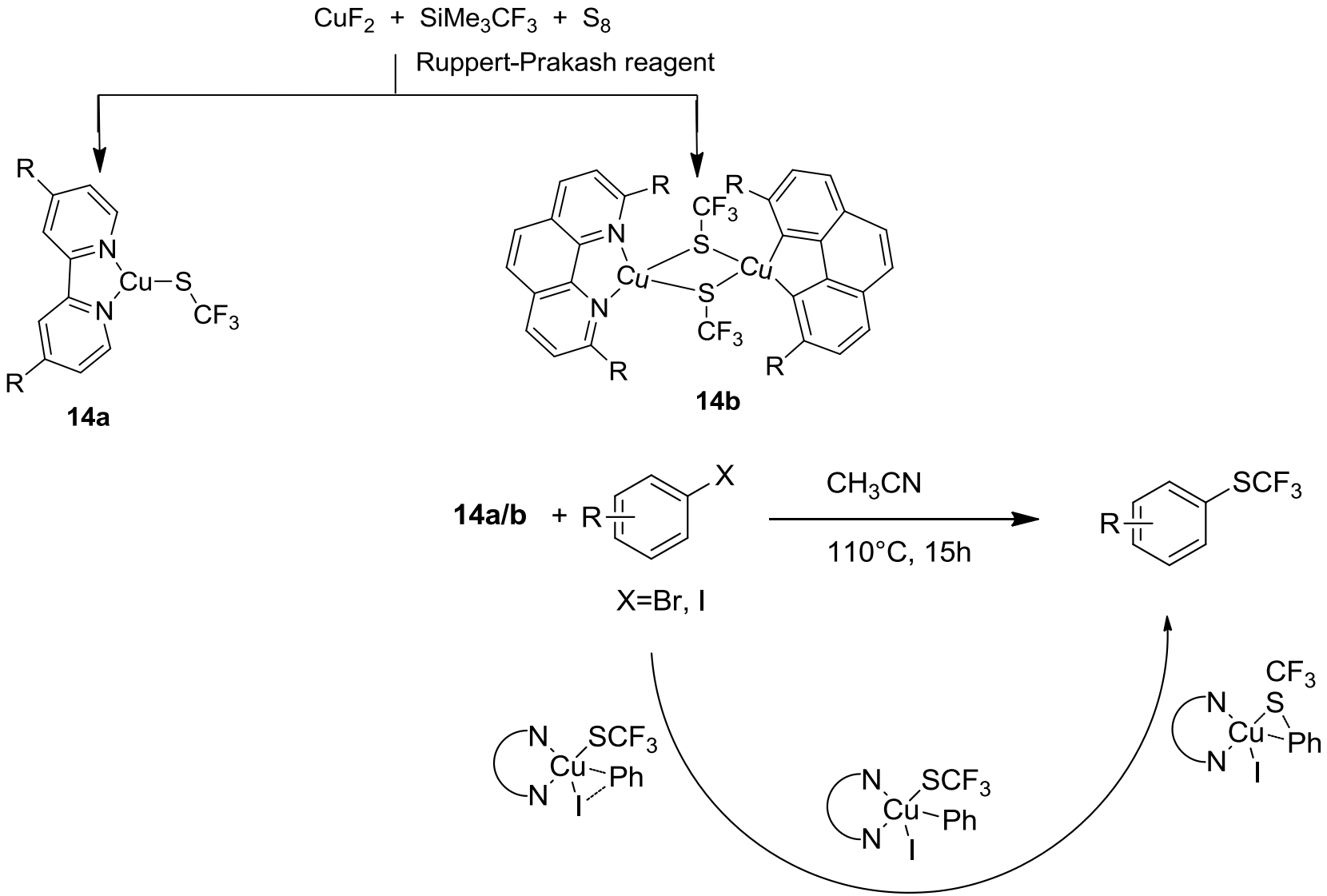




Zhang, C. P.; Vicic, D. A., *Chem. Asian J ,* **2012**, *7* , 1756-1758.

