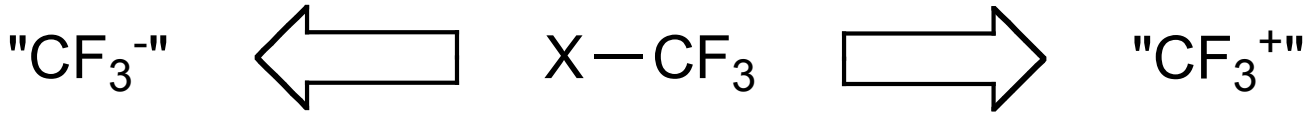
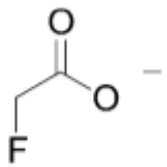
Nucleophilic and Electrophilic Trifluoromethylation



“The fury of the chemical world is the element fluorine. It exists peacefully in the company with calcium in fluorspar and also in a few other compounds; but when isolated, as it recently has been, it is a rabid gas that nothing can resist.”

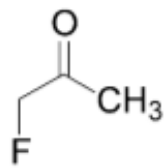
Scientific American, April 1888

There are 7 Natural Fluorinated Compounds



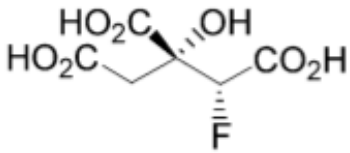
fluoroacetate

Principally *Dichapetalum Gastrolobium, Oxylobium spp.*



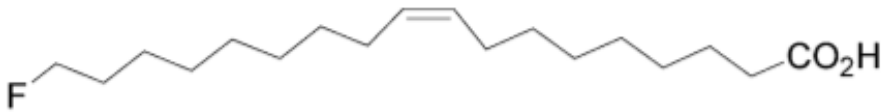
fluoroacetone

Acacia georginea



(*2R, 3R*)-fluorocitrate

several higher plants

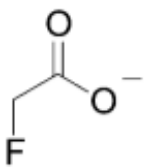


ω-fluoro-oleic acid

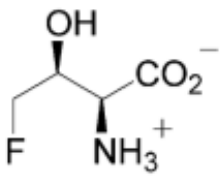
Dichapetalum toxicarium

Fluorine chemistry is <u>necessarily</u> a synthetic field

i.e. essentially all fluorine compounds must be man-made

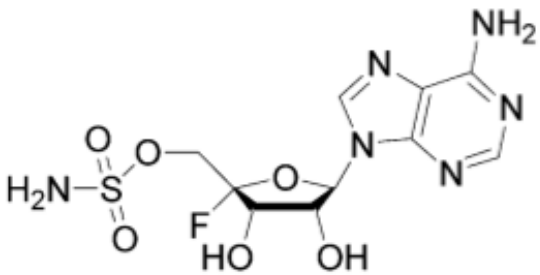


fluoroacetate



4-fluorothreonine

Streptomyces cattleya



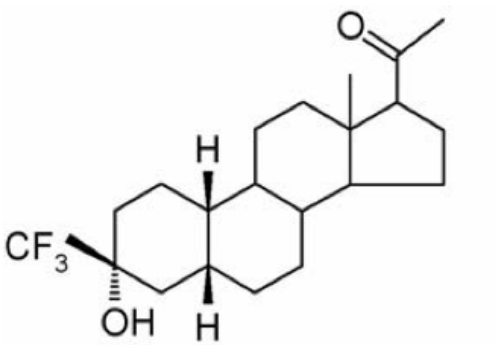
nucleocidin

Streptomyces calvus

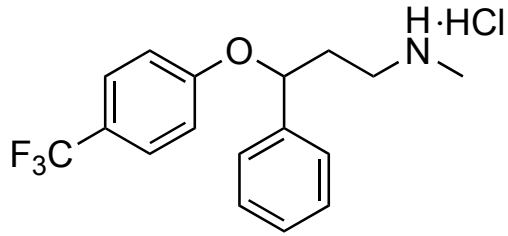
Scheme 1. Natural occurring fluoroorganic compounds [10].

Dolbier, W. R. *J. Fluorine Chem.* **2005**, *126*, 157.

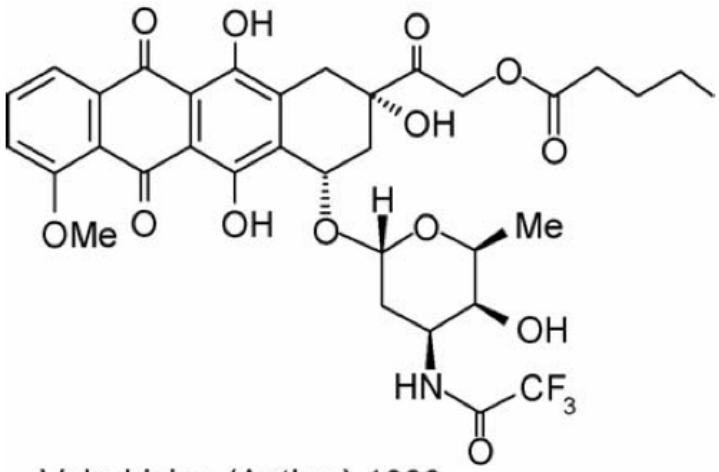
There are over 150 Pharmaceuticals



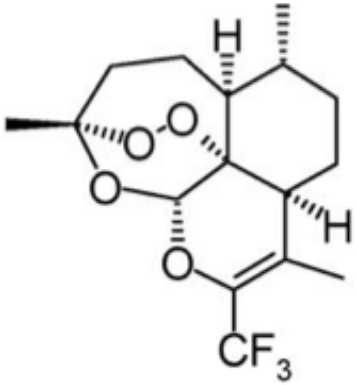
CCD-3693 (Purdue Pharma)
Sleep inducer Phase I



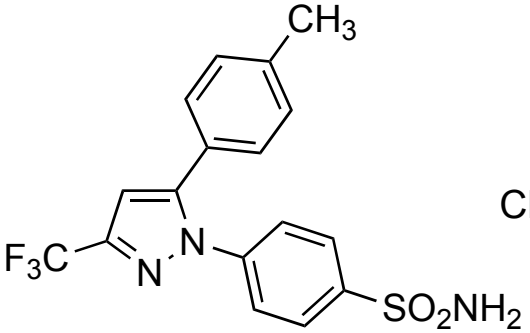
Prozac
(antidepressant)



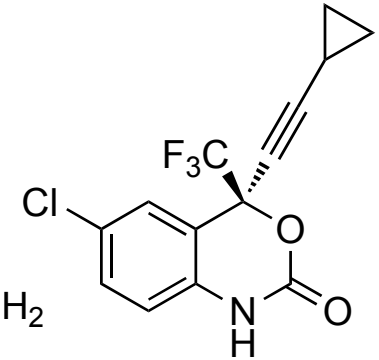
Valrubicine (Anthra) 1999
Resistant Bladder
Cancer



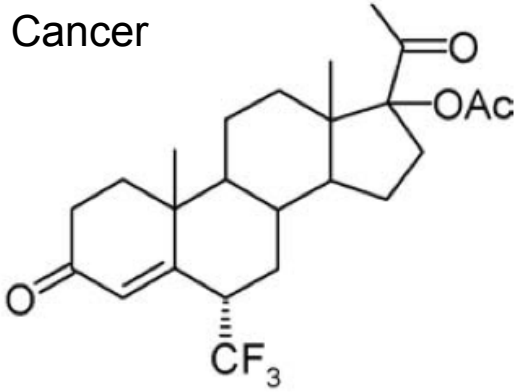
CF_3-deoxoartemisinin
Anti-malaria drug



Celebrex
(rheumatoid arthritis)



Efavirenz
HIV Inhibitor



Flumedroxone acetate
Demigran
Anti-migraine

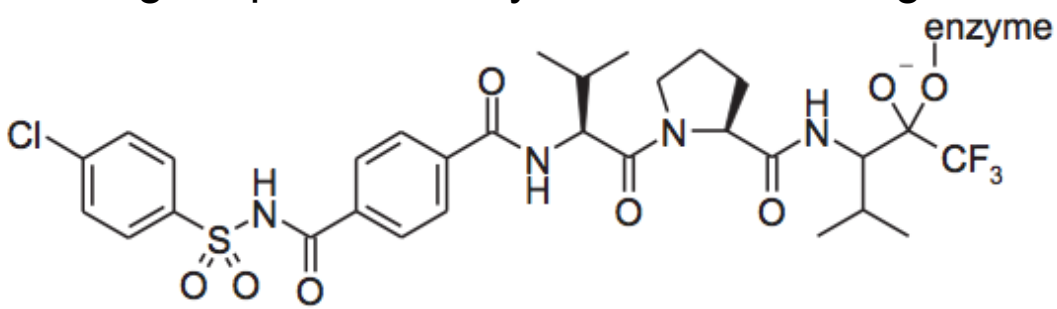
Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992.
Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

Why Fluorine in Pharmaceuticals?

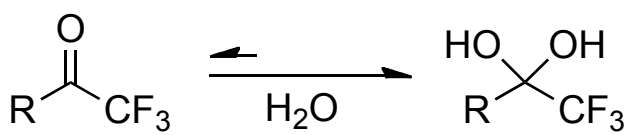
- Small size (similar to H) but with very different chemistry

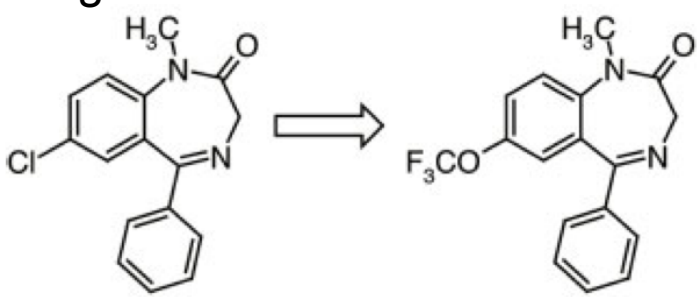
- Can have favorable electrostatic interactions in a binding pocket of the biological target

- Inhibition of biological processes by reversible binding to enzymes:



- Favor hydration as a mimic of “transition state” binding





- Bioisosteric Mimicking

- Fluorinated derivates often exhibit improved bioavailability and increased lipophilicity leading to a smaller effective dose

P. Kirsch, *Modern Fluoroorganic Applications*, Wiley-VCH, Weinheim **2004**.

Lipophilicity Parameters

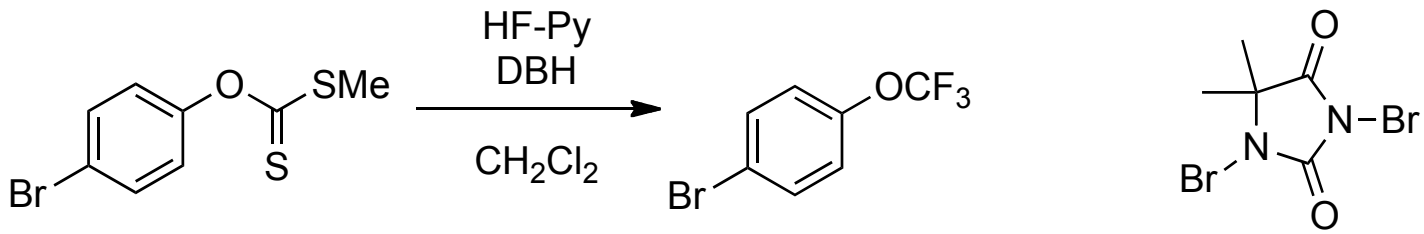
Substituent X	σ_m	σ_p	σ_I	σ_R	π_p
tert-Bu	−0.10	−0.20	–	–	+1.68
CH_3	−0.07	−0.17	–	–	+0.56
H	0	0	–	–	0
OCH_3	+0.12	−0.27	–	–	−0.04
OH	+0.12	−0.37	–	–	–
F	+0.34	+0.06	–	–	+0.14
Cl	+0.37	+0.23	–	–	+0.71
$COCH_3$	+0.38	+0.50	–	–	–
OCF_3	+0.38	+0.35	–	–	+1.04
Br	+0.39	+0.23	–	–	–
CF_3	+0.41	+0.53	+0.39	+0.12	+0.88
SCF_3	+0.44	+0.48	+0.41	+0.07	+1.44
CN	+0.56	+0.66	–	–	–
SF_5	+0.61	+0.68	+0.55	+0.11	+1.23
OSF_5	–	+0.44	–	–	–
NO_2	+0.71	+0.78	–	–	−0.28
$SOCF_3$	+0.77	+0.85	+0.69	+0.16	–
SO_2CF_3	+1.01	+1.17	+0.84	+0.34	+0.55
$S(CF_3)=NSO_2CF_3$	+1.27	+1.39	+1.15	+0.24	–
$SO(CF_3)=NSO_2CF_3$	+1.36	+1.55	+1.17	+0.38	–
$SF(=NSO_2CF_3)_2$	–	+1.78	+1.37	+0.41	–

P. Kirsch, *Modern Fluoroorganic Applications*, Wiley-VCH, Weinheim **2004**.

Classical Methods

Swarts Methods (1892):

Oxidative Fluorodesulfurizations:



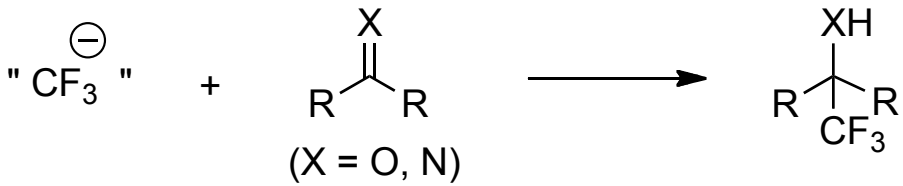
DBH

Despite advances in direct trifluoromethylation most applications rely on a “building block” approach.

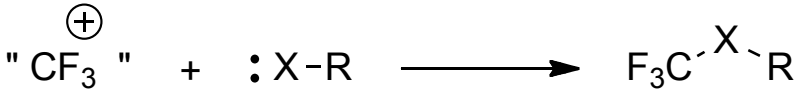
P. Kirsch, *Modern Fluoroorganic Applications*, Wiley-VCH, Weinheim **2004**.

4 Major Methods for Direct Trifluoromethylation

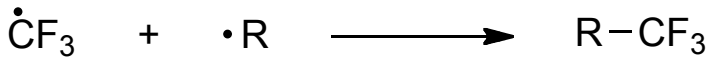
1. Nucleophilic



2. Electrophilic

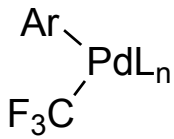


3. Radical



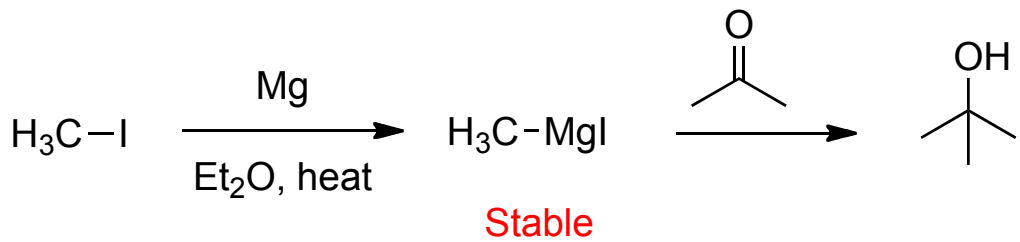
4. Metal Mediated

"CuCF3"

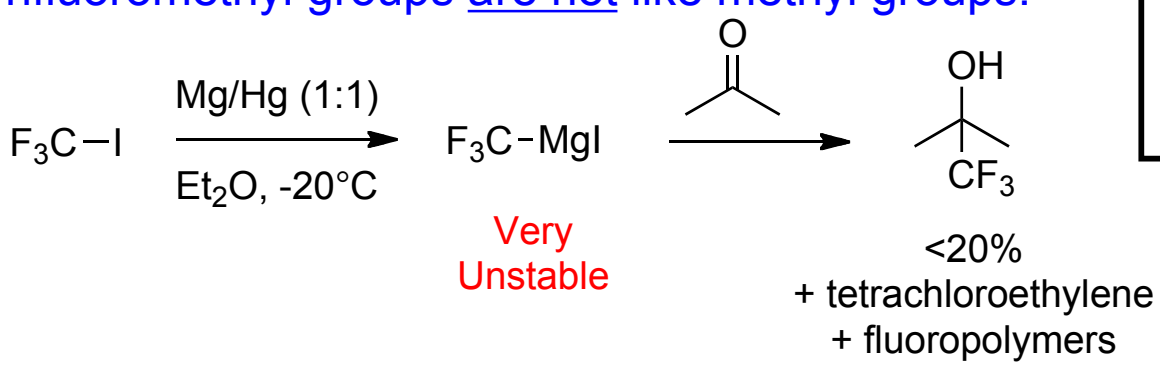


Nucleophilic Trifluoromethylation: Organometallic Reagents?

Grignard reagents are pretty easy for methylation:

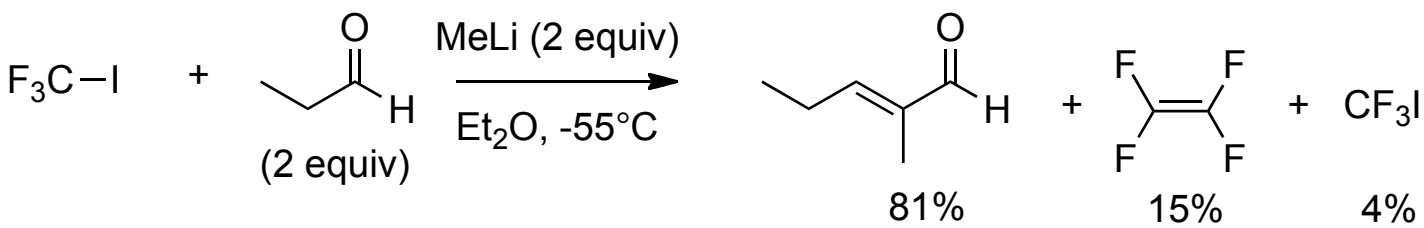


Trifluoromethyl groups <u>are not</u> like methyl groups:



$$CF_3M \longrightarrow MF + \ddot{C}F_2$$

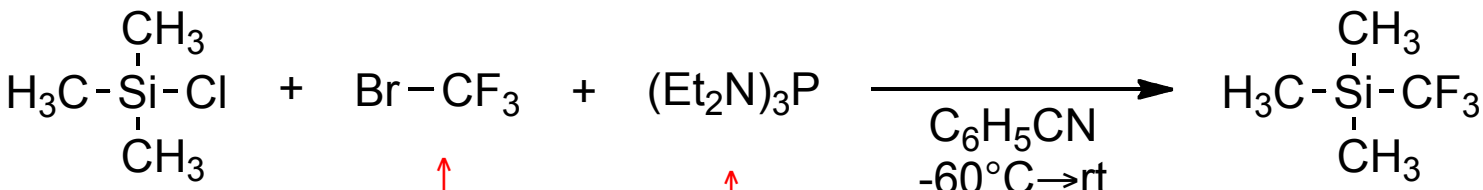
M = Li, MgX



Battershell, R. D. *et. al. J. Org. Chem.* **1963**, *28*, 1131.
Pierce, O. R.; McBee, E. T.; Judd, G. F. *J. Am. Chem. Soc.* **1954**, *76*, 474.

Preparation of the Ruppert–Prakash Reagent: $TMSCF_3$

Original preparation: Requires special apparatus



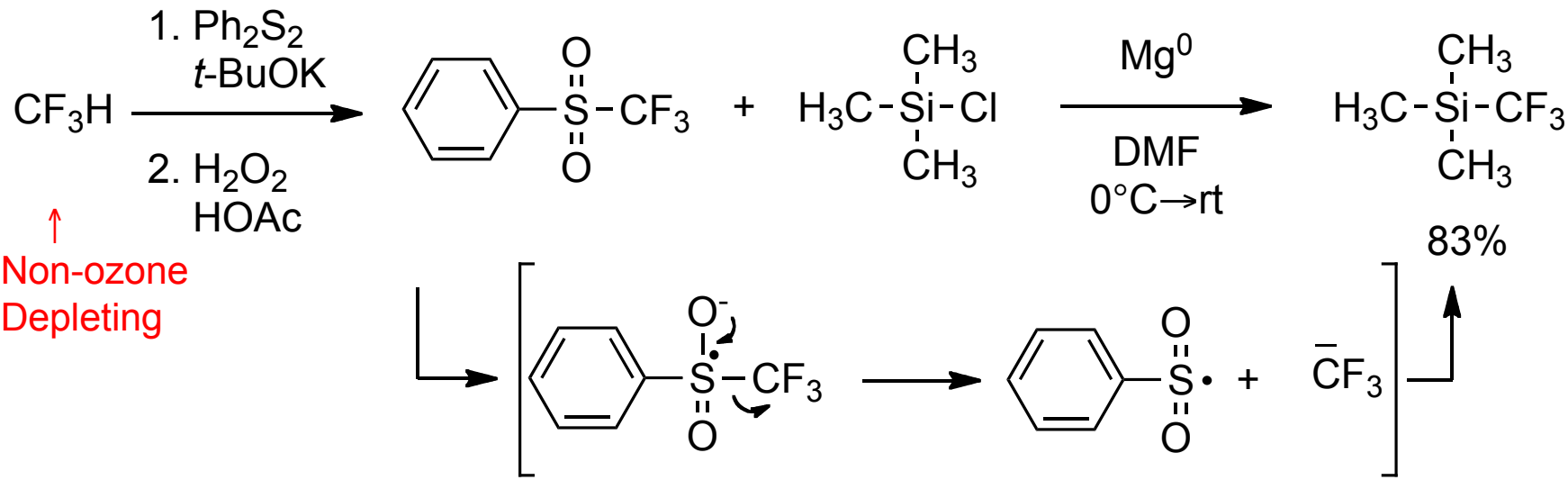
Ozone Depleting

Toxic

75%

Stable to acid & water

Improved preparation: Mg Reductive S-C bond cleavage

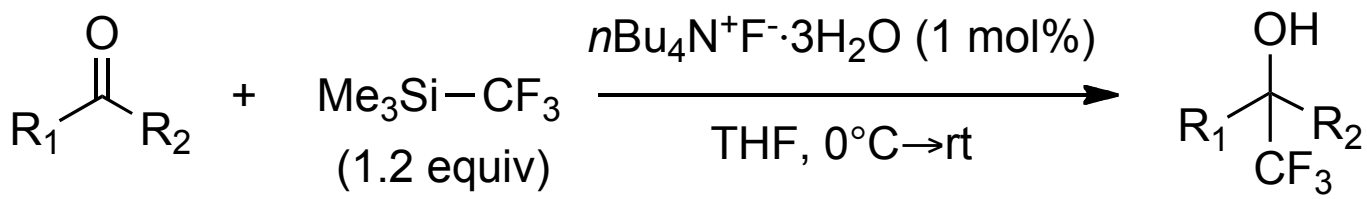


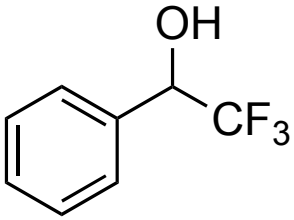
Non-ozone Depleting

Ruppert, I. *et. al. Tetrahedron Lett.* **1984**, *25*, 2195.
Prakash, G. K. S. *et. al. Org. Synth.* **1995**, 72, 232.
Prakash, G. K. S. *et. al. J. Org. Chem.* **2003**, *68*, 4457.

