Novel Building Blocks in Organofluorine Chemistry

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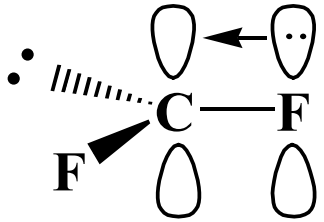
NSF
Air Products, Inc.

- **Difluorocarbene chemistry**
  - ➢ **TFDA – a potent CF_2: reagent**
- **SF_5 Chemistry**
  - ➢ **convenient use of SF_5Cl**
- **TDAE – based chemistry**
  - ➢ **Bromodifluoromethyl heterocycles**
  - ➢ **Trifluoromethylation/perfluoralkylation**

Difluorocarbene Chemistry

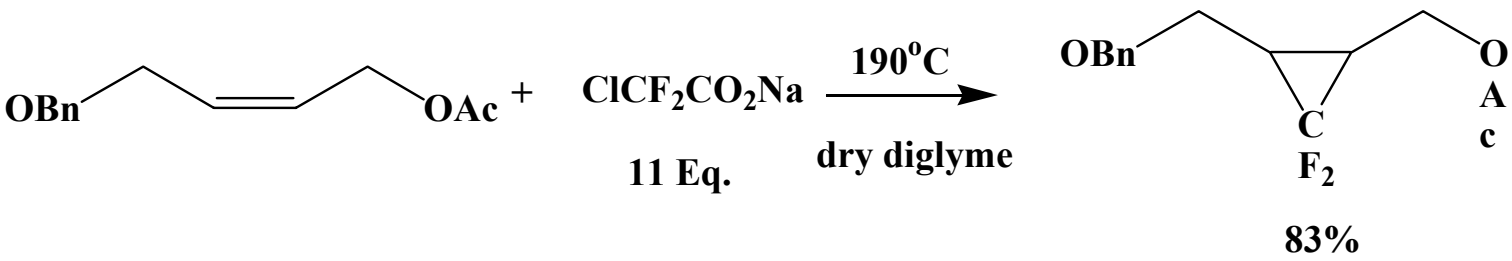
- **:CF_2 more highly stabilized and less reactive than other halocarbenes**



- **Under mild conditions, :CF_2 reacts easily with electron-rich alkenes and not with less nucleophilic substrates**

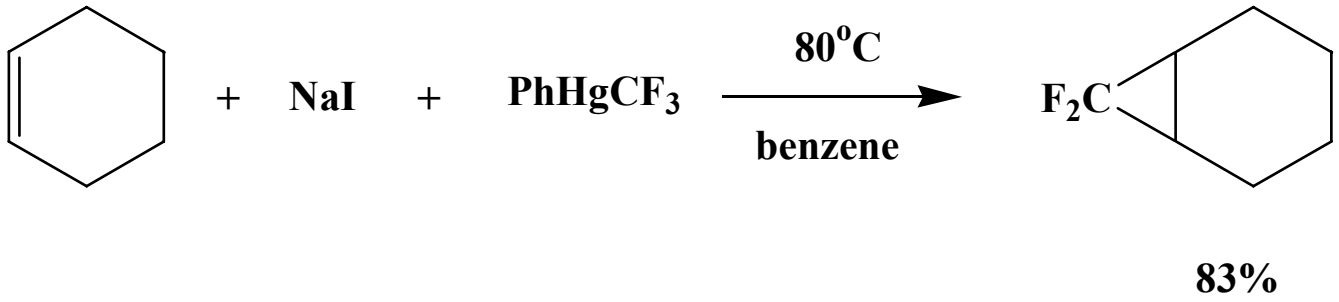
Commonly used difluorocarbene reagents

- **Sodium chlorodifluoroacetate**



Csuk, R.; Eversmann, L. *Tetrahedron* 1998, 54, 6445.