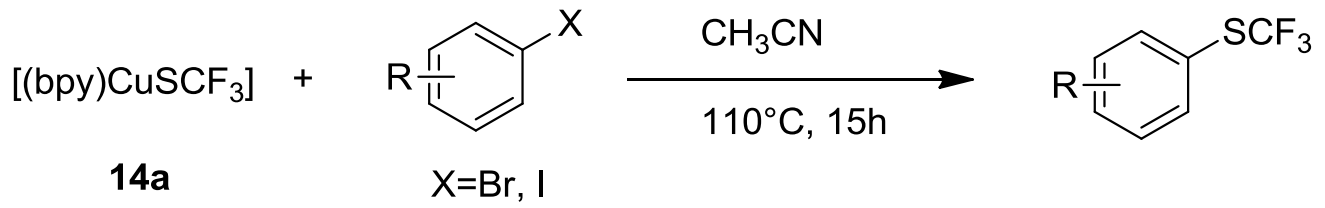
Nucleophilic trifluoromethylthiolation

From element Sulfur



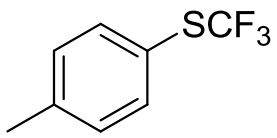
Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K. W., *Angew. Chem. Int. Ed* , **2013**, *52*, 1548-1552.

Nucleophilic trifluoromethylthiolation

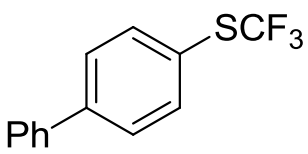


14a

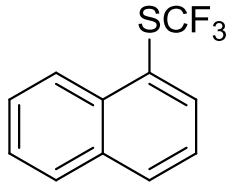
X=Br, I



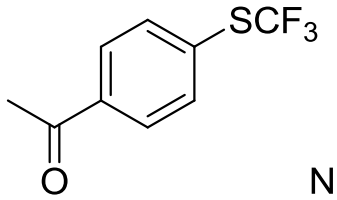
X= I, 76%



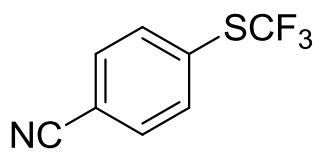
X= I, 81%



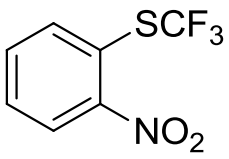
X= I, 90%