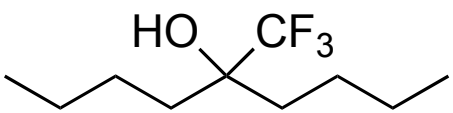
Aldrich: $15 / g

Additions to Carbonyl Compounds Using $TMSCF_3$

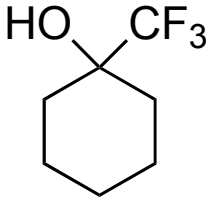




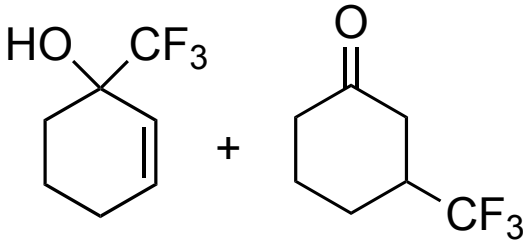
85%



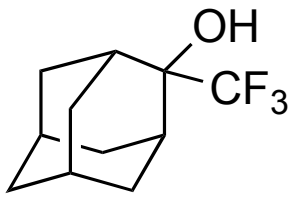
87%



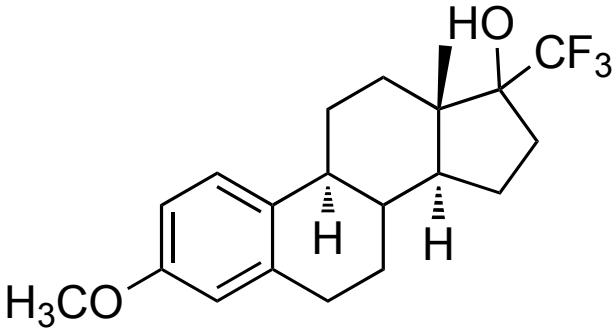
77%



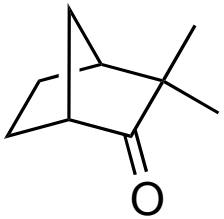
60% (9:1)



24 h, 72%



24h, 2 equiv TBAF
62%

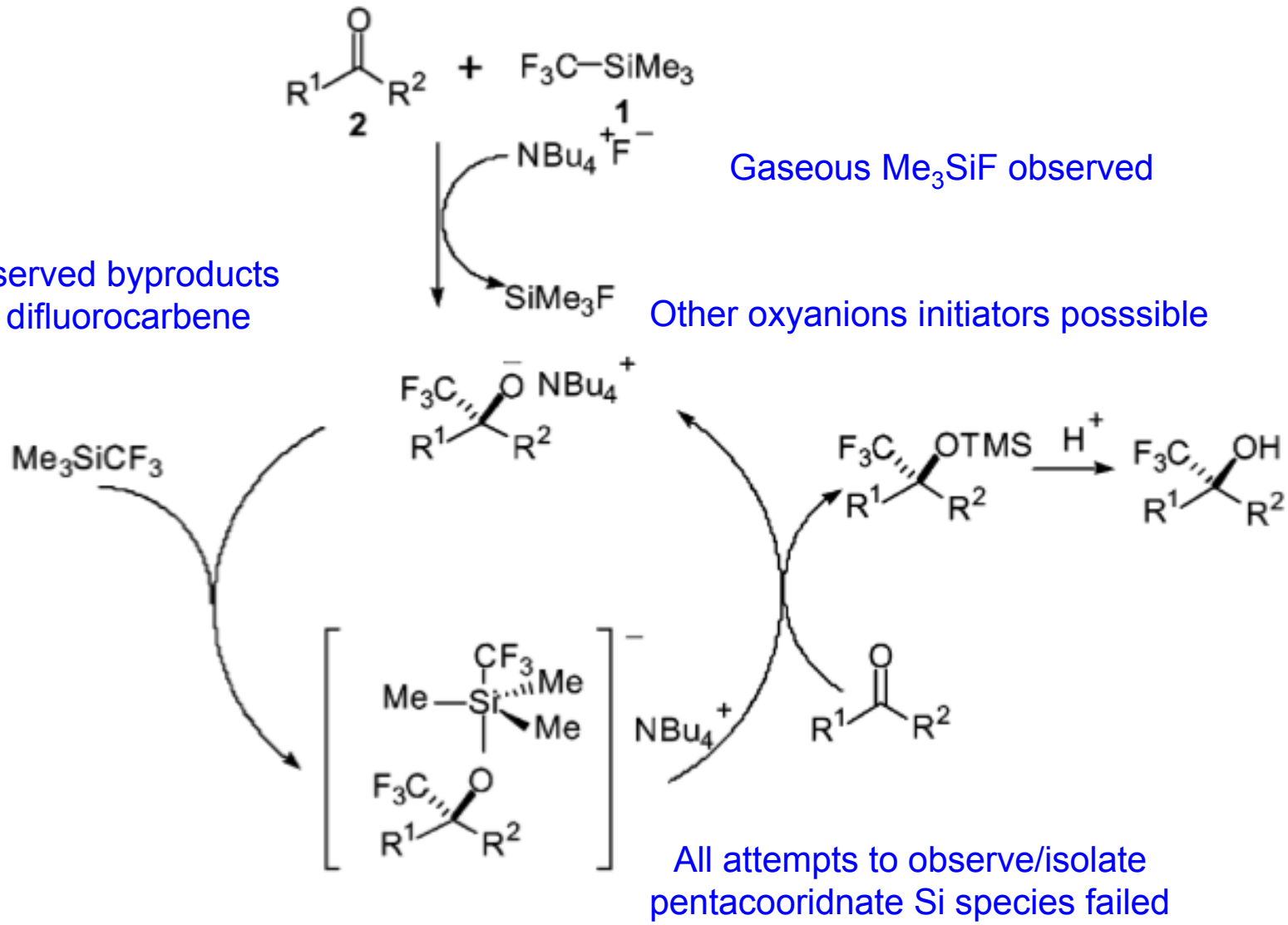


0%

Minor improvements to yield were seen utilizing CsF as an initiator.

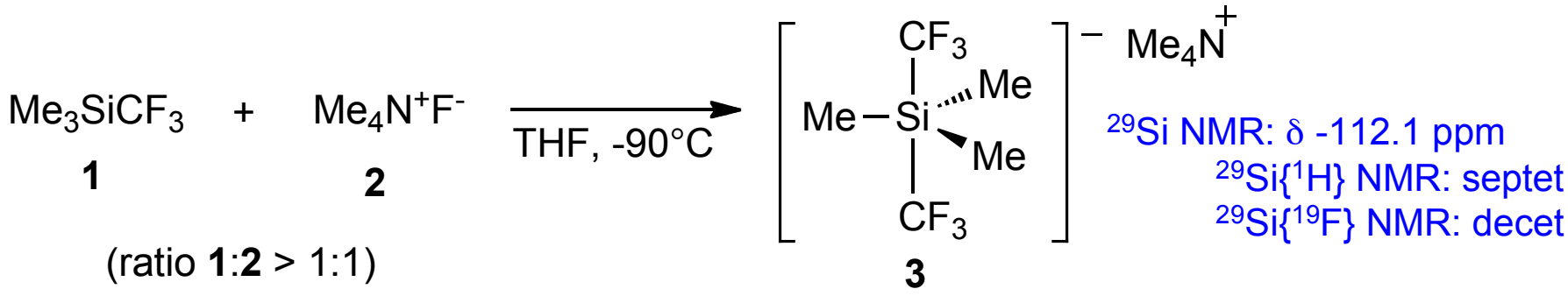
Prakash, G. K. S. *et. al. J. Am. Chem. Soc.* **1989**, *111*, 393.
Prakash, G. K. S. *et. al. J. Org. Chem.* **1991**, *56*, 984.

Fluoride Ion Initiated Mechanism



Prakash, G. K. S. *et. al. Chem. Rev.* **1997**, *97*, 757.
Prakash, G. K. S. *et. al. J. Fluorine Chem.* **2001**, *112*, 123.

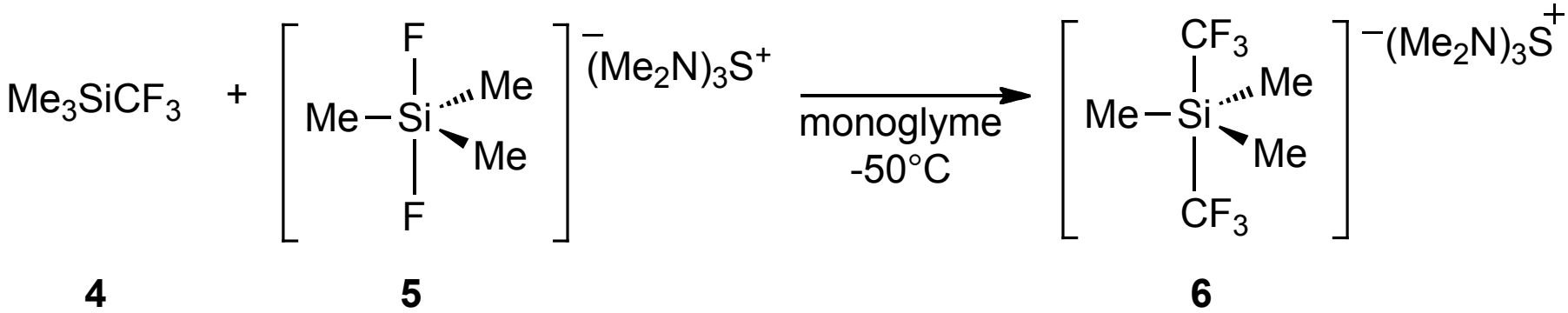
Study and Isolation of Pentavalent Silicon Species



(ratio **1**:**2** > 1:1)

^{2}J(Si, F) = 36.2 Hz
^{1}J(F, C) = 322 Hz

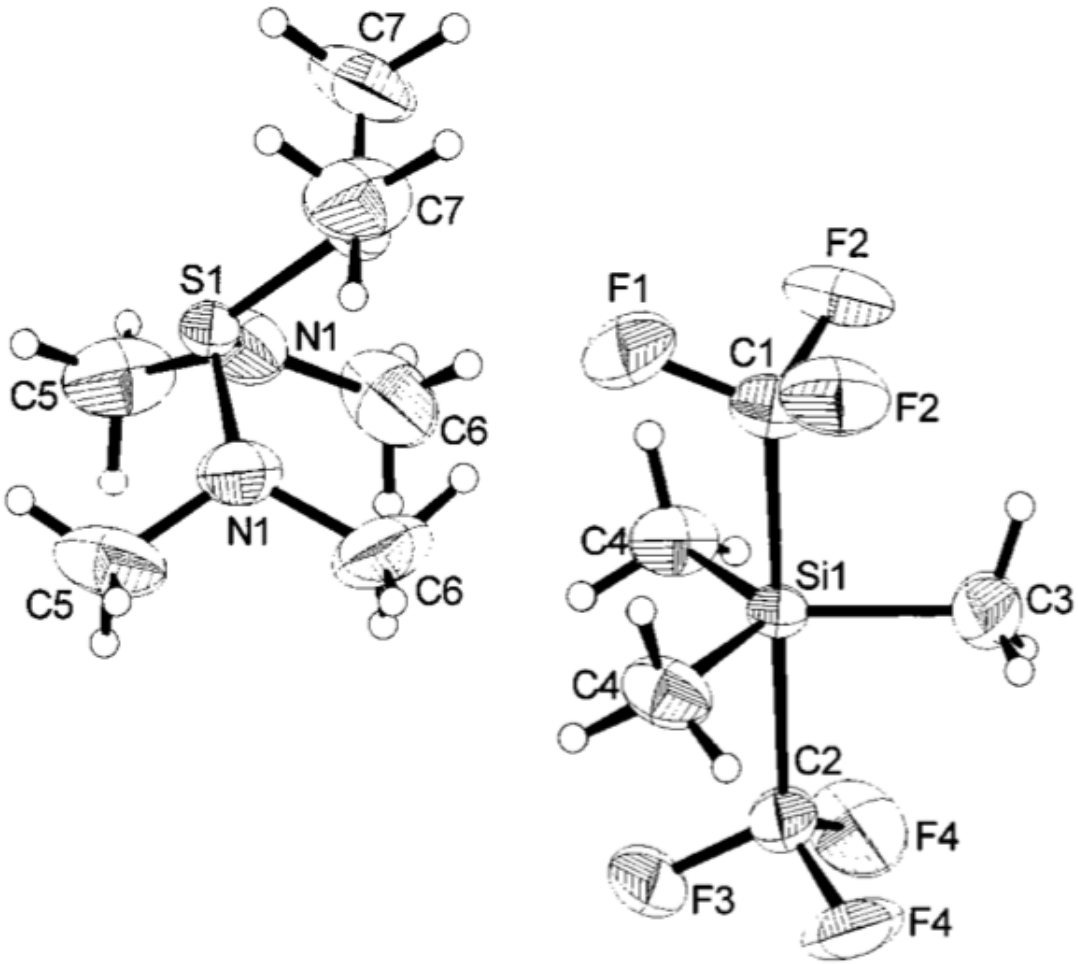
^{2}J(Si, F) = 6.0 Hz
^{1}J(F, C) = 378 Hz



^{19}F NMR: δ -63.7 ppm
isolated, stable solid below 0 ºC

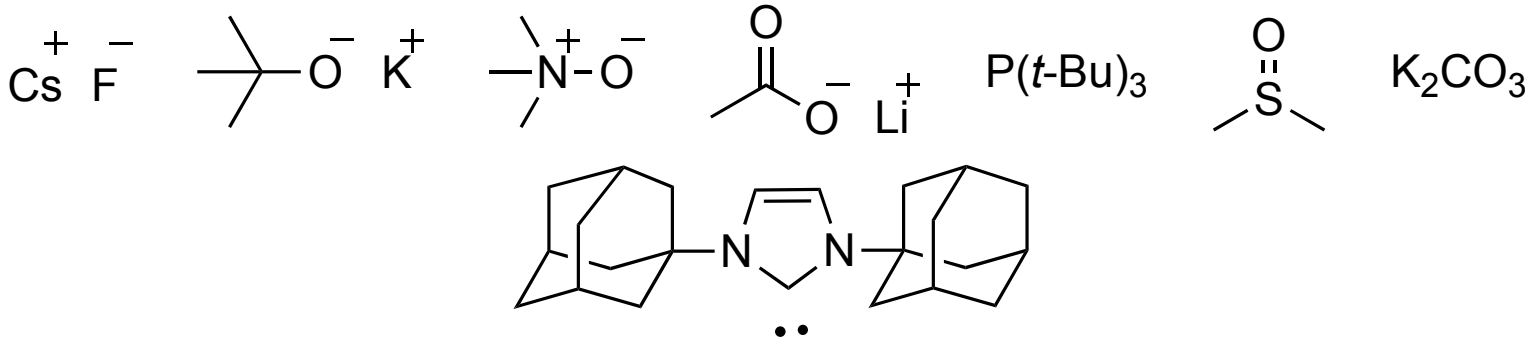
Naumann, D. *et. al. Angew. Chem. Int. Ed.* **1999**, *38*, 2252.
Roschenthalener, G. -V. *et. al. J. Chem. Soc., Chem. Comm.* **1999**, 1017.

Study and Isolation of Pentavalent Silicon Species

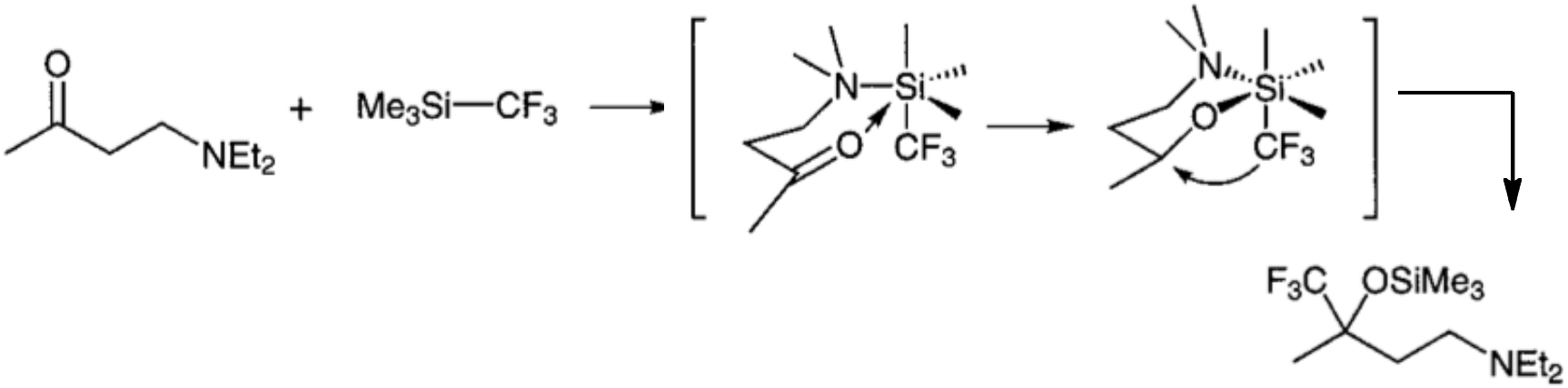


Roschenthalener, G. -V. *et. al. J. Chem. Soc., Chem. Comm.* **1999**, 1017.

Alternative Lewis Base Initiators

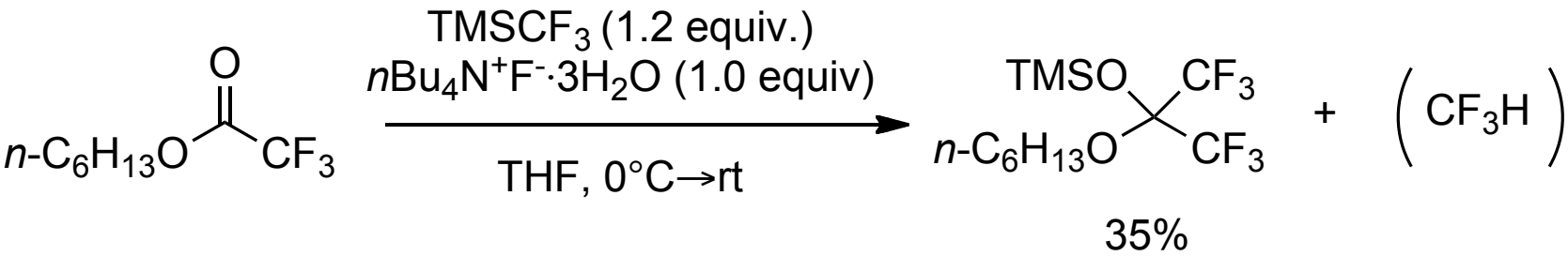


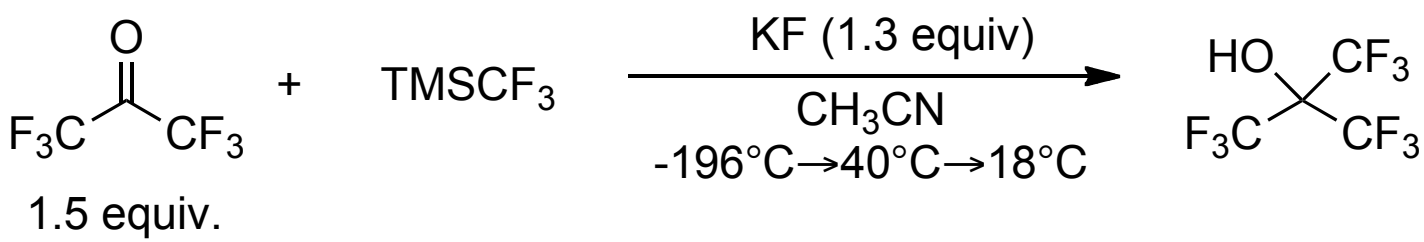
Intramolecular assistance by β-amine:



Cahard, D.; Ma, J. *J. Fluorine Chem.* **2007**, *128*, 975. and references within.
Fuchikami, T. *Synlett* 1**997**, 587.