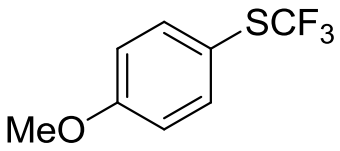
X= I, 84%



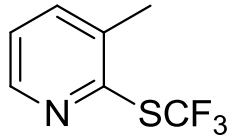
X= I, 81%



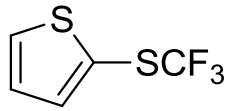
X= Br, 73%



X= I, 72%



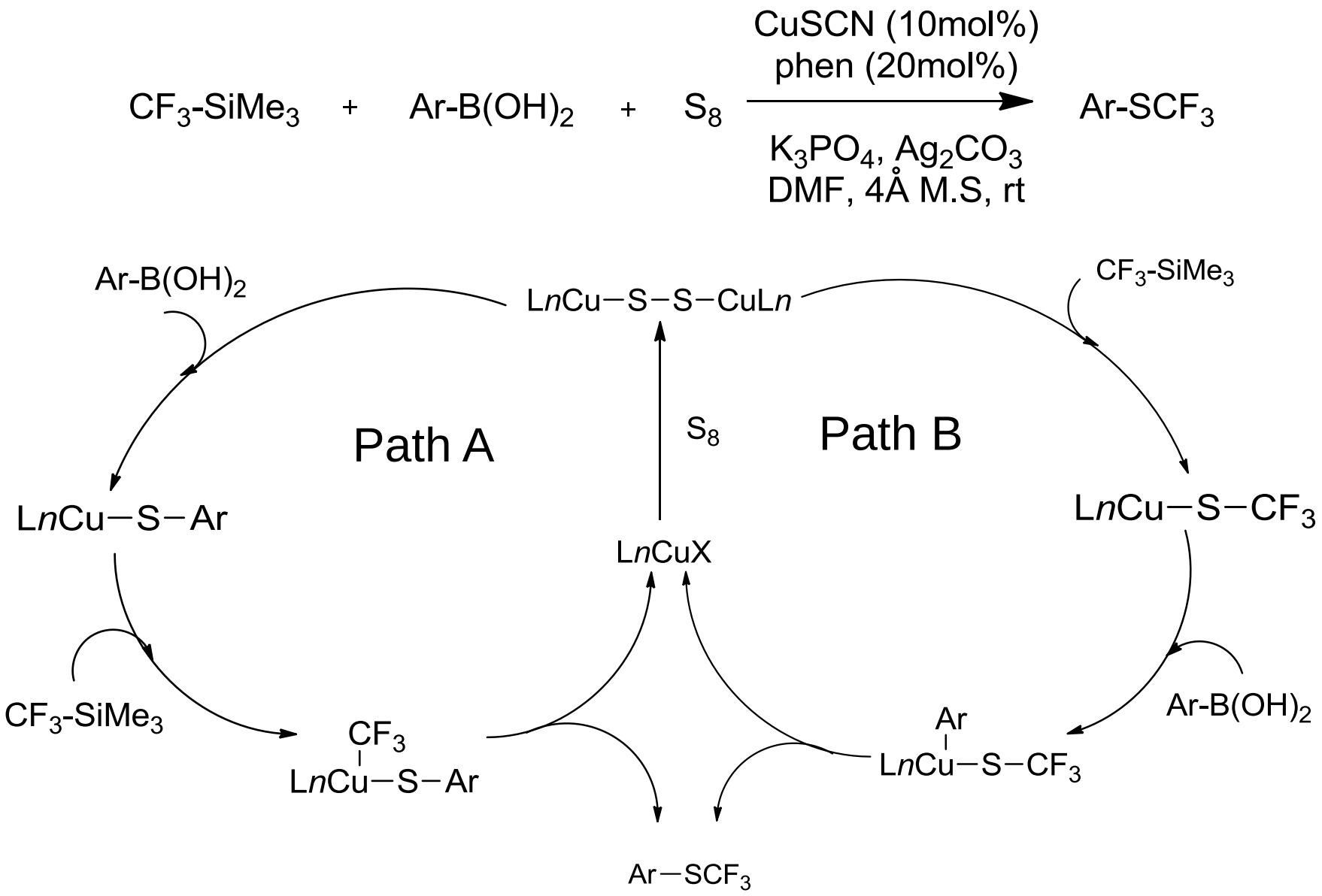
X= Br, 71%



X= I, 77%

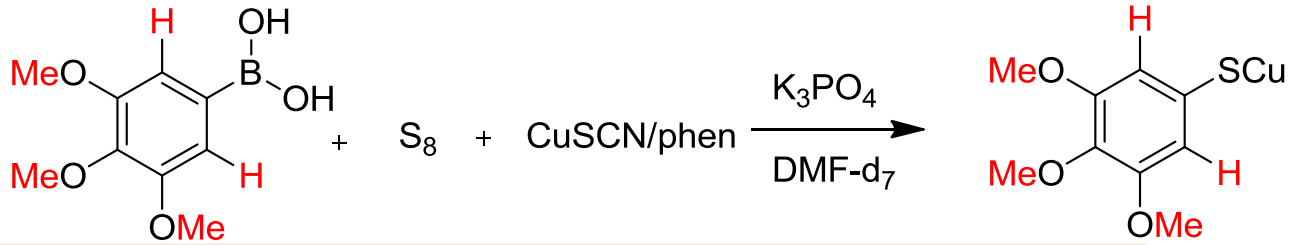
Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K. W., *Angew. Chem. Int. Ed* , **2013**, *52*, 1548-1552.

Nucleophilic trifluoromethylthiolation



Chen, C.; Xie, Y.; Chu, L.; Wang, R. W.; Zhang, X.; Qing, F. L., *Angew. Chem. Int. Ed* , **2012**, *51* , 2492-2495.

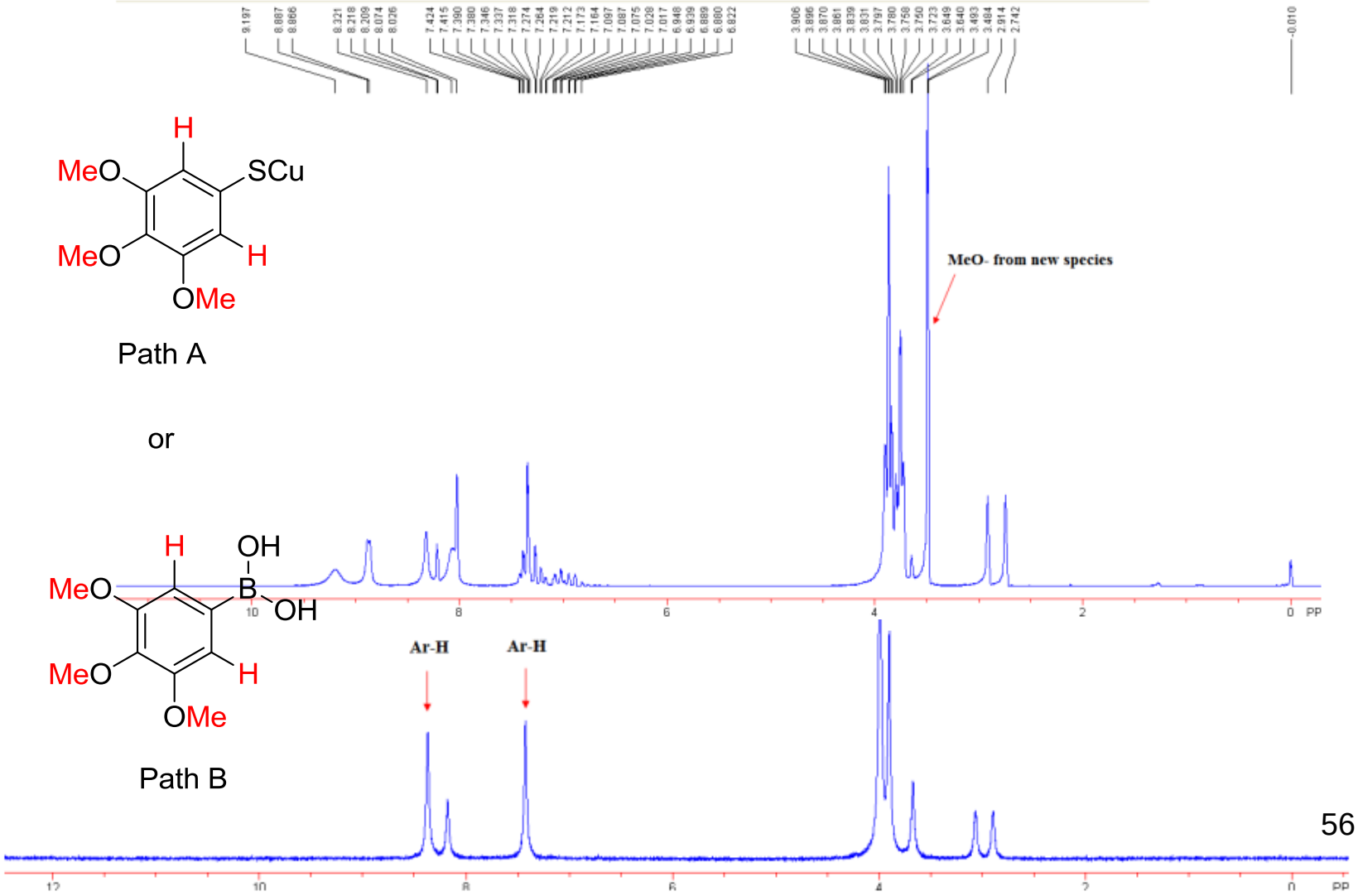
Nucleophilic trifluoromethylthiolation



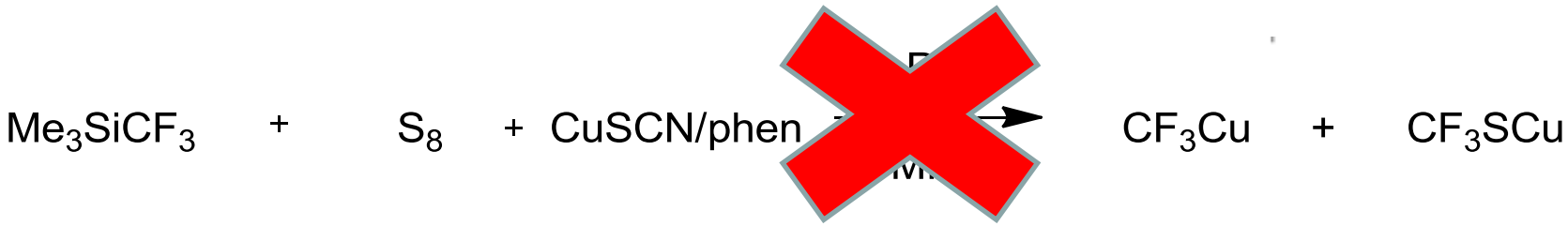
Path A