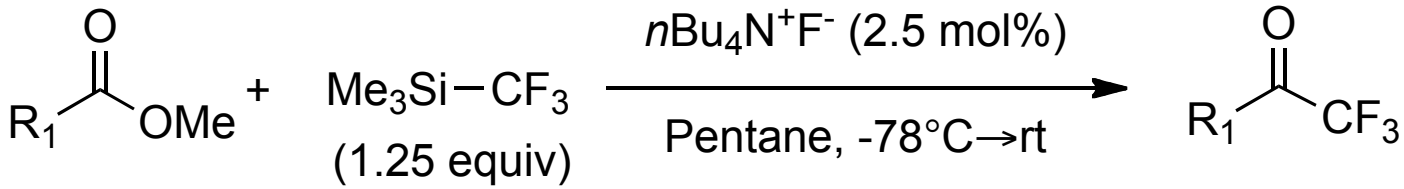
Not All Systems Can Be Catalytic in Initiator

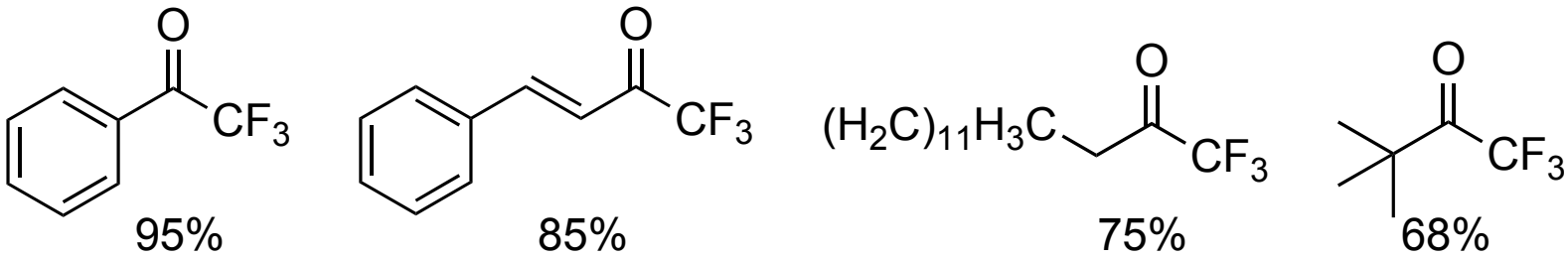




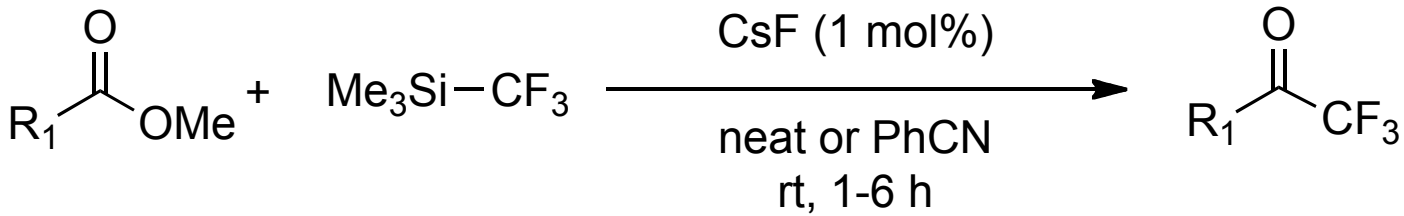
Prakash, G. K. S. *et. al. J. Org. Chem.* **1991**, *56*, 984.
DesMarteau, D. D. *et. al. J. Org. Chem.* **1992**, *57*, 1124.

Simple Esters Generate Trifluoromethyl Ketones





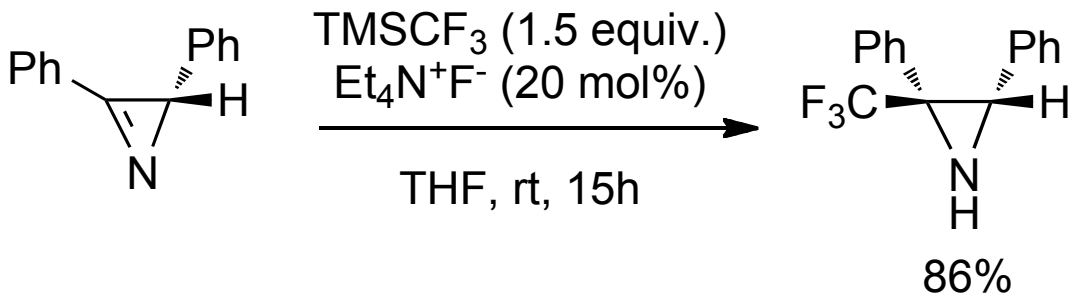
Requires very dry reagents. THF undergoes ring opening. Double addition observed at different temperatures.



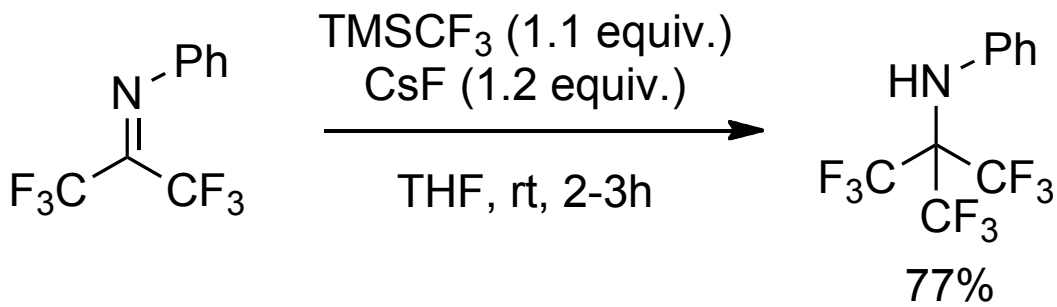
Use of CsF generally gave higher yields at rt with decreased rxn times. Avoid vigorous drying of TBAF.

Prakash, G. K. S. *et. al. Angew. Chem. Int. Ed.* **1998**, *37*, 820.
Shreeve, J. M. *et. al. J. Org. Chem.* **1999**, *64*, 2873.

Nitrogen Electrophiles Need Activation



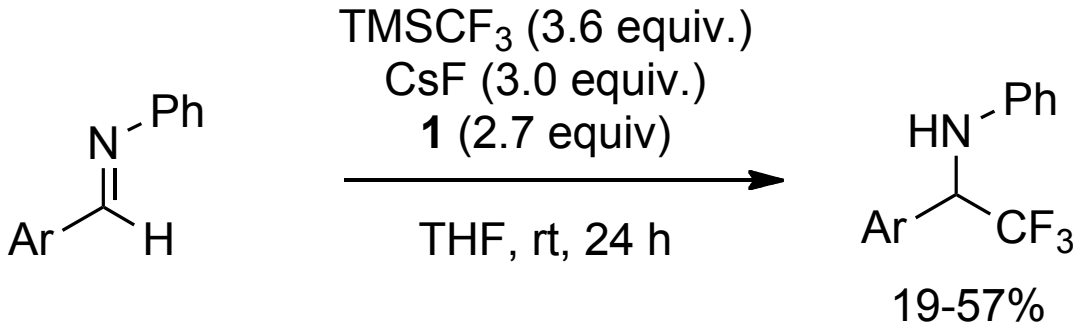
Release of ring strain allows for catalytic amount of fluoride.

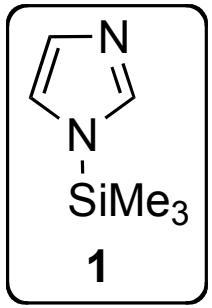


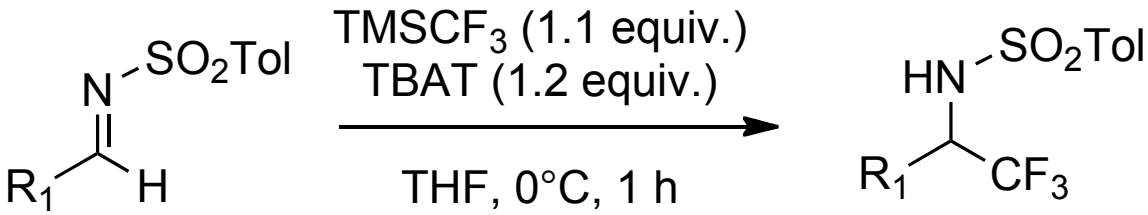
Extrememly electrophilic imines were reactive.

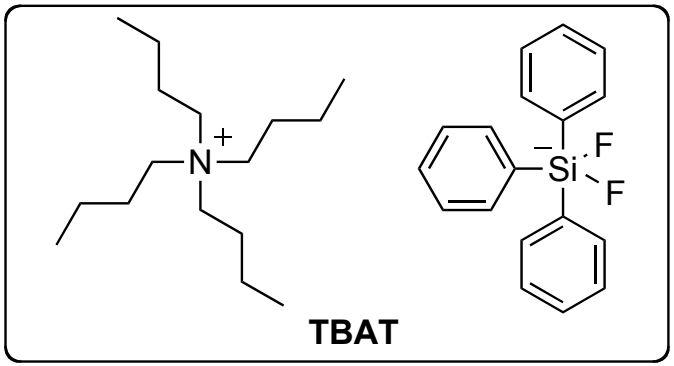
Laurent, A. J. *et. al. Tetrahedron Lett.* **1994**, *35*, 3303.
Petrov, V. A. *Tetrahedron Lett.* **2000**, *41*, 6959.

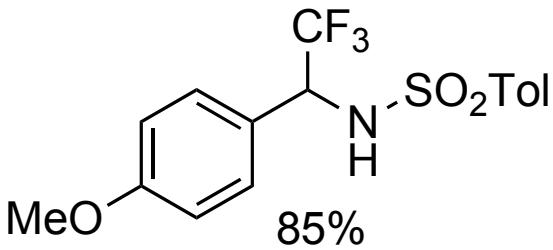
Additions to Aldimines

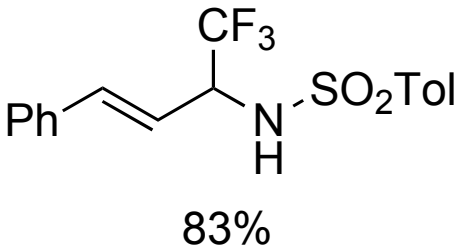


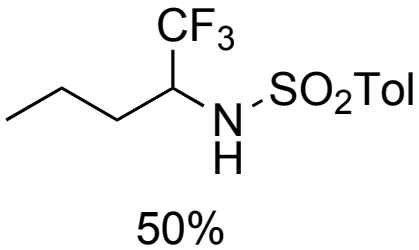










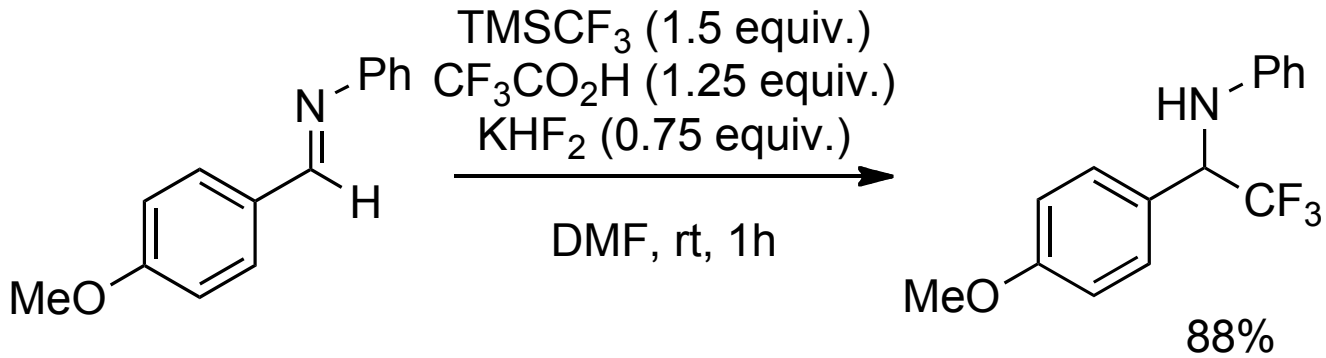


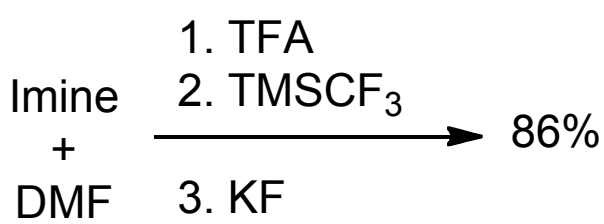
Metal fluorides were too basic.

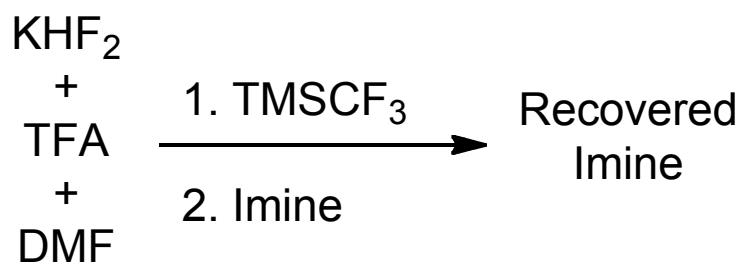
TBAF gave CF_3H

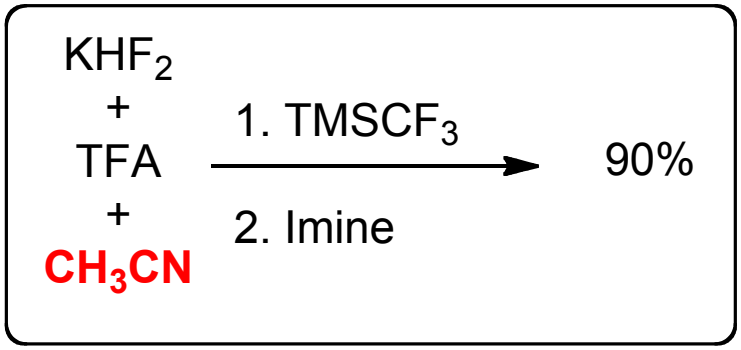
Prakash, G. K. S. *et. al. Synlett* **2001**, *1*, 77.
Blazejewski, J. -C. *et. al. Tetrahedron Lett.* **1999**, *40*, 5475.

Nucleophilic Trifluoromethylation in Acid?





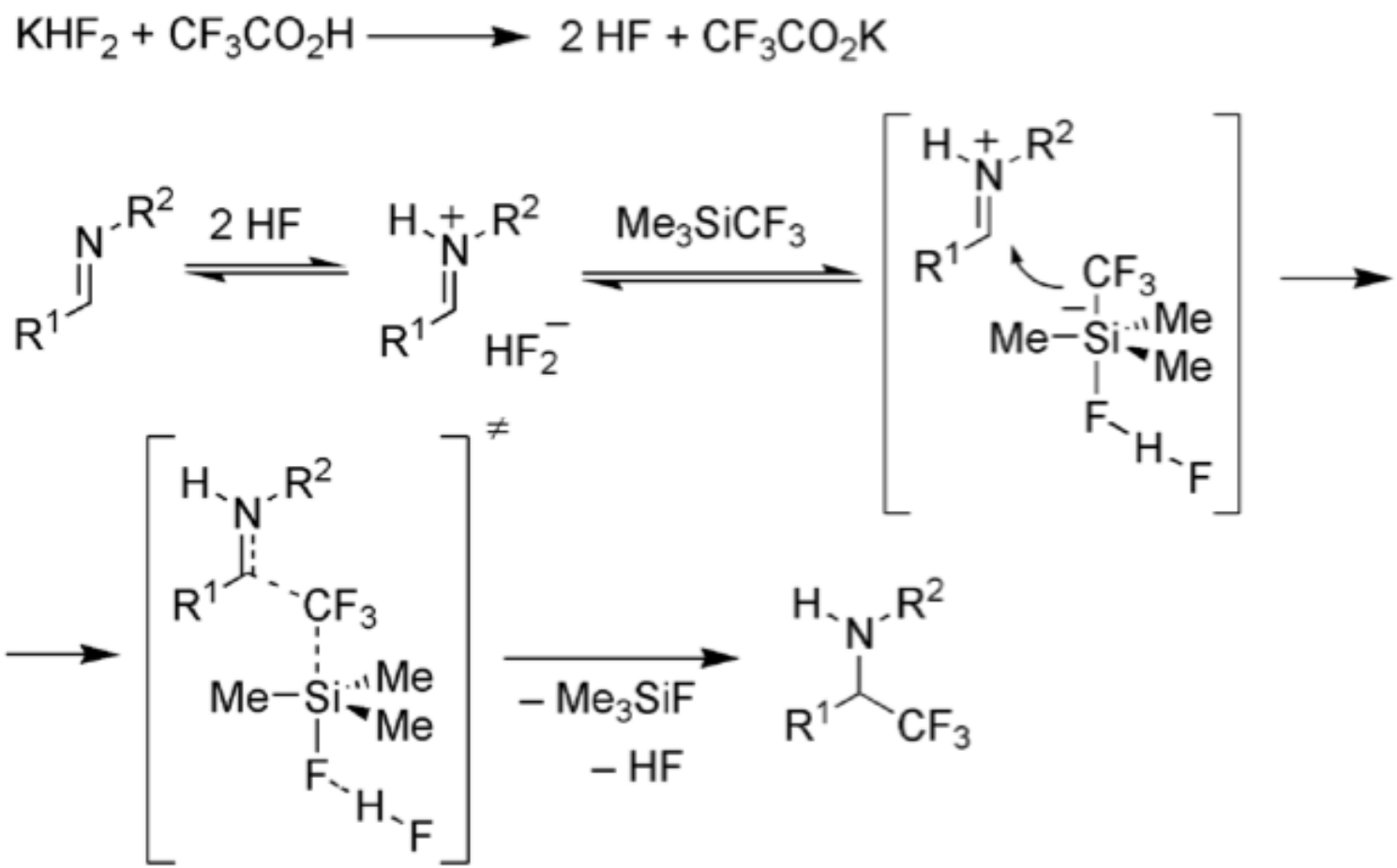




HF & $TMSCF_3$ are compatible in CH_3CN!
($t_{1/2}$ ~ 3 d by ^{19}F NMR)

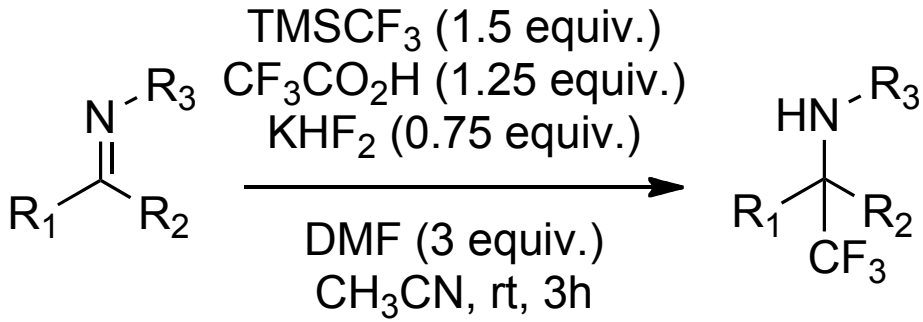
Dilman, A. D. *et. al*. *Eur J. Org. Chem.* **2008**, 5226.

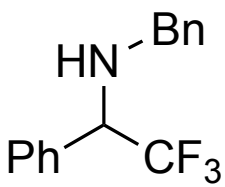
Acidic Activation of Imines



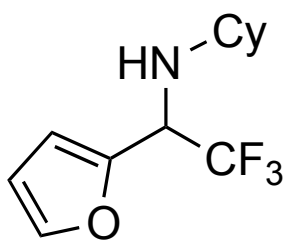
Dilman, A. D. *et. al*. *Eur J. Org. Chem.* **2008**, 5226.

Acidic Activation Leads to Wide Scope

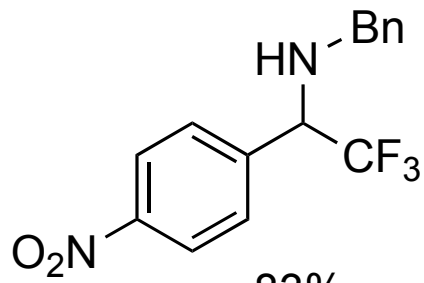




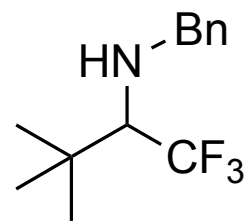
90%



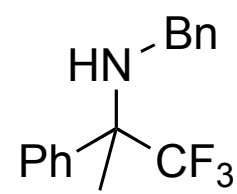
75%



83%
(TfOH)

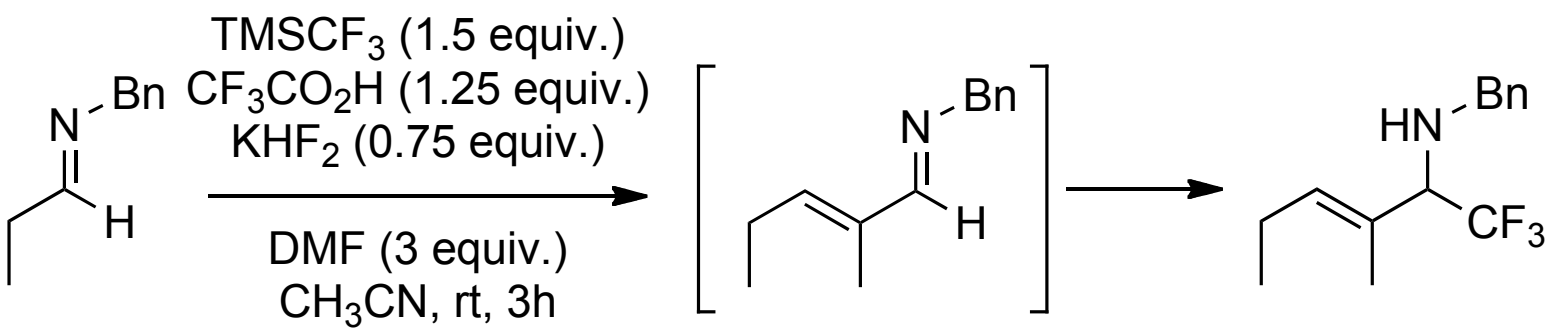


90%



67%

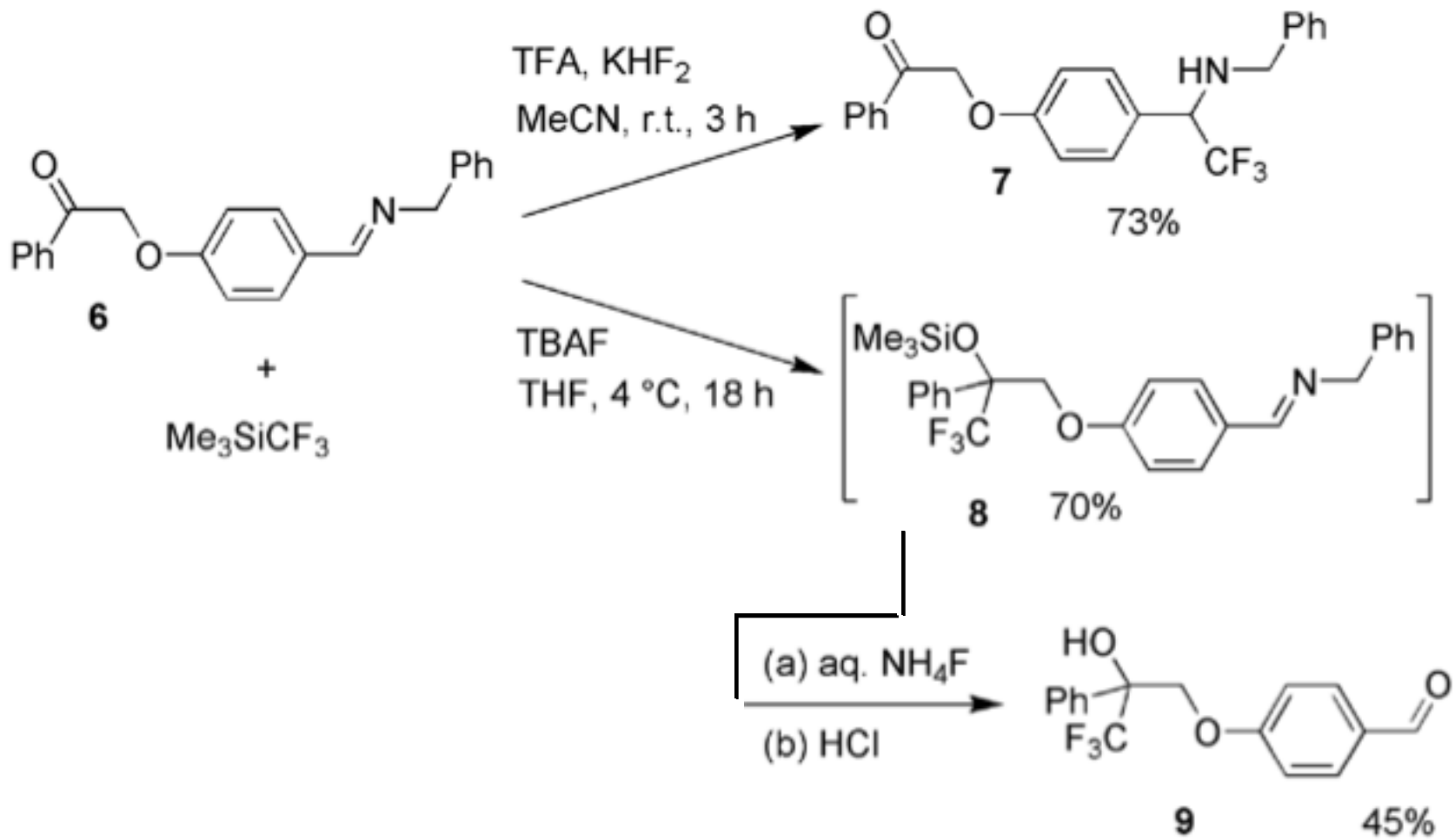
Aldol reaction with enolizable aldimines:



38%

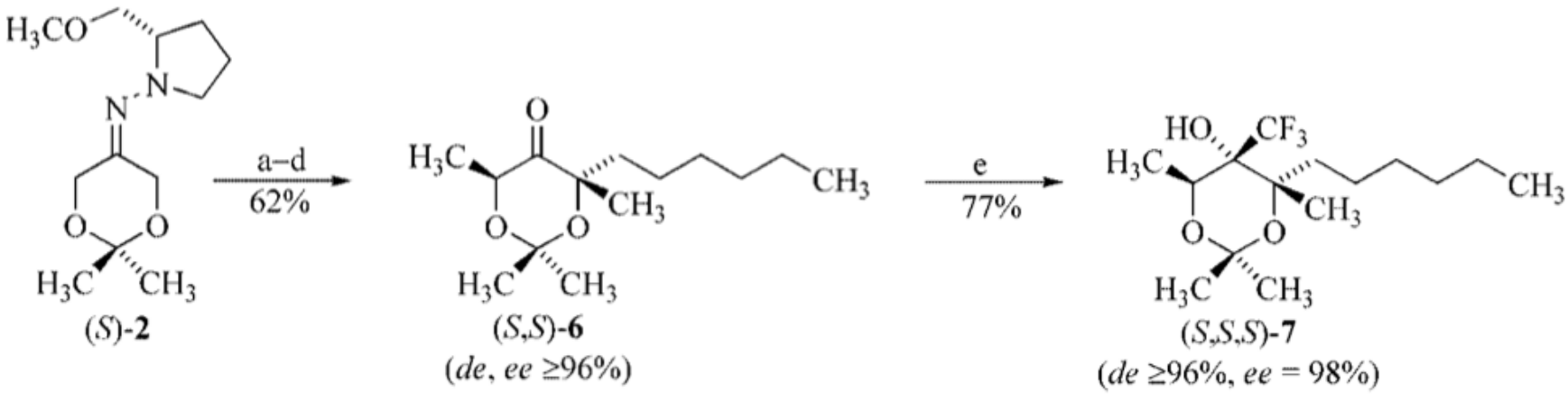
Dilman, A. D. *et. al*. *Eur J. Org. Chem.* **2008**, 5226.

Chemoselective Trifluoromethylation

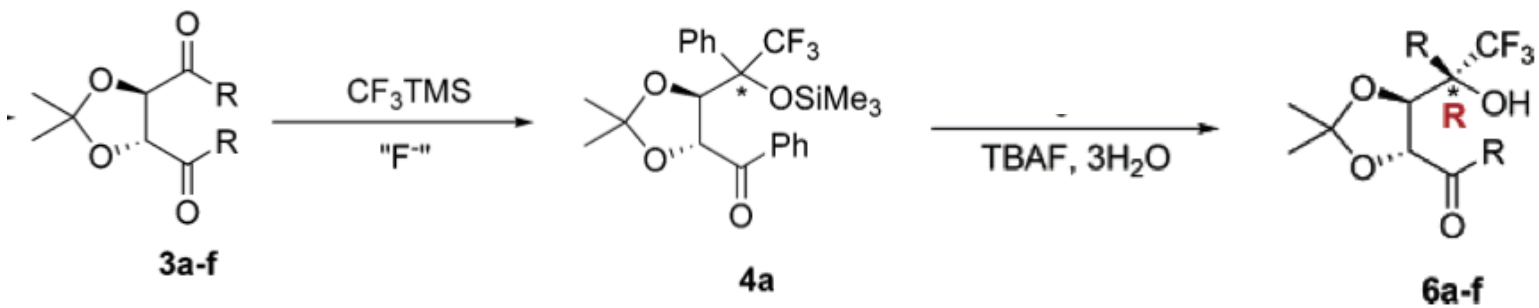


Dilman, A. D. *et. al*. *Eur J. Org. Chem.* **2008**, 5226.

Diastereoselective Trifluoromethylation: Adjacent Stereocenters



e) 1.5 equiv. $TMSCF_3$, 0.07 equiv. TBAF, THF, 0 °C; after completion: 1.5 equiv. TBAF, 1 h.



[a] The reactions were carried out by adding 0.08 equiv of TBAF, $3H_2O$ at −40 °C to a mixture of CF_3TMS (1.05 equiv) and compounds **3a–f** in THF; desilylation of intermediates products were carried out by reaction with TBAF, $3H_2O$ (1 equiv) in CH_2Cl_2 at room temperature for 3 h.

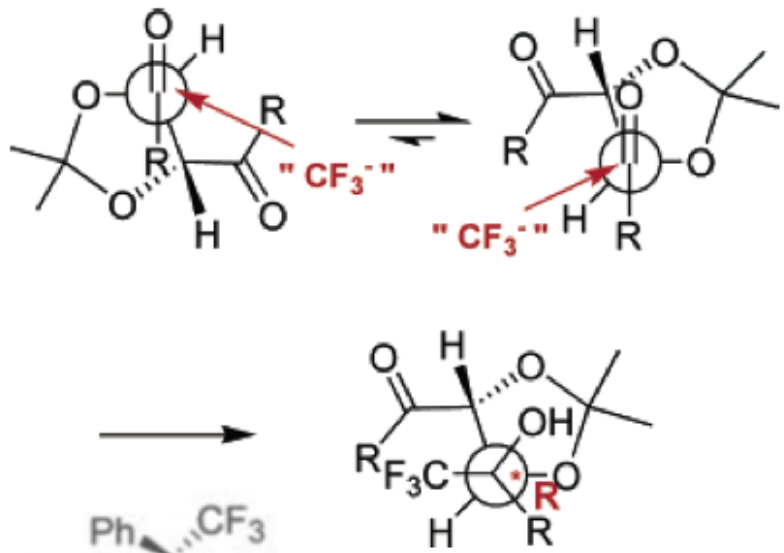
60-93%
70-99% de

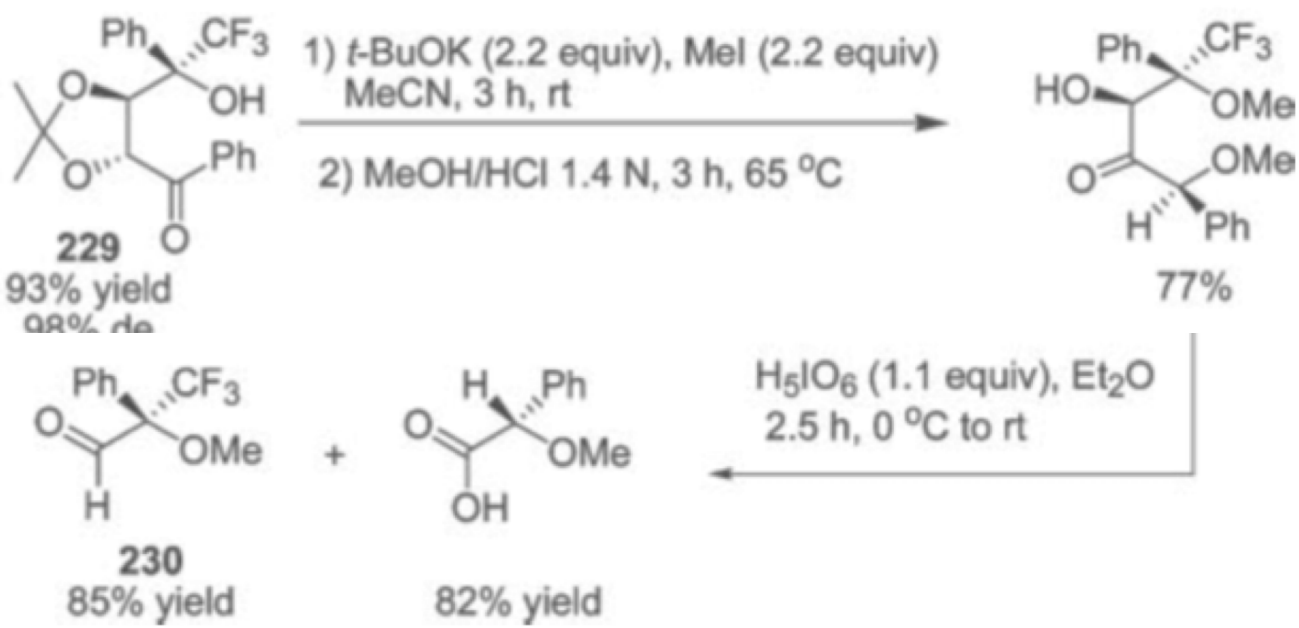
Enders, D.; Herriger, C. *Eur. J. Org. Chem.* **2007**, 1085.
Portella, C. *et. al. J. Org. Chem.* **2007**, *72*, 1174.

Diastereoselective Trifluoromethylation: Adjacent Stereocenters

Non-chelation
Felkin-Anh model:

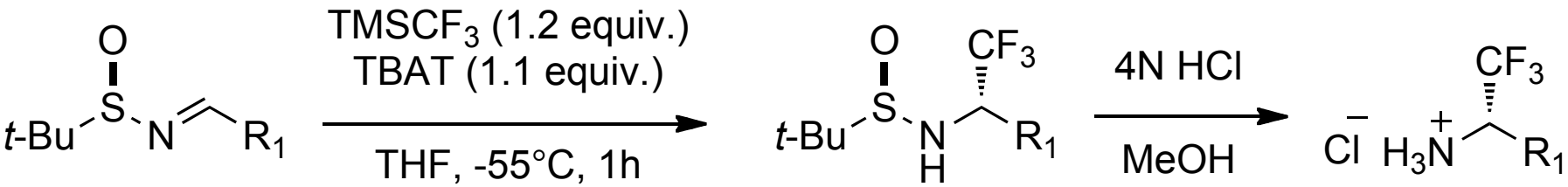
Electronic replusion
between CF_3 and ketone

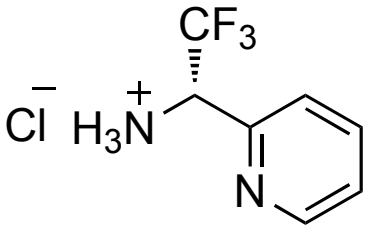




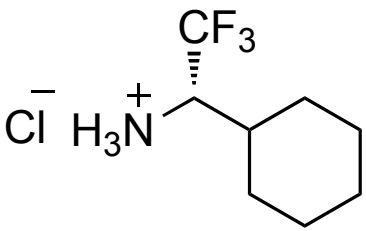
Portella, C. *et. al. J. Org. Chem.* **2007**, *72*, 1174.

Chiral Sulfinimines

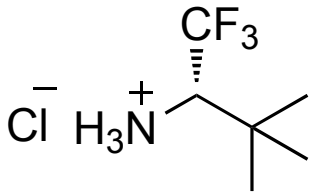




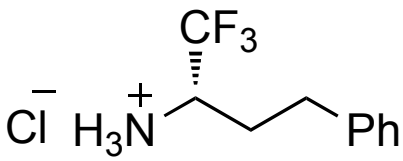
92%, dr 99:1



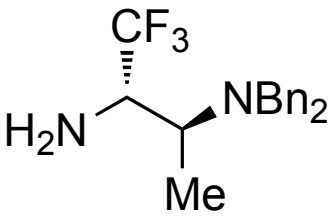
88%, dr 99:1



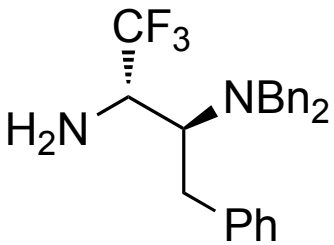
75%, dr 99:1



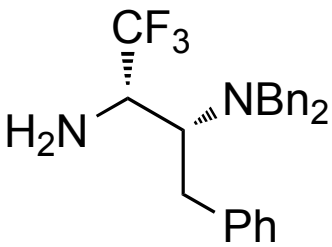
84%, dr 90:10



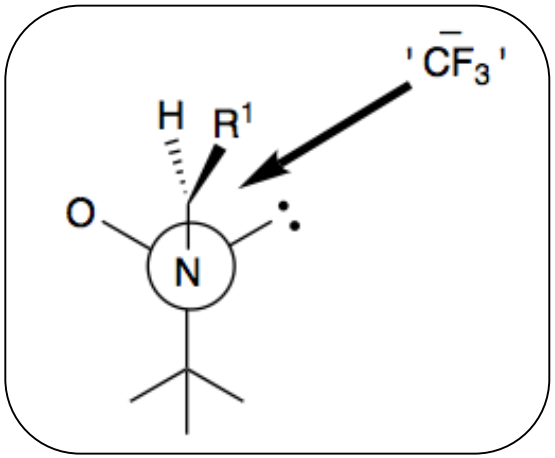
86%, dr >99:1
(with TMAF)



81%, dr >99:1
(with TMAF)

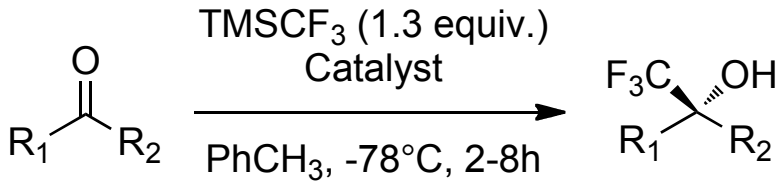


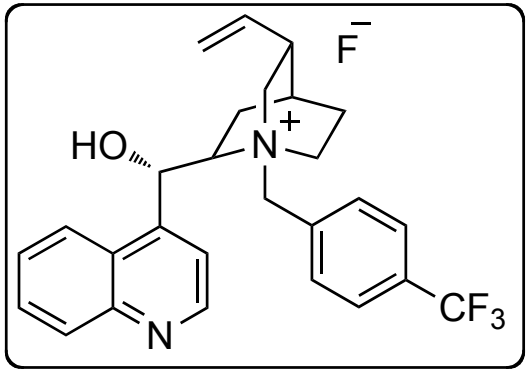
60%, dr 80:20
(with TMAF)

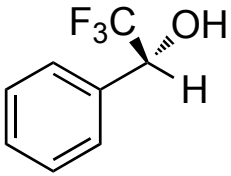


Prakash, G. K. S. *et. al. Angew. Chem. Int. Ed.* **2001**, *40*, 589.
Prakash, G. K. S. *et. al. J. Am. Chem. Soc.* **2002**, *124*, 6538.

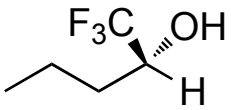
Asymmetric Trilfuoromethylation: Chiral Fluoride Salts



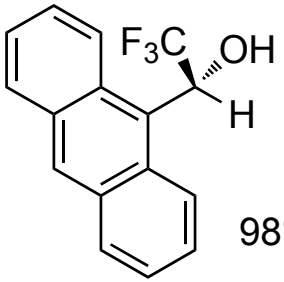




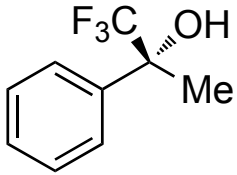
99%, 37% ee



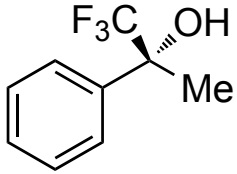
99%, 15% ee



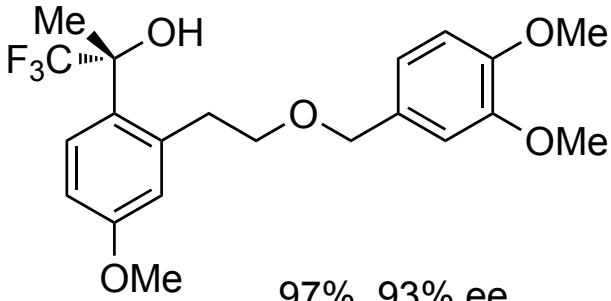
98%, 45% ee



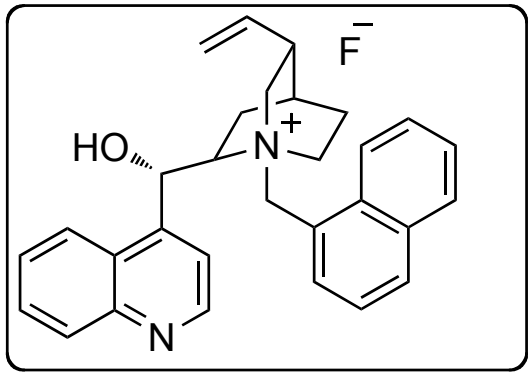
91%, 48% ee



87%, 51% ee

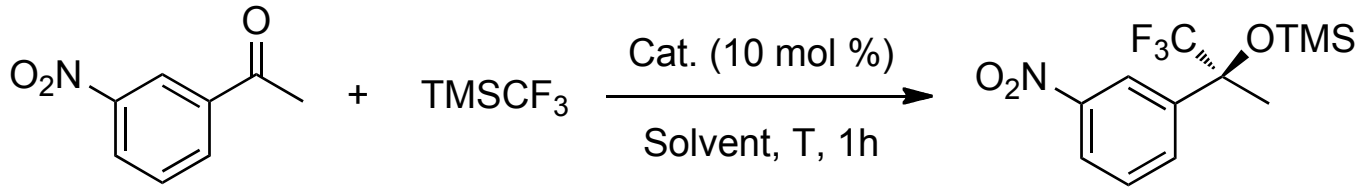


97%, 93% ee
in CH_2Cl_2, -78°C

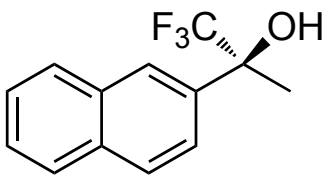


Kobayashi, Y. *et. al. Tetrahedron Lett.* **1994**, *35*, 3137.
Caron, S. *et. al. Synthesis* **2003**, *11*, 1693.