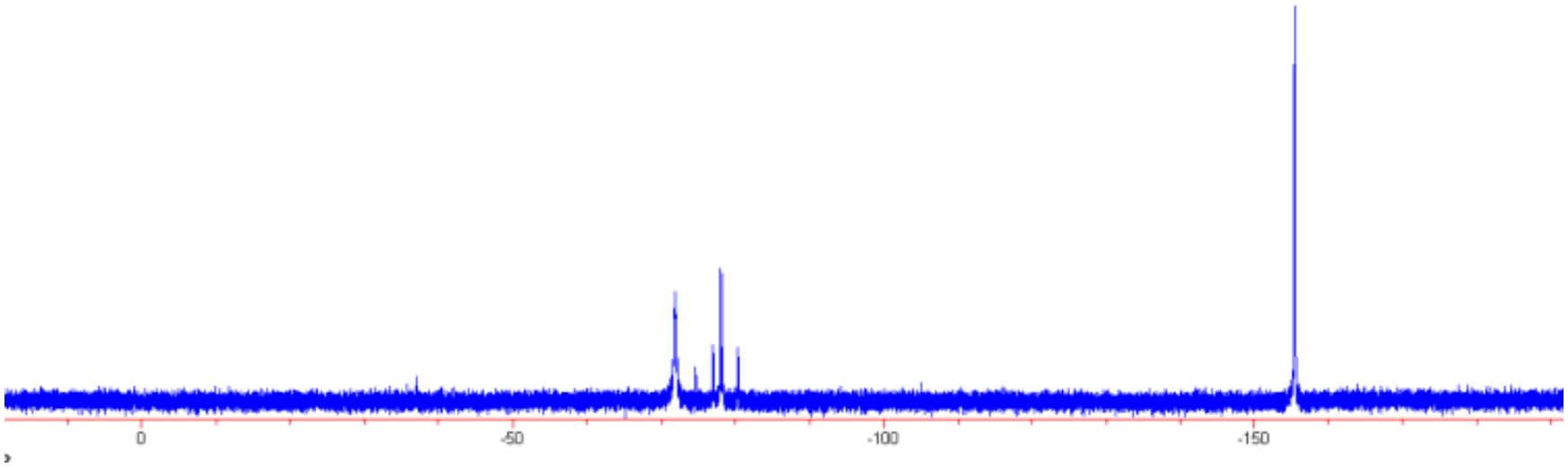
or

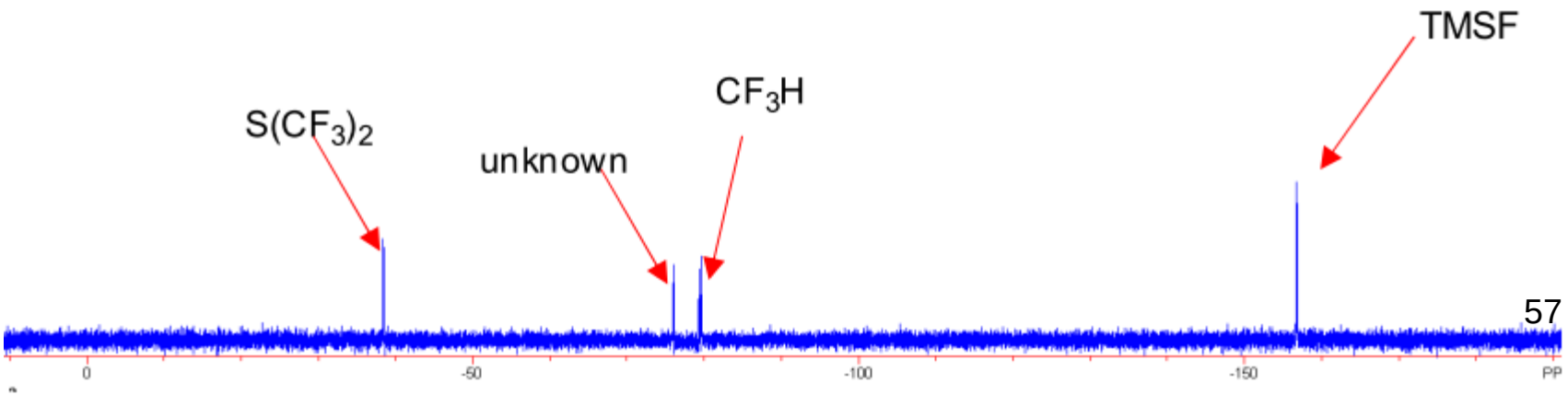
Path B



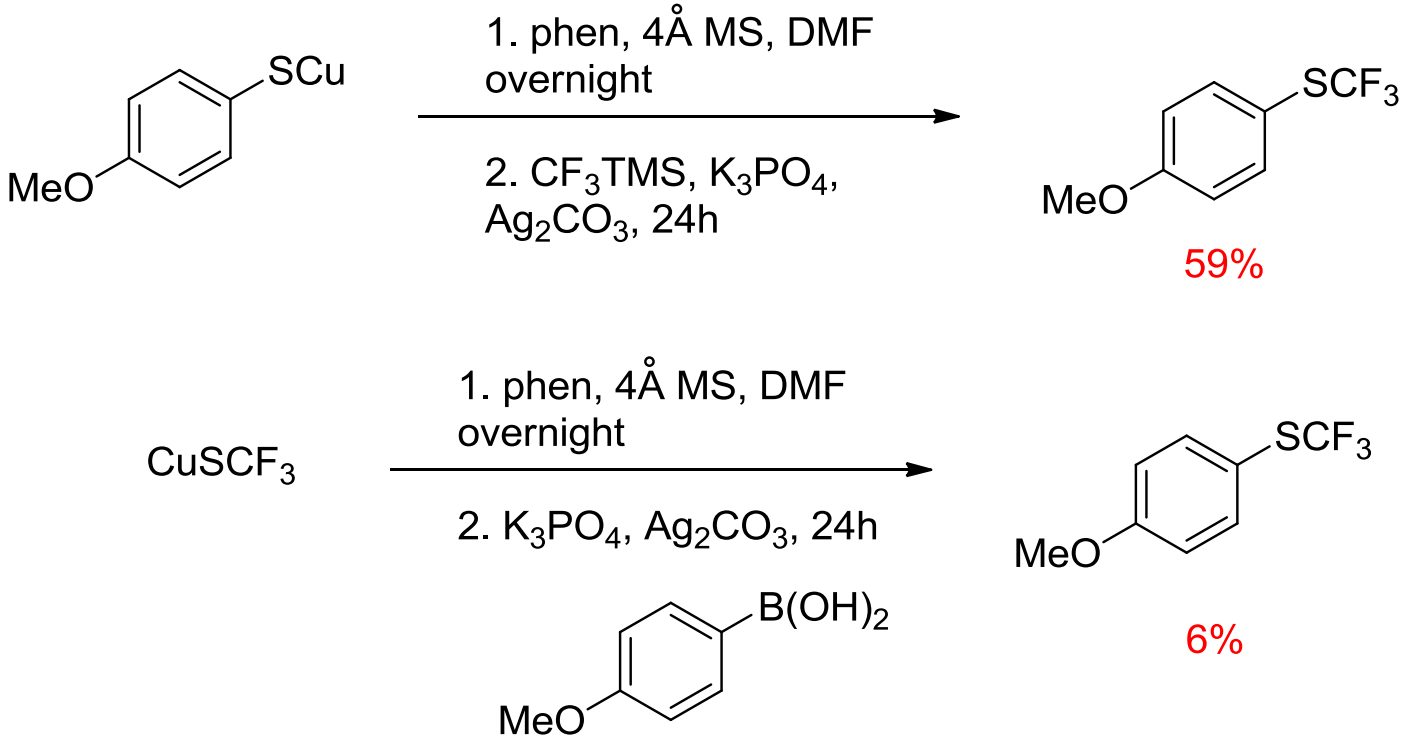
Nucleophilic trifluoromethylthiolation