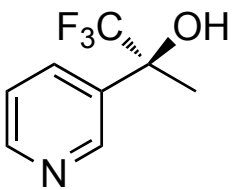
Chiral Quaternary Ammonium Phenoxides



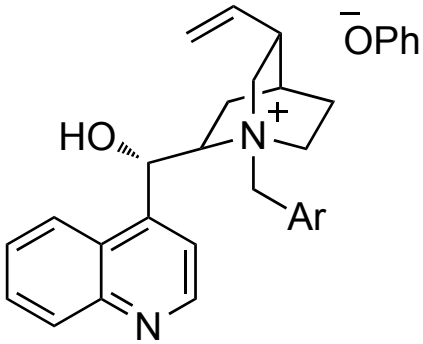
Entry	Ar	Solvent	T (C°)	Yield (%)	%ee
1	Ph	CH_2Cl_2	-78	93	13
2	3,5-(*t*-Bu)$_2$C$_6$H$_3$	CH_2Cl_2	-78	96	17
3	3,5-(Ph)$_2$C$_6$H$_3$	CH_2Cl_2	-78	95	50
4	3,5-[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_2$C$_6$H$_3$	CH_2Cl_2	-78	99	62
5	3,5-[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_2$C$_6$H$_3$	Tol	-20	99	79
6	3,5-[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_2$C$_6$H$_3$	EtCN	-20	65	19
7	3,5-[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_2$C$_6$H$_3$	Tol/CH_2Cl_2 7:3	-78	98	87



95%, 77% ee

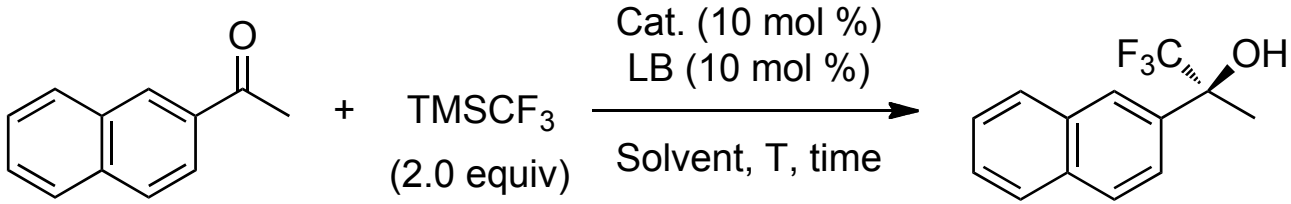


90%, 46% ee

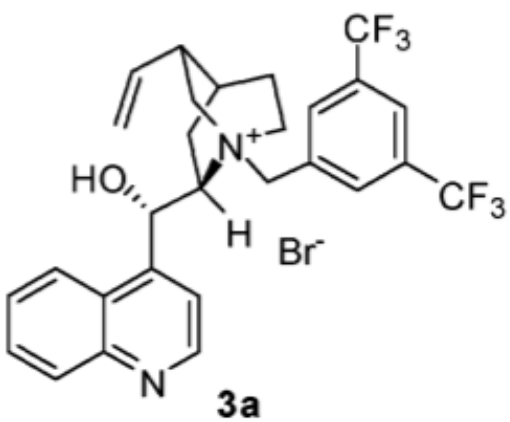


Mukaiyama, T. *et. al. Chem. Lett.* **2007**, *36*, 666.

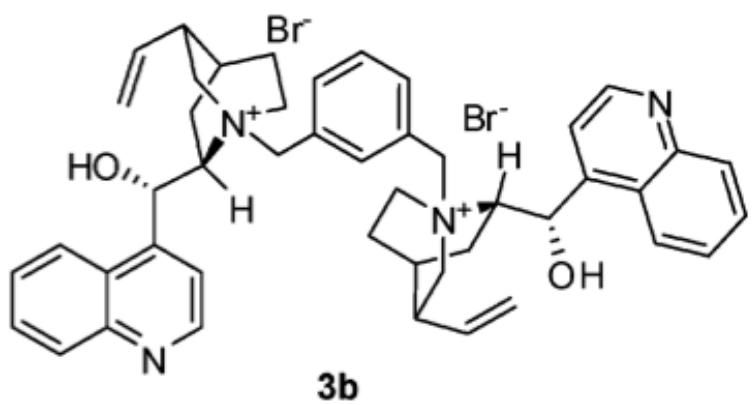
Cinchona Salt / TMAF Combination



Entry	Additive	Solvent (2:1)	T (C°)	Yield (%)	%ee
1	$KF{\cdot}2H_2O$	Tol/CH_2Cl_2	-40	-	-
2	$TBAF/H_2O$	Tol/CH_2Cl_2	-40	94	22
3	$TEAF/H_2O$	Tol/CH_2Cl_2	-40	38	66
4	TMAF	Tol/CH_2Cl_2	-40	65	70
5	TMAF (20 mol %)	Tol/CH_2Cl_2	-80	98	87



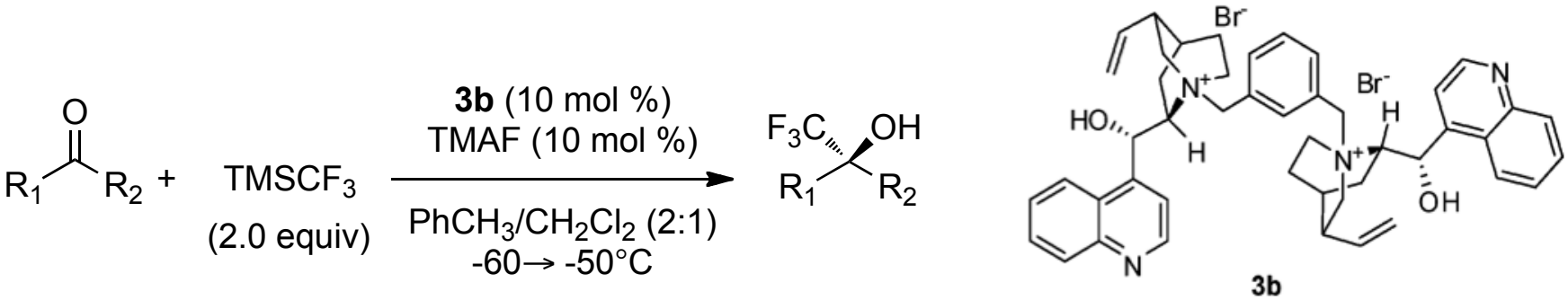
3a

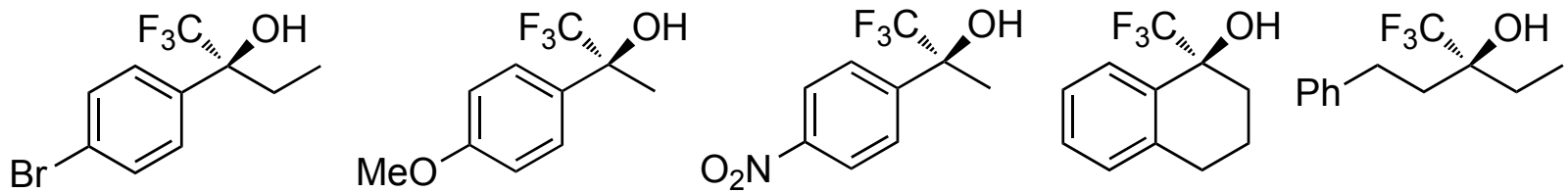


3b

Shibata, N. *et. al. Org. Lett.* **2007**, *9*, 3707.

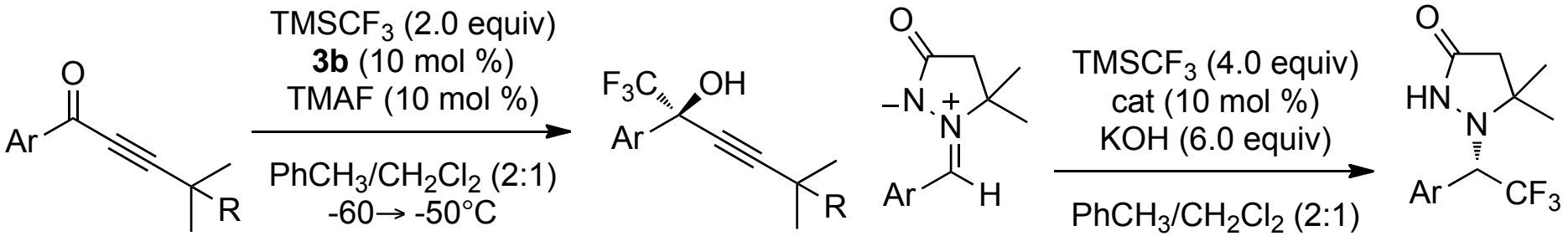
Highly Enantioselective Trifluoromethylation





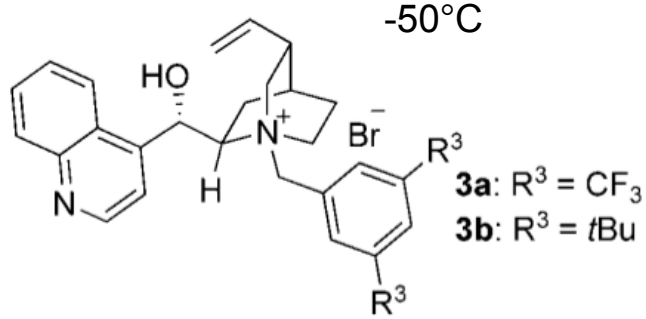
84%, 93% ee | 84%, 89% ee | 97%, 52% ee | 75%, 94% ee | 37%, 10% ee

---



71-99%
78-96% ee

74-95%
80-98% ee

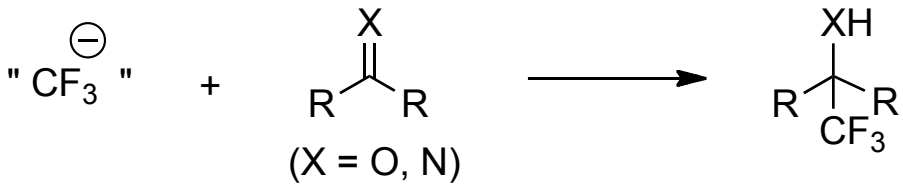


3a: $R^3 = CF_3$
3b: $R^3 = t$Bu

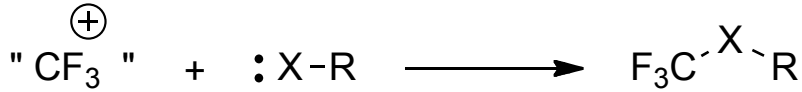
Shibata, N. *et. al. Org. Lett.* **2007**, *9*, 3707.
Shibata, N. *et. al. Org. Lett.* **2010**, *22*, 5104.
Shibata, N. *et. al. Angew. Chem. Int. Ed.* **2009**, *48*, 6324.

Methods for Direct Trifluoromethylation

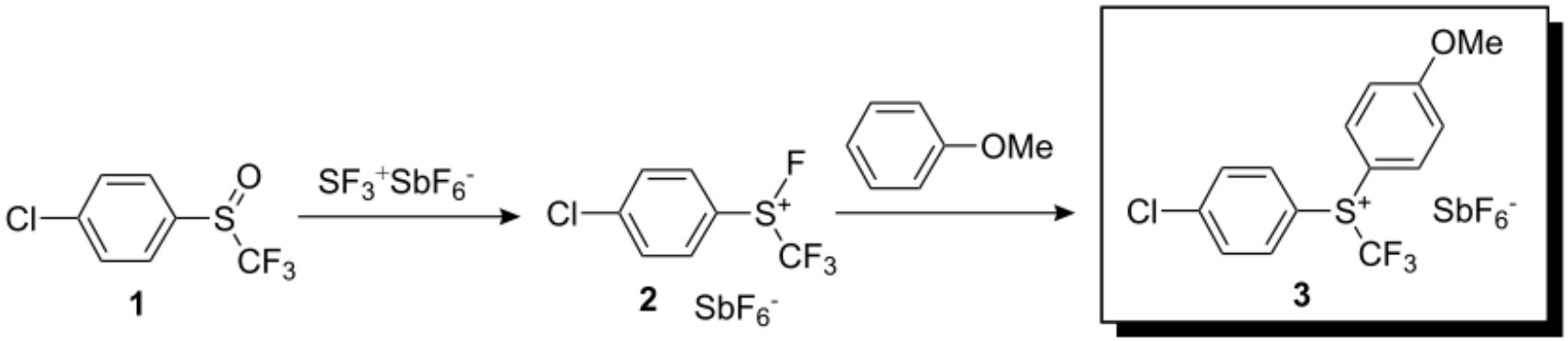
1. Nucleophilic



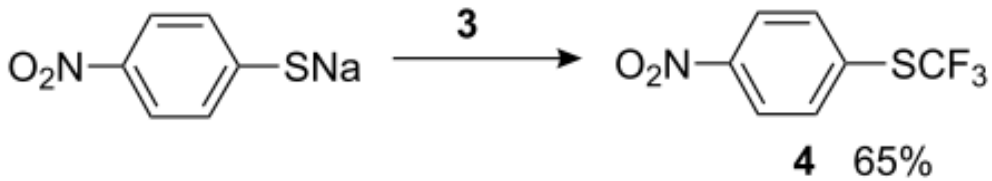
2. Electrophilic



The First Electrophilic Trifluoromethylating Reagent

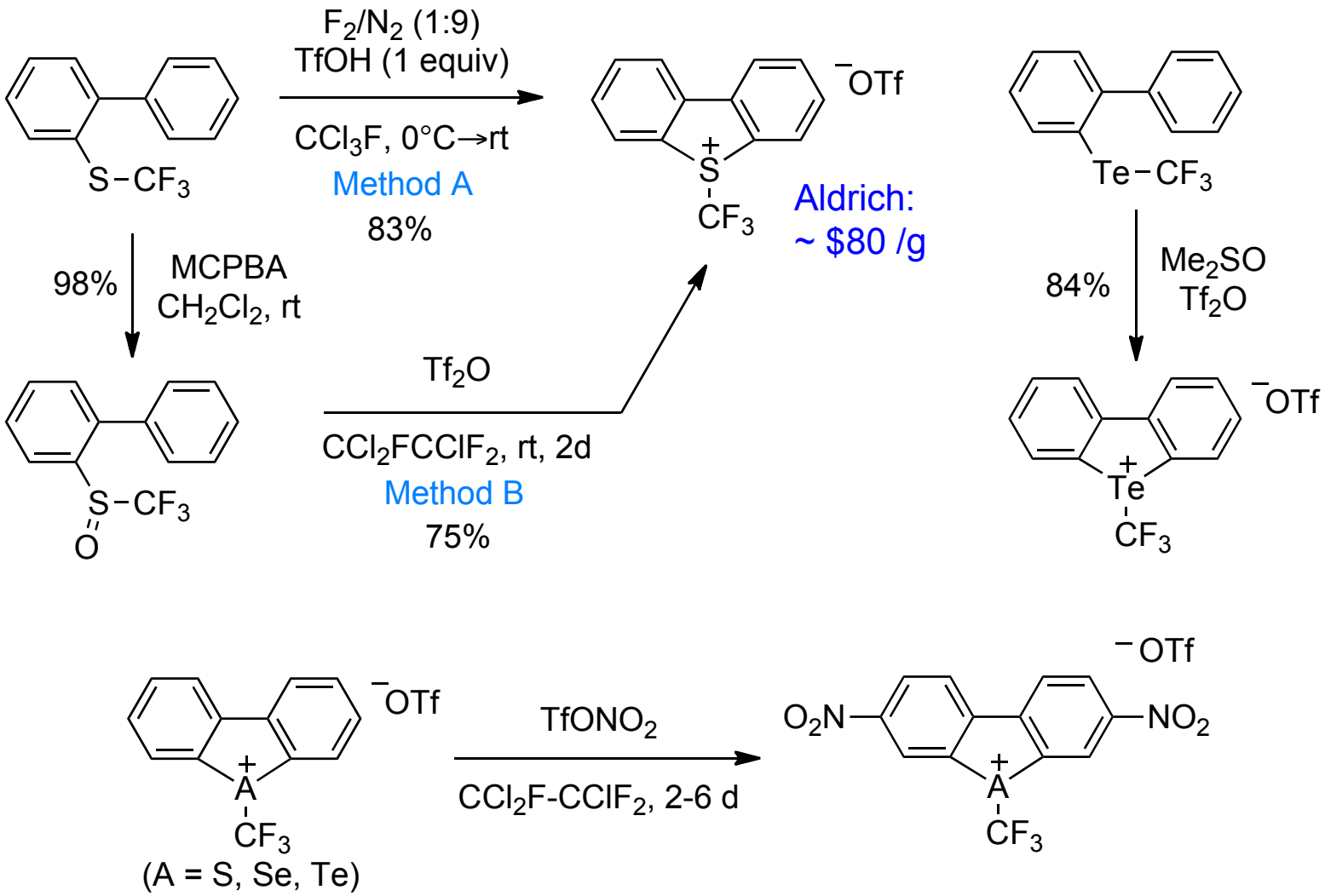


the electron-rich arene diminished
the overall reactivity



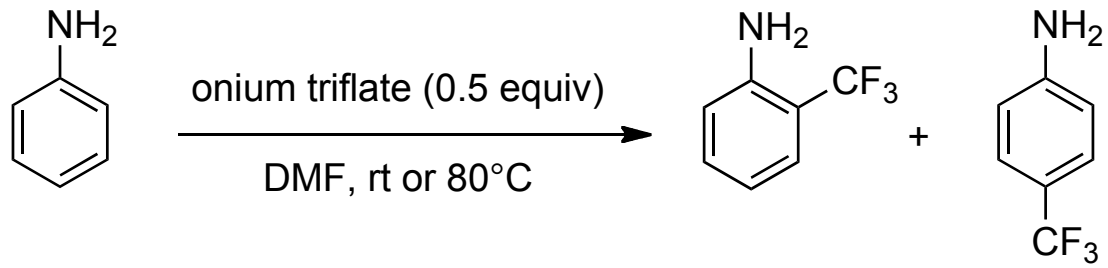
Yagupolskii, L. M. *et. al. J. Org. Chem. USSR.* **1984**, *20*, 103.
Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, 1.

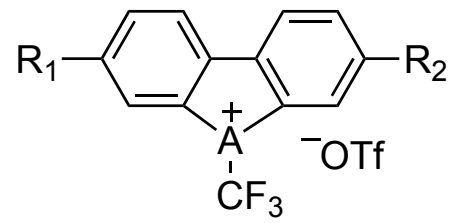
Umemoto's Tunable Sulfonium Salts



Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156.
Umemoto, T.; Ishihara, S. *J. Fluorine Chem.* **1999**, *98*, 75.

Trifluoromethylation Power





(A = S, Se, Te)

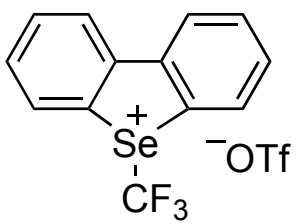
Entry	A	R_1	R_2	T (C°)	time (h)	Yield (%) *o*-CF_3	Yield (%) *p*-CF_3	Remaining "CF_3^+"	^{19}F NMR δ (ppm)
1	S	H	H	rt	0.5	0	0	100	52.6
2	S	H	H	80	1	31	15	27	52.6
3	S	NO_2	H	rt	0.5	18	11	71	50.5
4	S	NO_2	NO_2	rt	0.5	54	20	5	48.4
5	Se	H	H	rt	20	7	4	83	45.6
6	Se	NO_2	NO_2	rt	0.5	39	16	30	41.8
7	Te	H	H	80	28	3	1	71	41.0
8	Te	NO_2	NO_2	rt	20	12	6	82	39.3

Reactivity Order: S > Se > Te

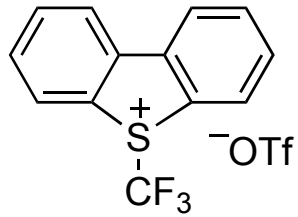
Introduction of NO_2 groups dramatically increase reactivity.

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

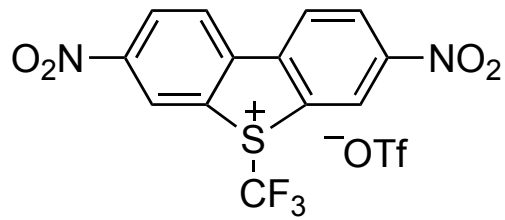
Tune "CF_3^+" to Nucleophile



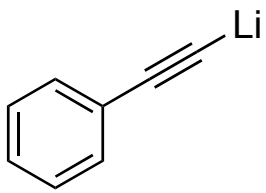
Least Reactive



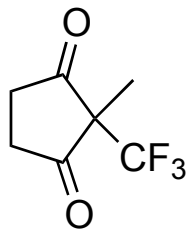
Intermediate



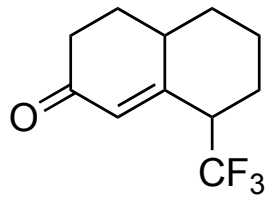
Most Reactive



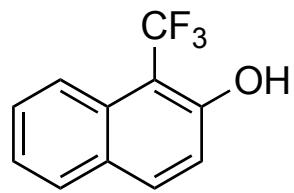
58%



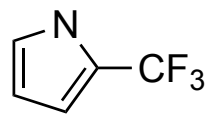
84%



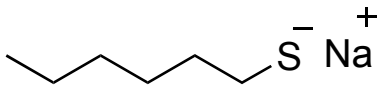
69%



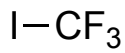
52%



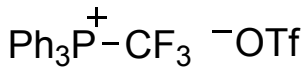
90%



87%



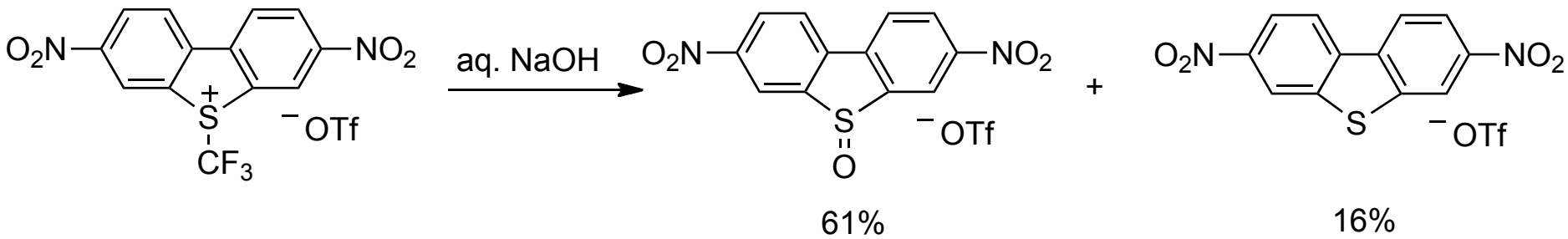
70%



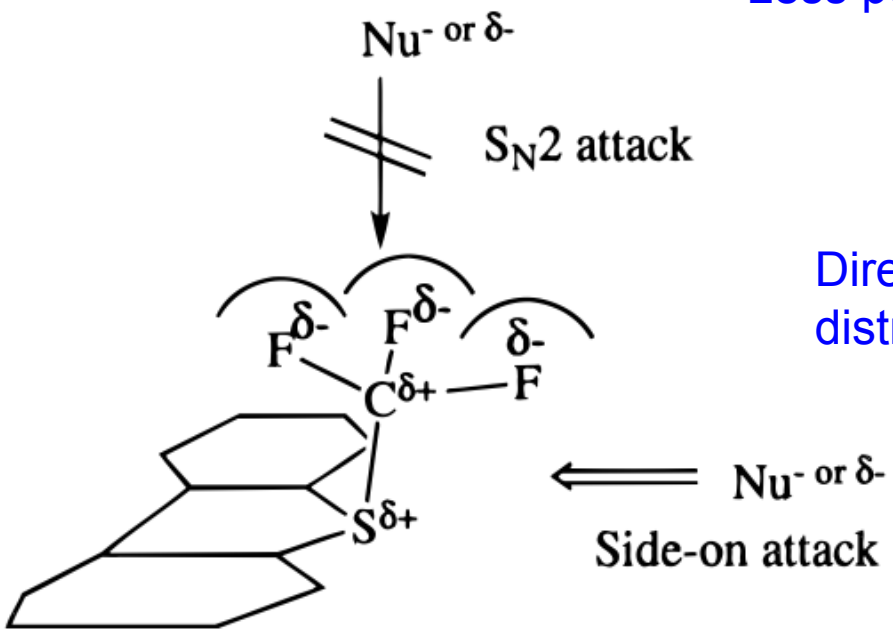
78%

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

Possible Mechanism



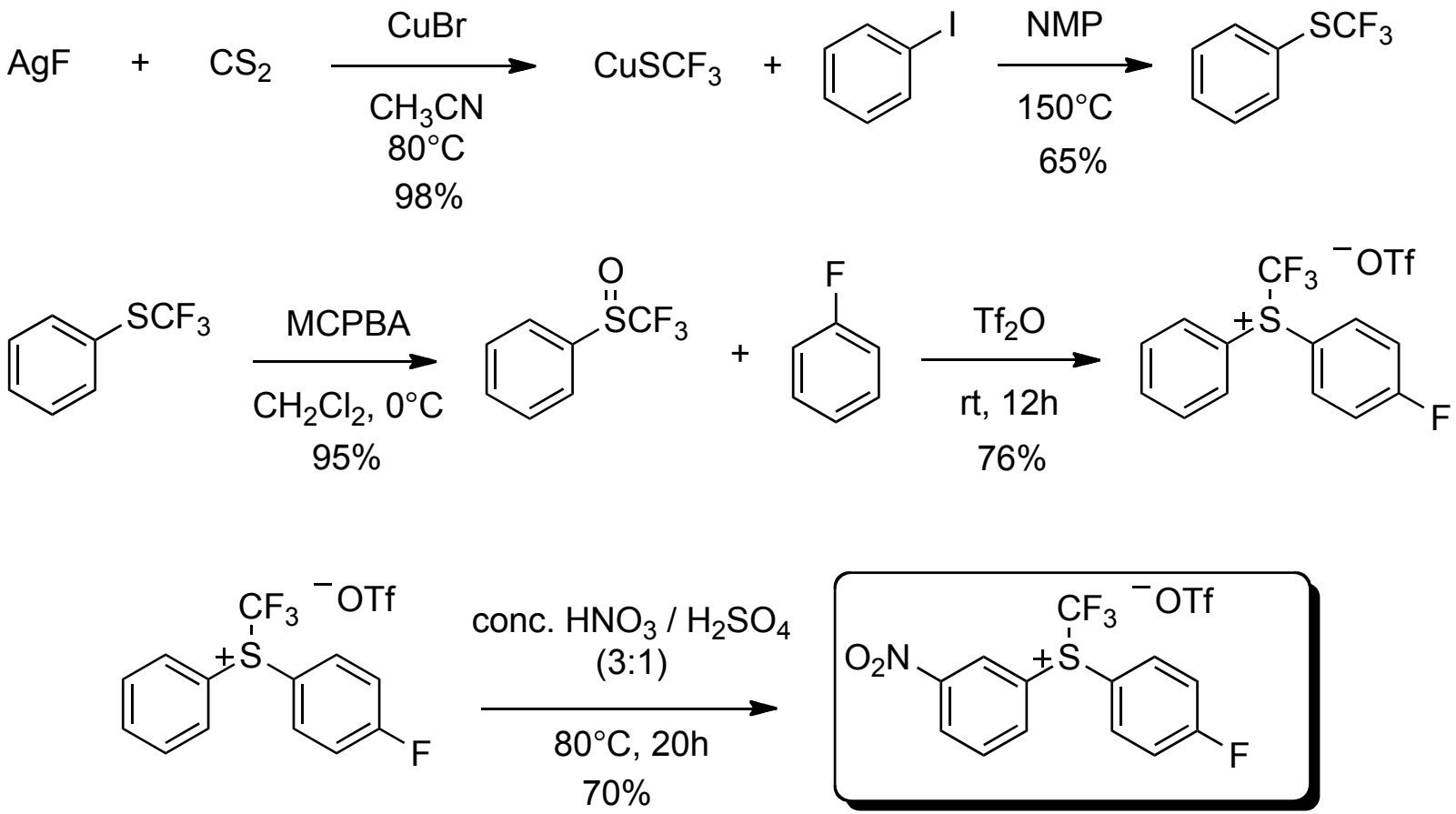
Less powerful reagents only gave *S*-oxide.



Direct S_N2 is unlikely due to the electron distribution between the C-F bonds.

Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156.
Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757.

Shreeve's Sulfonium Reagents

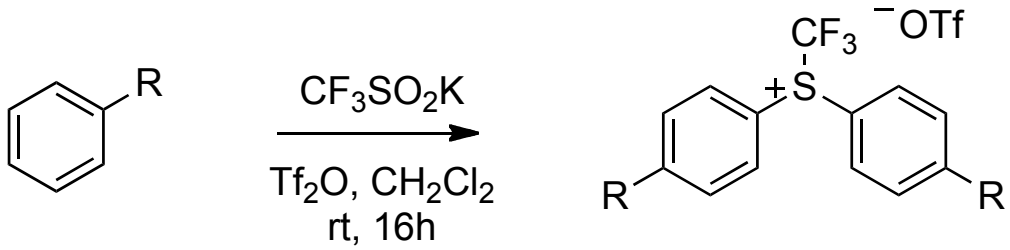


Demonstrated similar scope to Umemoto.

Shreeve, J. M. *et. al. J. Org. Chem.* **1998**, *63*, 2656.

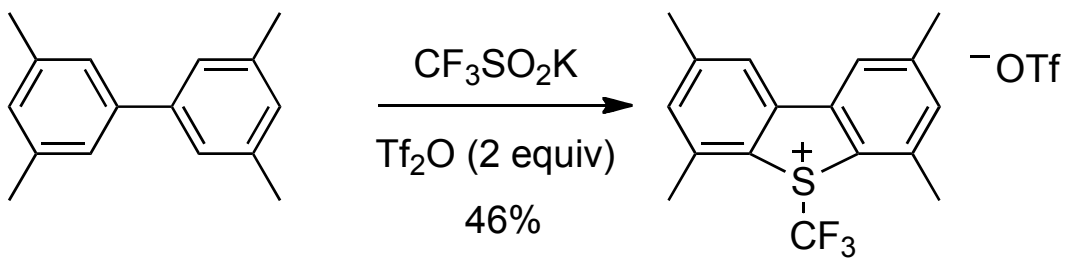
One-Pot Preparations

A practical preparation is needed to avoid starting from CF_3Br (banned) and AgF (expensive).



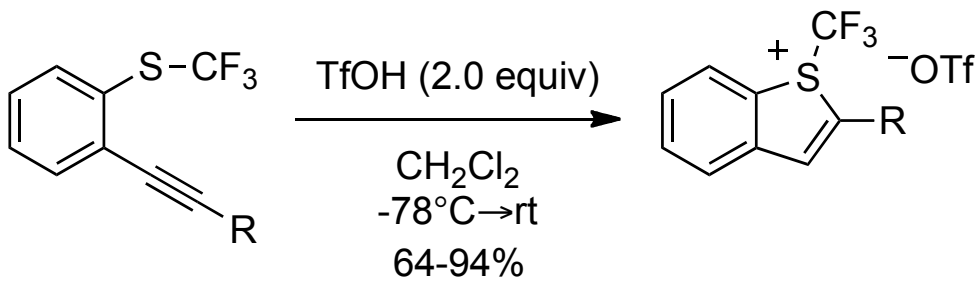
R = H, 60%
R = Cl, 50%
R = F, 46%
R = OCF_3 = 15%

Less applicable to cyclic sulfonium salts like Umemoto's due to inefficient preparation of the corresponding sulfoxide in the *ortho* position.

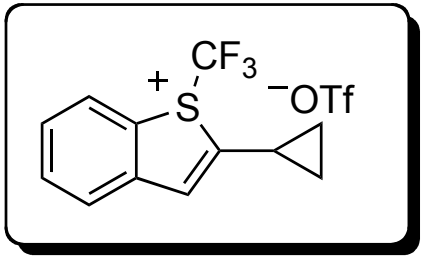


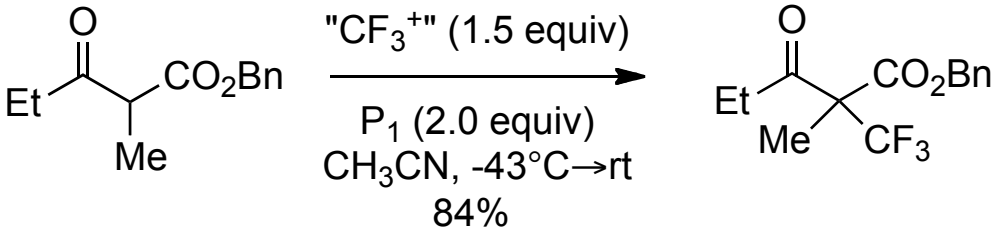
Blazejewski, J. -C. *et. al. Angew. Chem. Int. Ed.* **2006**, *45*, 1279.
Blazejewski, J. -C. *et. al. Eur. J. Org. Chem.* **2009**, 1390.

Extended Yagupolskii-Umemoto-Type Reagents

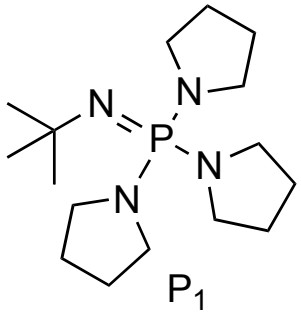


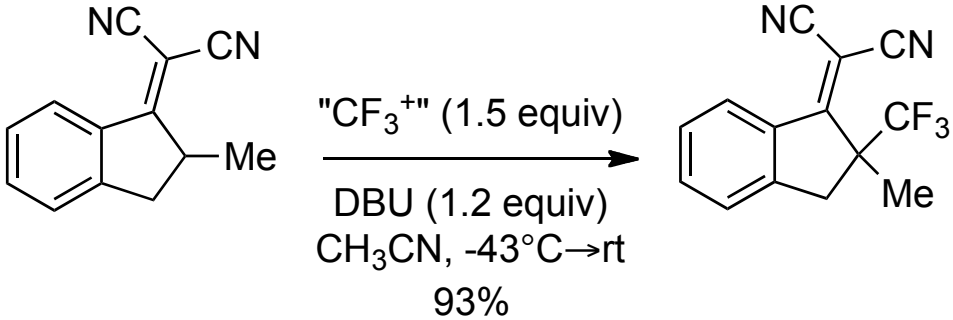
R = Ar, *t*-Bu, *c*-Pr



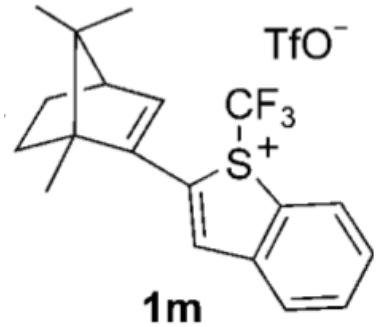


Umemoto's reagent gives 59%





Can we make it chiral?

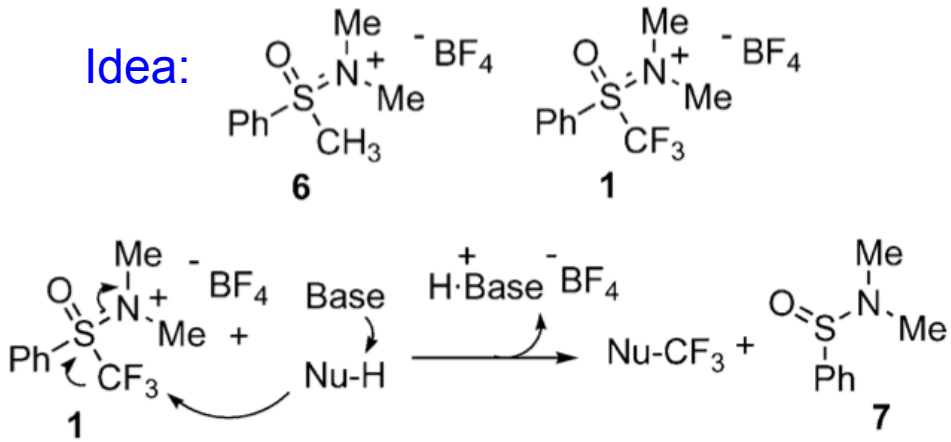


Yes.....but the product is <u>completely racemic.</u>

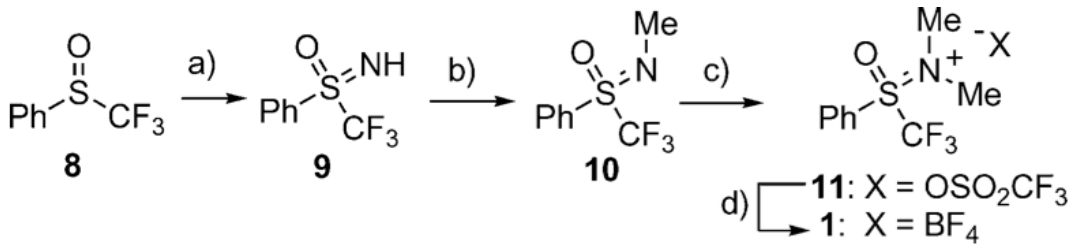
Shibata, N. *et. al. Angew. Chem. Int. Ed.* **2010**, *49*, 572.

Fluorinated Johnson Reagent for Carbon Nucleophiles

Idea:



Synthesis:

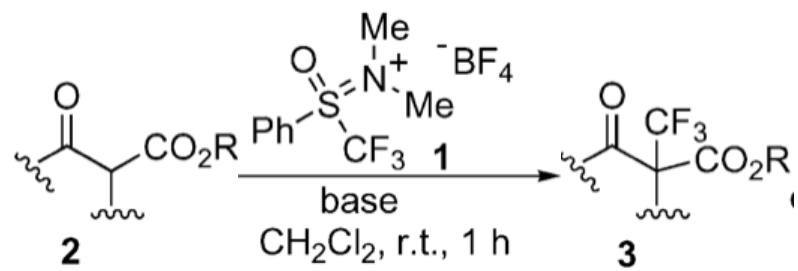


TCI: $~200 /g

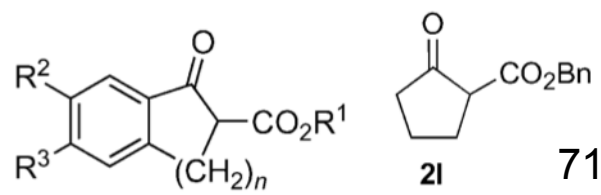
Scheme 3. a) NaN_3, 25% fuming H_2SO_4, 70 °C, 3 h, 81%; b) CH_3I, K_2CO_3, THF, reflux, 7 h, 97%; c) methyl trifluoromethansulfonate, neat, room temp., 6 h, 93%; d) sat. $NaBF_4$ aq., MeOH, room temp., 13 h, 92%.

Use:

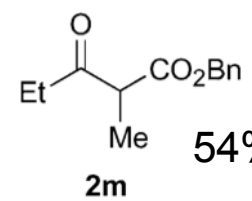
63-92%



Base usually DBU



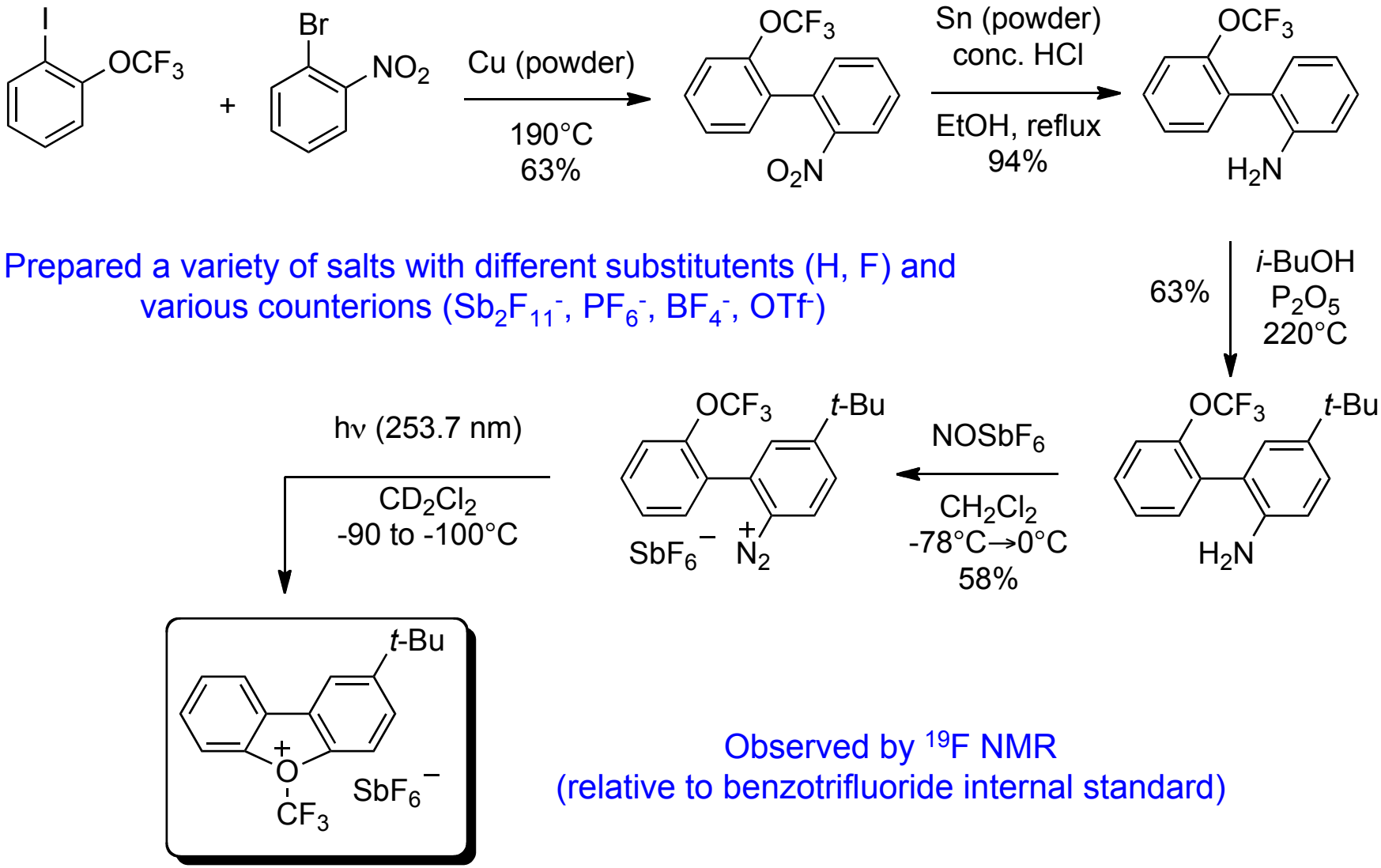
71%



54%

Shibata, N. *et. al. Eur. J. Org. Chem.* **2008**, 3465.