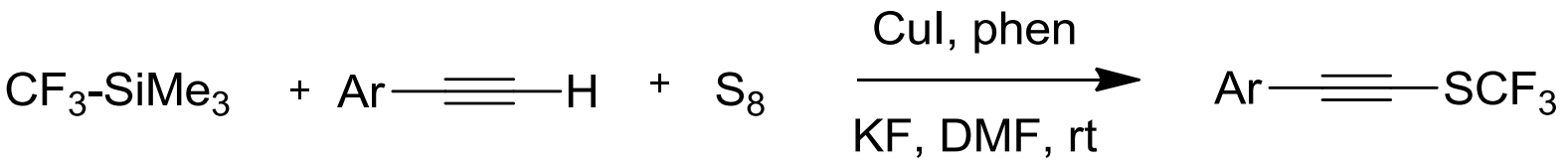


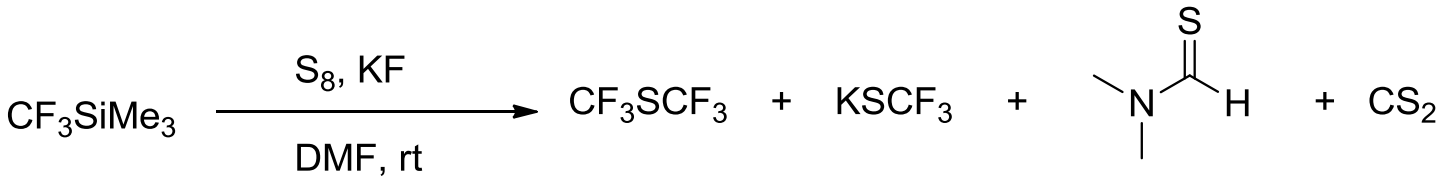
Nucleophilic trifluoromethylthiolation