Preparation of Elusive CF_3 Oxonium Salts

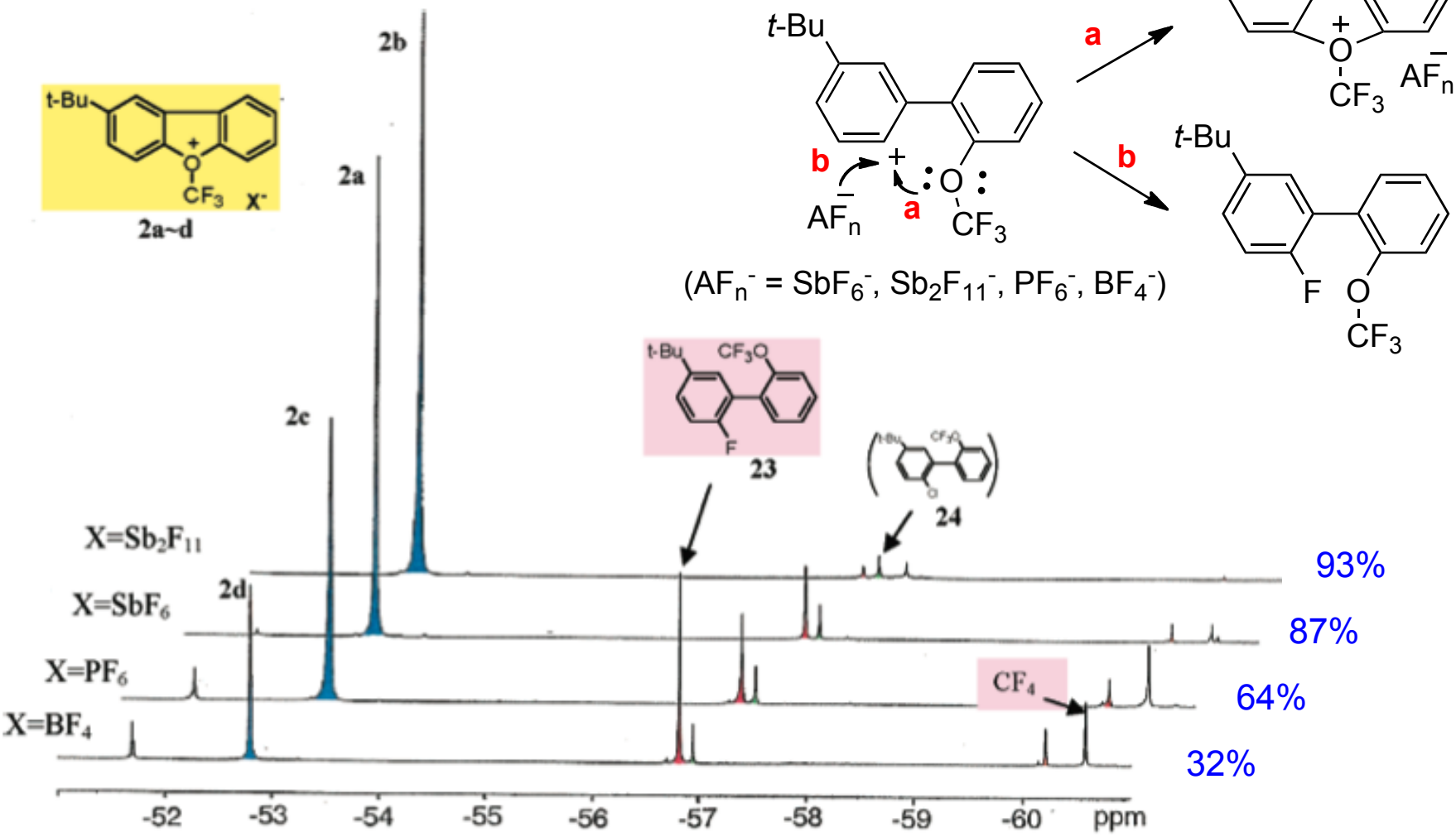


Prepared a variety of salts with different substitutents (H, F) and various counterions ($Sb_2F_{11}^-$, PF_6^-, BF_4^-, OTf^-)

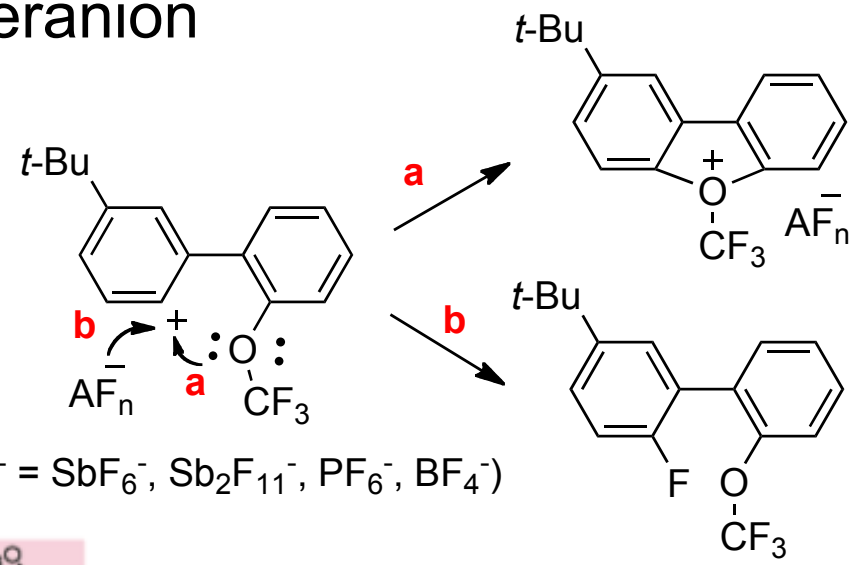
Observed by ^{19}F NMR
(relative to benzotrifluoride internal standard)

Umemoto, T. *et. al. J. Org. Chem.* **2007**, *72*, 6905.

Formation of CF_3 Oxonium Salts Dependent on Counteranion



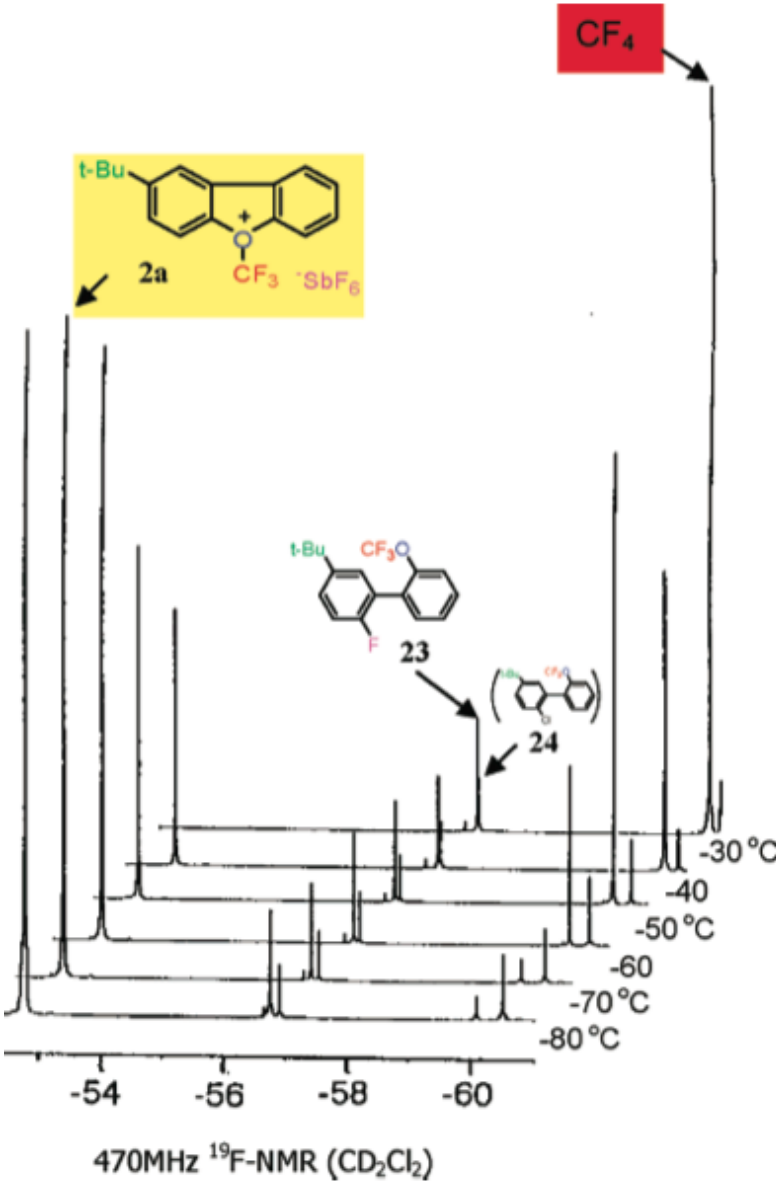
470MHz ^{19}F-NMR(CD_2Cl_2) at –70°C

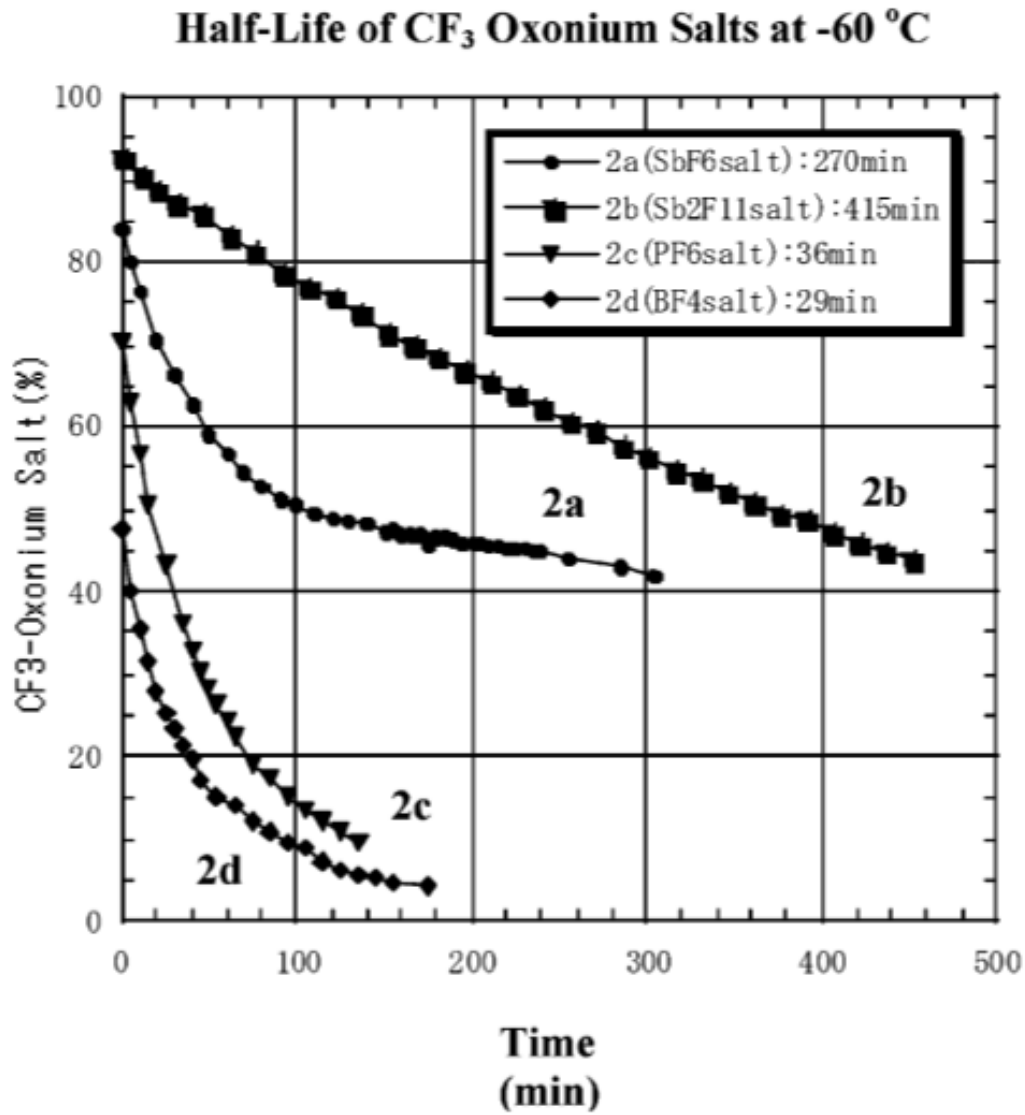


(AF_n^- = SbF_6^-, $Sb_2F_{11}^-$, PF_6^-, BF_4^-)

Umemoto, T. *et. al. J. Org. Chem.* **2007**, *72*, 6905.

Half-Life of CF_3 Oxonium Salts



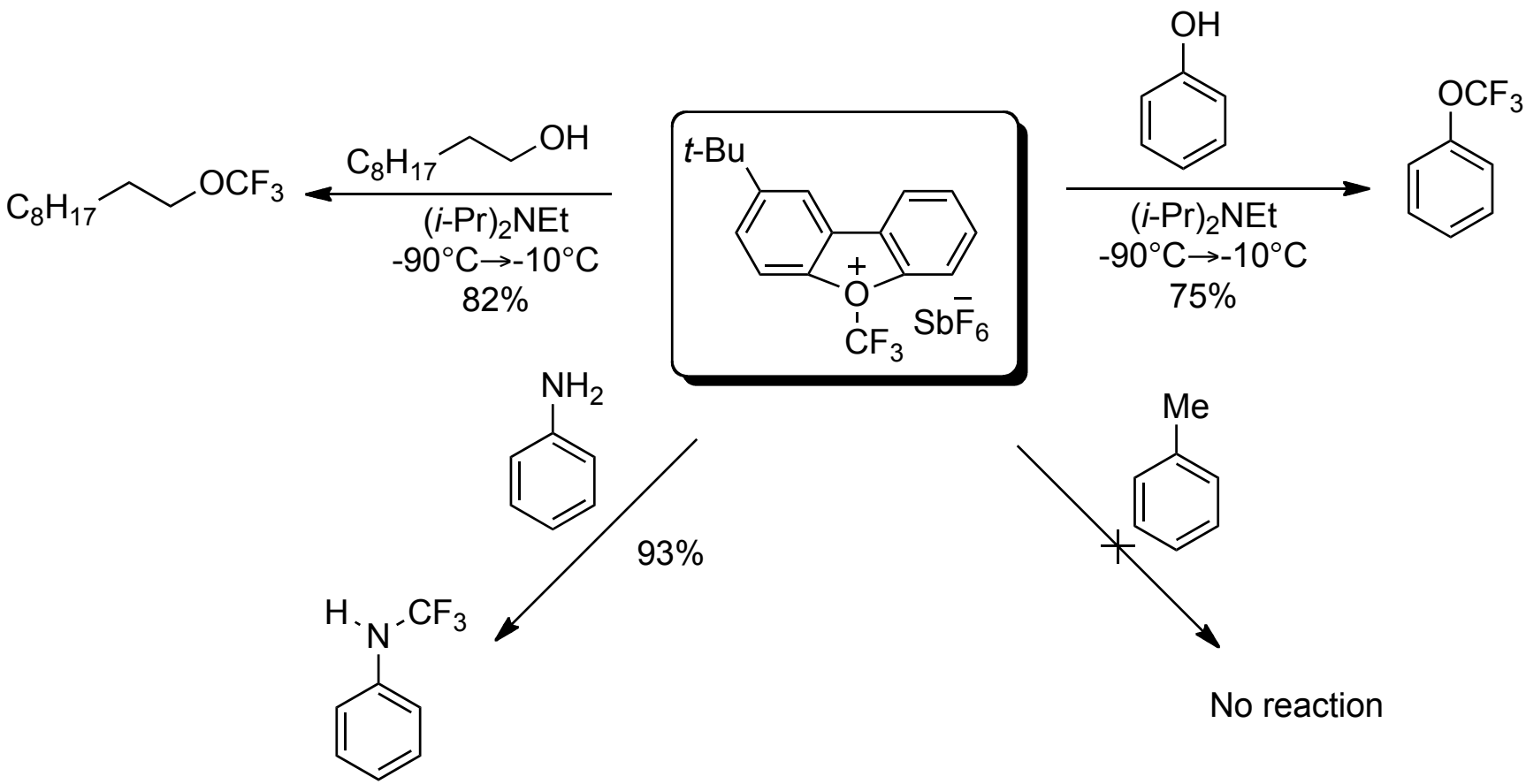


2d BF_4^- = 29 min **2a** SbF_6^- = 270 min
2c PF_6^- = 36 min **2b** $Sb_2F_{11}^-$ = 415 min

Umemoto, T. *et. al. J. Org. Chem.* **2007**, *72*, 6905.

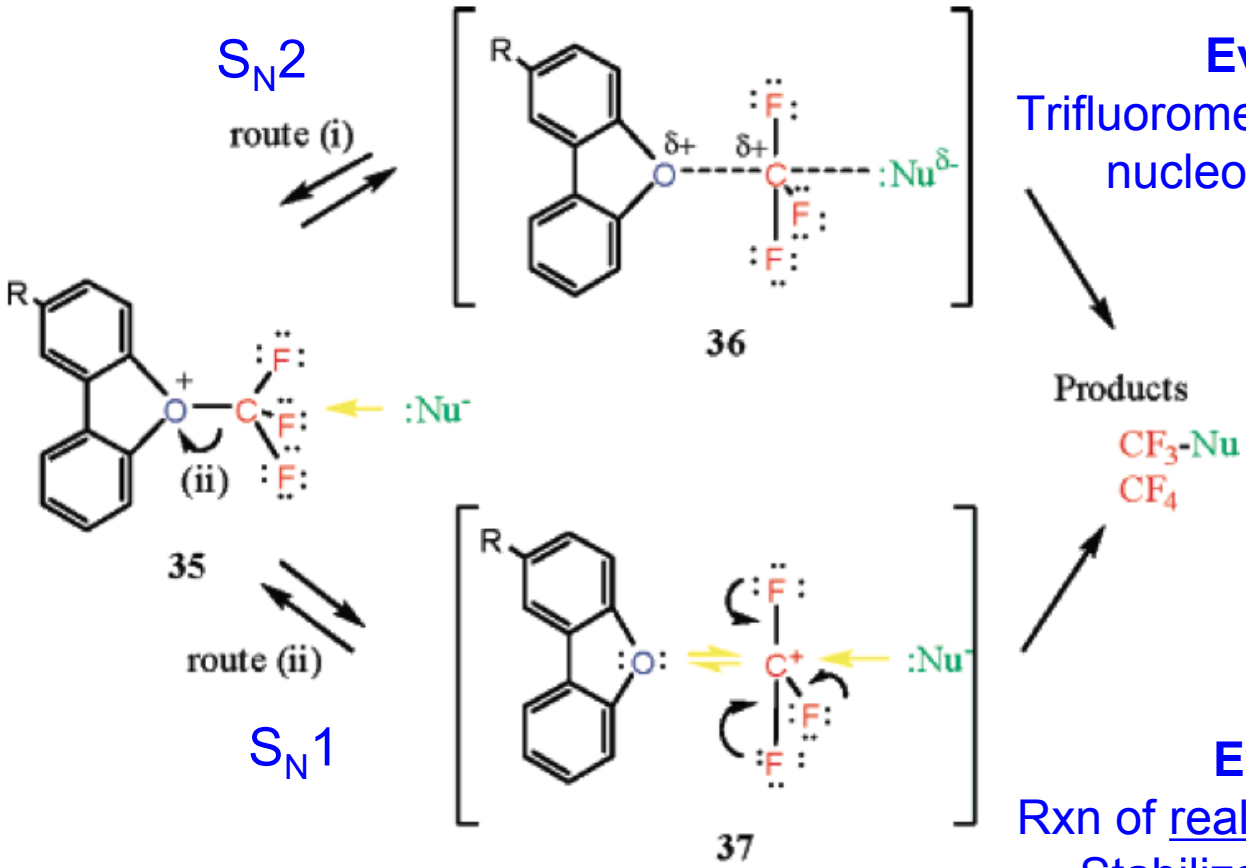
Oxonium Salts for Hard Nucleophiles

Prepare oxonium salt *in situ* from diazonium:



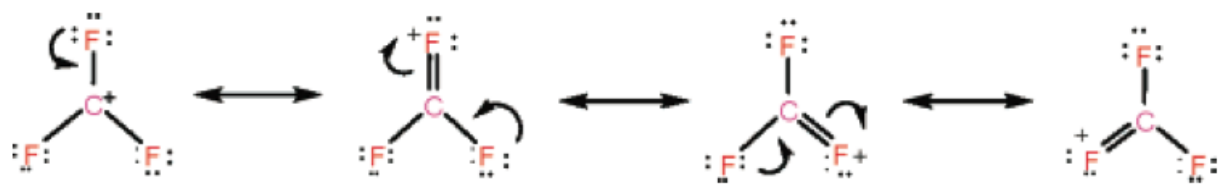
Umemoto, T. *et. al. J. Org. Chem.* **2007**, *72*, 6905.

So What's the Mechanism?



Evidence for S_N2:
Trifluoromethylation is dependent on nucleophilicty of nucleophile

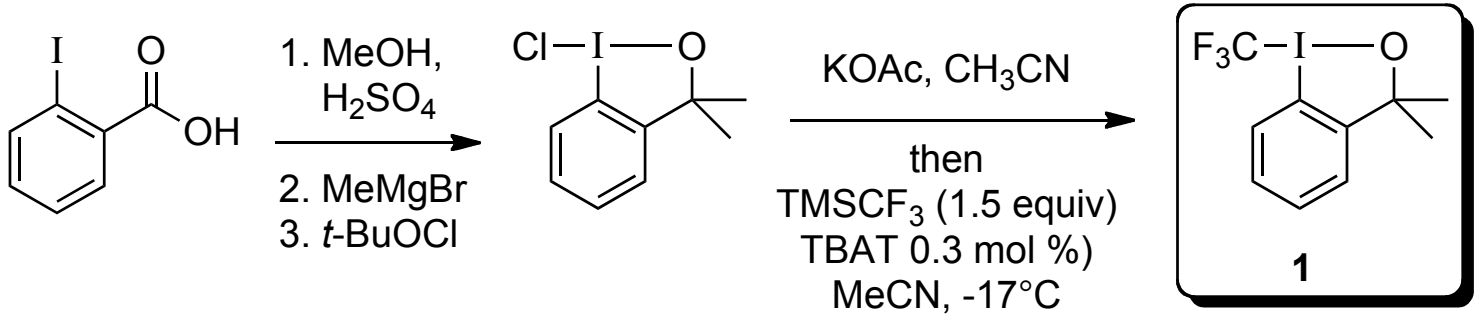
Evidence for S_N1:
Rxn of <u>really</u> non-nucleophilic $Sb_2F_{11}^-$
Stabilization by long pairs of F?



Umemoto, T. *et. al. J. Org. Chem.* **2007**, *72*, 6905.

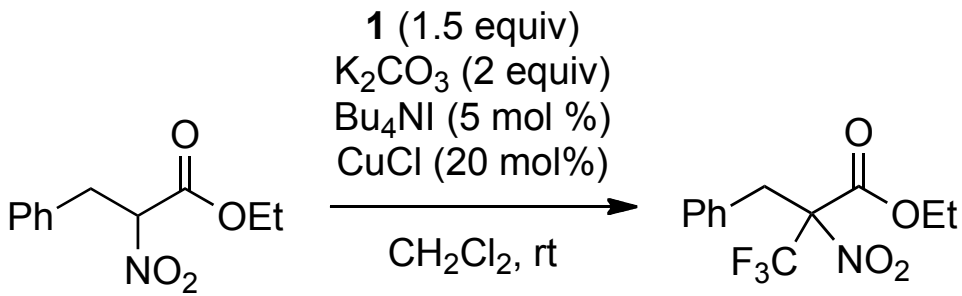
Hypervalent Iodine(III)-CF_3 Reagents

Readily prepared in 3 steps from 2-iodobenzoic acid with anionic ligand exchange

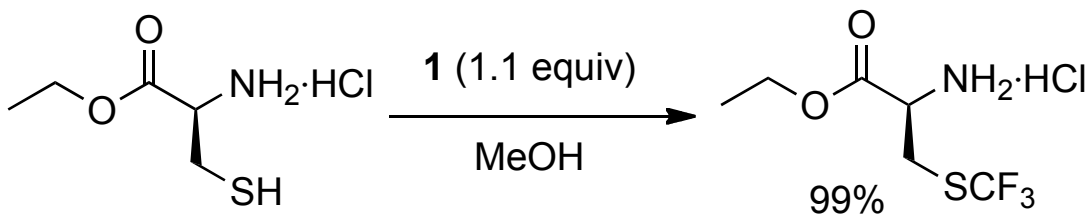


TCI: $~230 /g

Electrophilic trifluoromethylation of carbon and sulfur nucleophiles:



59%

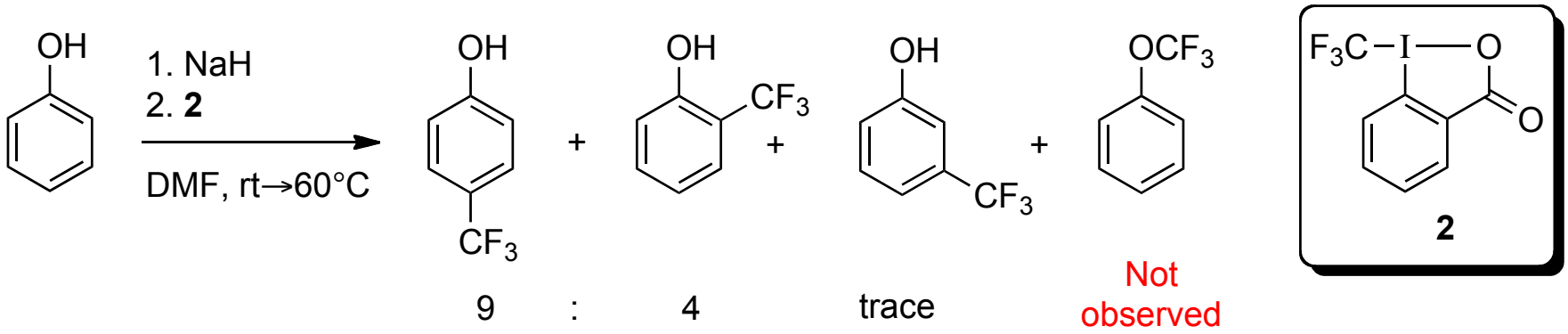


99%

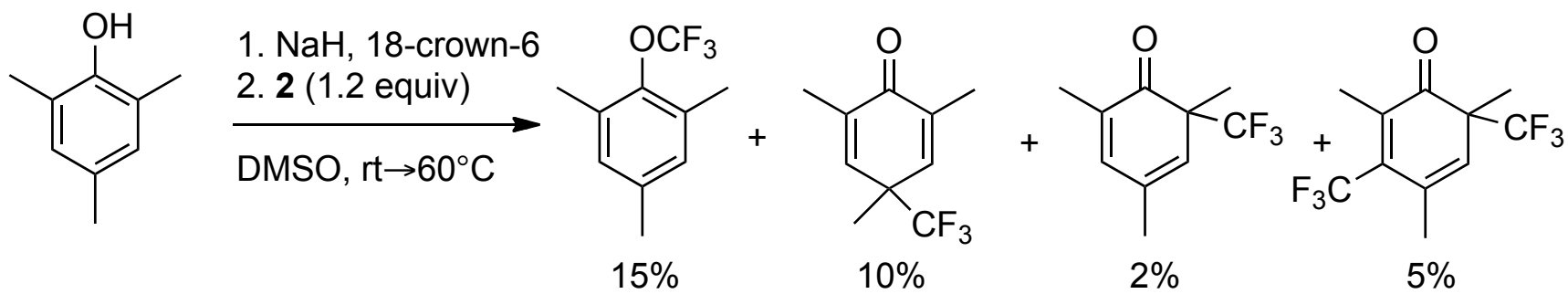
Togni, A. *et. al. J. Org. Chem.* **2008**, *73*, 7678.
Togni, A. *et. al. Angew. Chem. Int. Ed.* **2007**, *46*, 754.

Unsolved Problem: Trifluoromethylation of Phenol

Readily prepared in 3 steps from 2-iodobenzoic acid with anionic ligand exchange



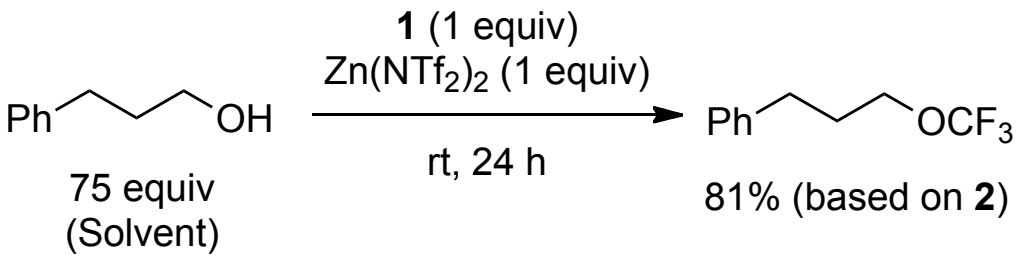
Best result:

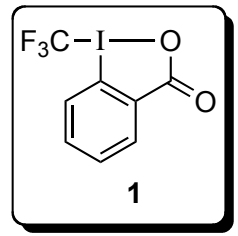


Togni, A. *et. al. J. Org. Chem.* **2008**, *73*, 7678.

Zn Aids in Trifluoromethylation of Aliphatic Alcohols

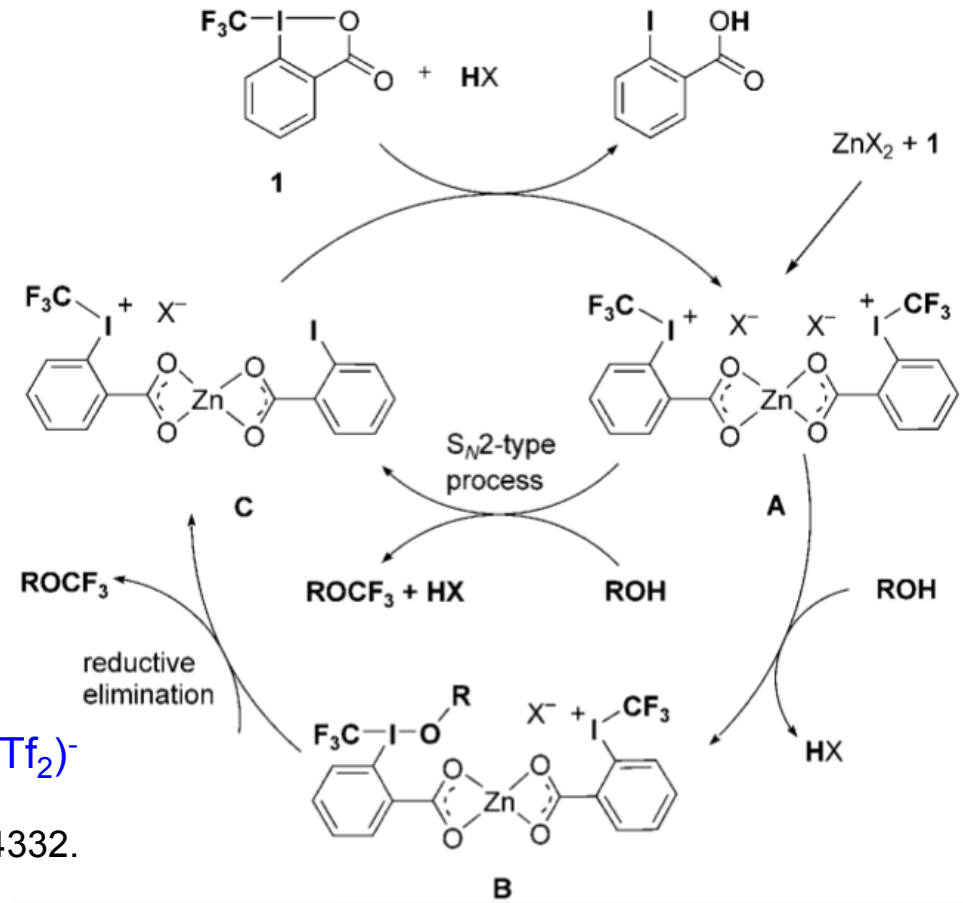
Readily prepared in 3 steps from 2-iodobenzoic acid with anionic ligand exchange





Yields highly variable: 12-90%
Using less alcohol (5 equiv) gives much lower yields.

Does not work for phenol ot *t*-BuOH



Evidence:

- Observed 1:2 adduct bt $Zn(NTf_2)_2$ and **1** by ESI-MS (A?)
- Crystallization of Zn complex: $[Zn(\mathbf{1})_2(4\text{-}NO_2C_6H_4CH_2OH)_2(H_2O)_2]^{2+}\ 2(NTf_2)^-$

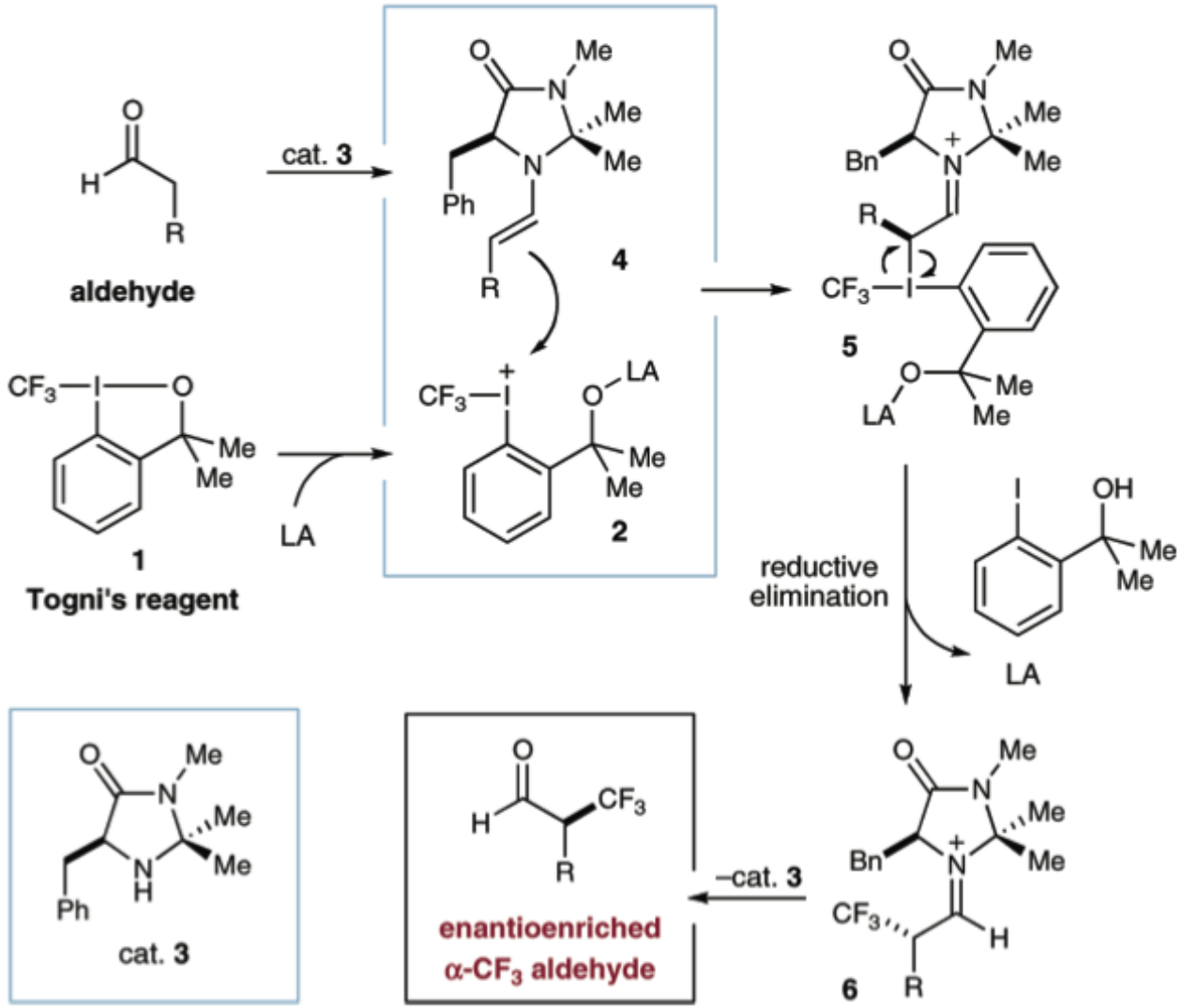
Togni, A. *et. al. Angew. Chem. Int. Ed.* **2009**, *48*, 4332.

Combining Iodonium Salt with Organocatalysis

Idea: Using a Lewis acid activator for reaction with chiral enamines:

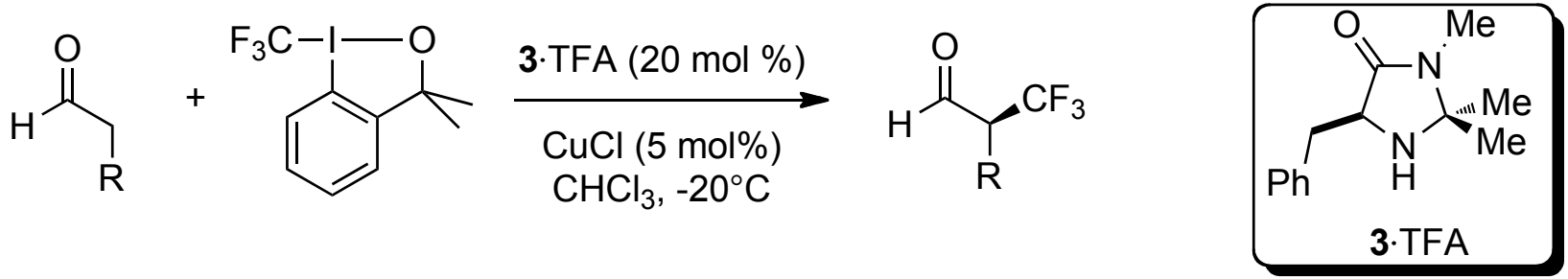
LA aids in bond cleavage to form more electrophilic iodonium salt

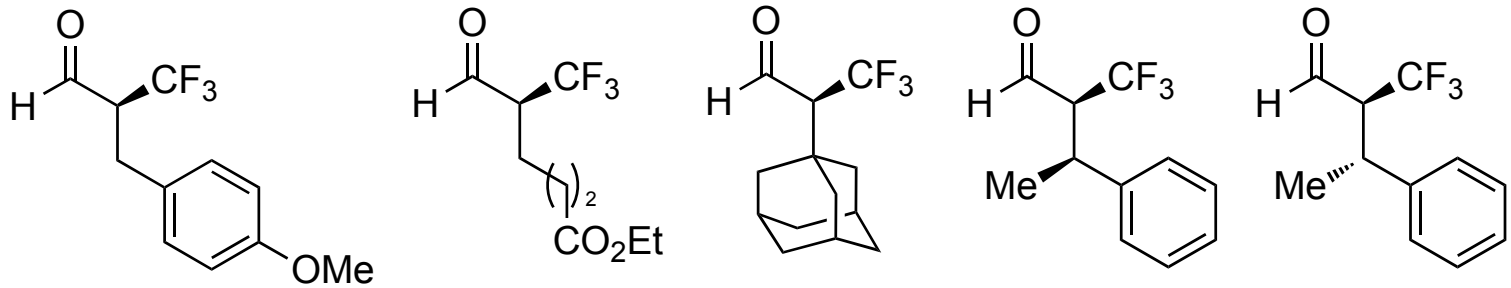
Amine cat. **3** control facial attack by enamine



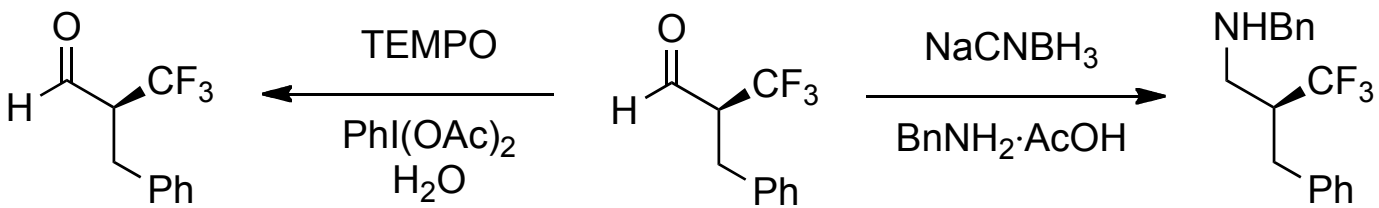
MacMillan, D. W. C.; Allen, A. E. *J. Am. Chem. Soc.* **2010**, *132*, 4986.

Enantioselective α-Trifluoromethylation of Aldehydes





87%, 96% ee | 79%, 93% ee | 70%, 97% ee | 76%, >20:1 dr | 74%, 19:1 dr



93%
94% ee

94% ee

90%
86% ee

MacMillan, D. W. C.; Allen, A. E. *J. Am. Chem. Soc.* **2010**, *132*, 4986.

Conclusions

- Introducing a trifluoromethyl group is NOT like adding a methyl group!

- The Ruppert-Prakash reagent ($TMSCF_3$) revolutionized direct trifluoromethylation, allowing reaction with a variety of carbonyl electrophiles.

- Nucleophilic trifluoromethylation of imines is much improved by activiation in acidic conditions.

- Enantioselective nucleophilic trifluoromethylation has only been realized using chiral quaternary ammonium salts.

  - Future directions: Application to other electrophiles? 1,4-addition?

- The major limitation to electrophilic trifluoromethylation has been the efficient synthesis of reagents

  - Ineffective in reactions with hard nucleophiles (phenol?)

  - Further work necessary to achieve desired reactivity

Cahard, D.; Ma, J. -A. *J. Fluorine. Chem.* **2007**, *128*, 975.

Cahard, D.; Ma, J. -A. *Chem. Rev.* **2004**, *104*, 6119.