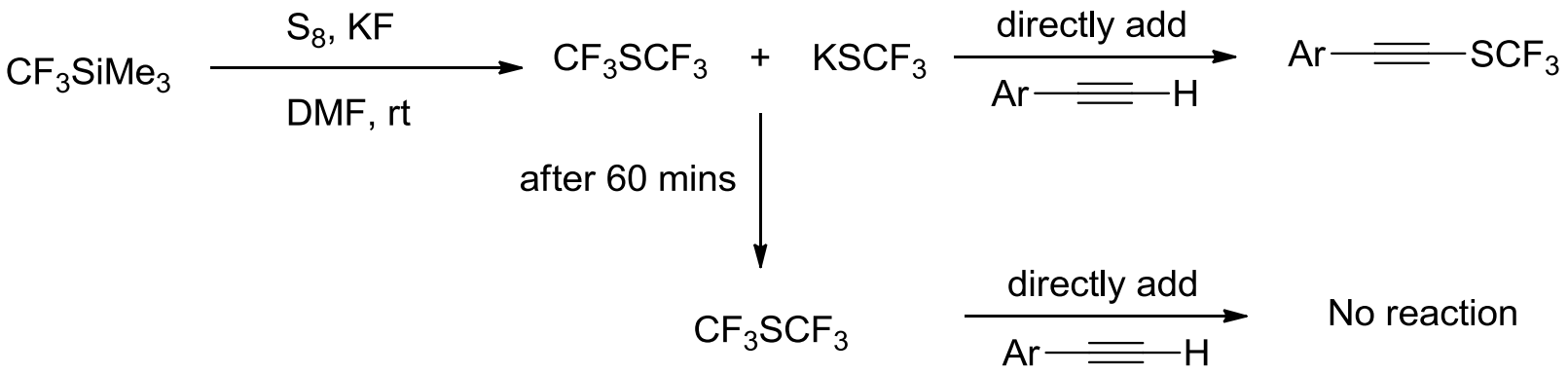


Chen, C.; Xie, Y.; Chu, L.; Wang, R. W.; Zhang, X.; Qing, F. L., *Angew. Chem. Int. Ed* , **2012**, *51* , 2492-2495.

Nucleophilic trifluoromethylthiolation



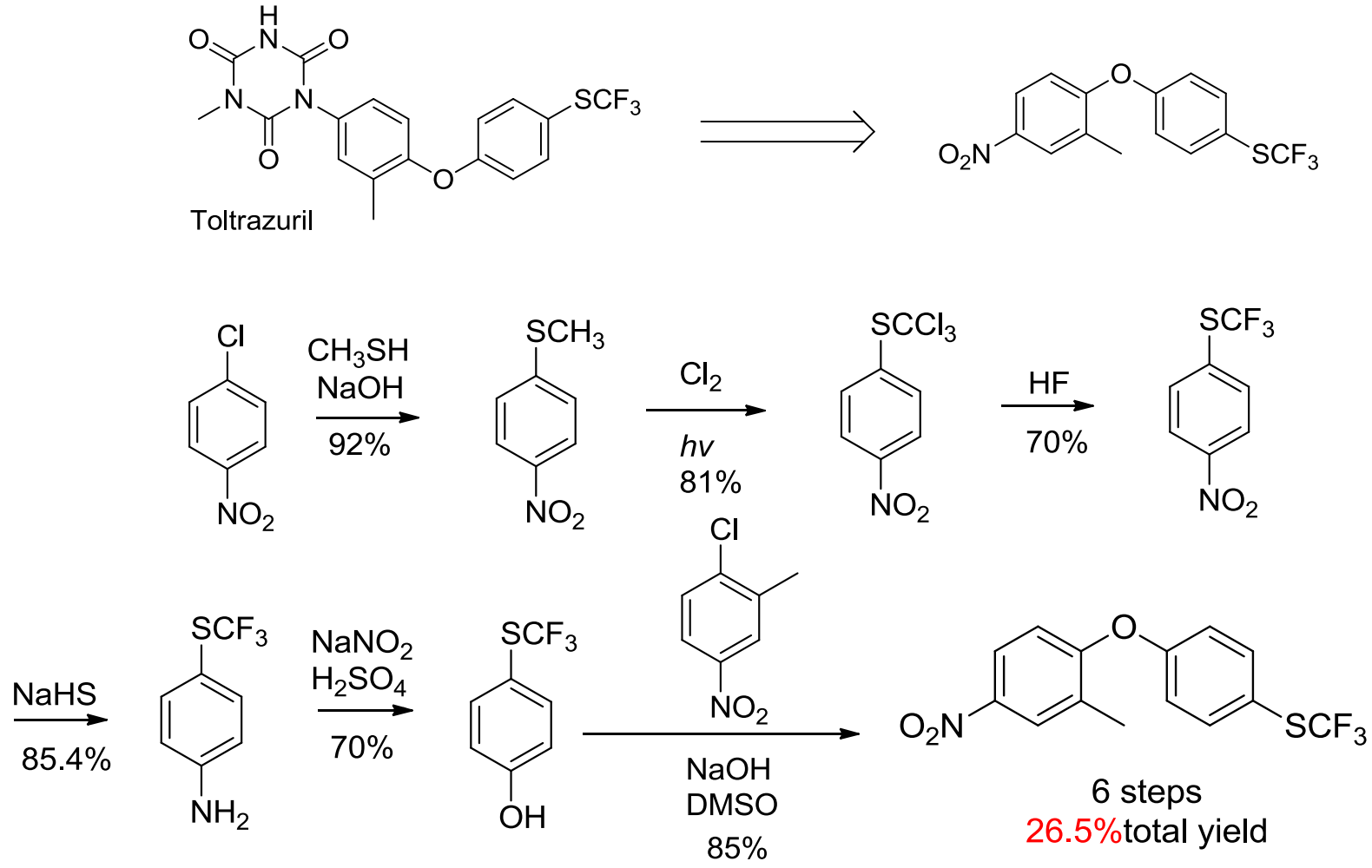




Chen, C.; Chu, L.; Qing, F. L., *J. Am. Chem. Soc* **2012**, *134* , 12454-12457.

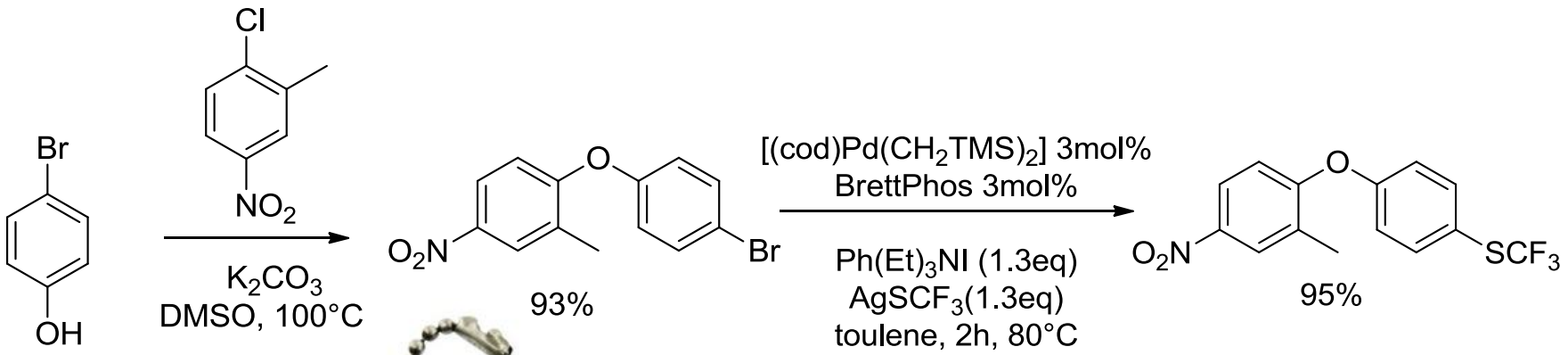
Nucleophilic trifluoromethylthiolation

Total synthesis of Toltrazuril



A. Gunther, K.-H. Mohrmann, M. Stubbe, H. Ziemann (Bayer AG), DE3516630, **1986**

Nucleophilic trifluoromethylthiolation



- Pd catalyst ~ $260/g
- Ligand ~ $200/g

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

Nucleophilic methods

- From Palladium to Nickel, then to Copper, to find a cheaper but highly efficient catalyst.
- Improvement of unstable or inconvient M-SCF_3 source.

Summary

- Electrophilic methods
  - Hypervalent Iodine reagent
  - Trifluoromethanesulfenamide
  - Trifluoromethanesulfony hypervalent iodonium ylide
- Nucleophilic methods
  - Optimize the reaction catalyst.
  - One pot reaction.

Acknowledgements

- Dr. Xuefei Huang
- Group members: Zhaojun, Weizhun, Hovig, Herbert, Qian, Berm, Peng, Mehdi, Jicheng, Bo, Keisuke, Jingguang, Issac, Sherif
- My friends
- All your attention