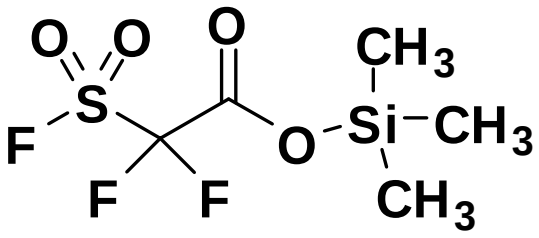
- **Seyferth's reagent**



Seyferth, D.; Hopper, S.P. *J. Organomet. Chem.* 1971, 26, C62-4.

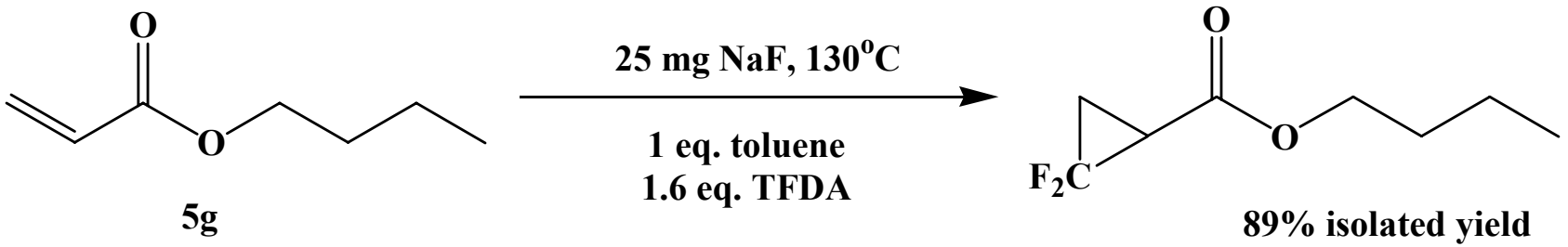
Trimethylsilyl Fluorosulfonyl-DifluoroAcetate

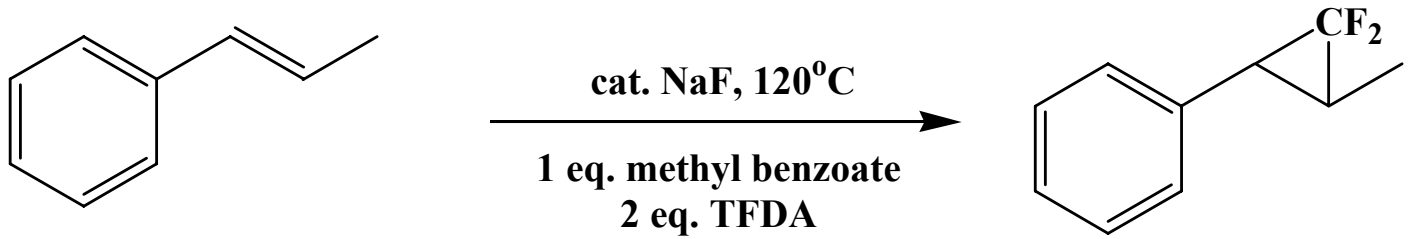
TFDA

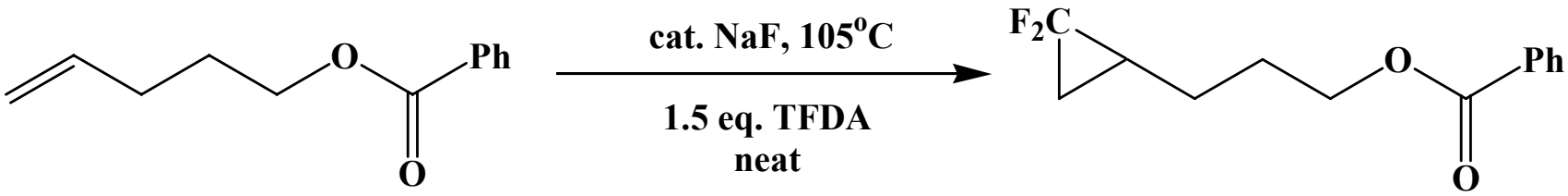


- **A new and highly effective difluorocarbene precursor**
- **Reacts with both electron rich and deficient alkenes at temperatures from 80°C to 140°C**
- **TFDA is stable at room temperature**
- **All by-products are gases**

Typical examples of the use of TFDA as a source of CF_2: carbene







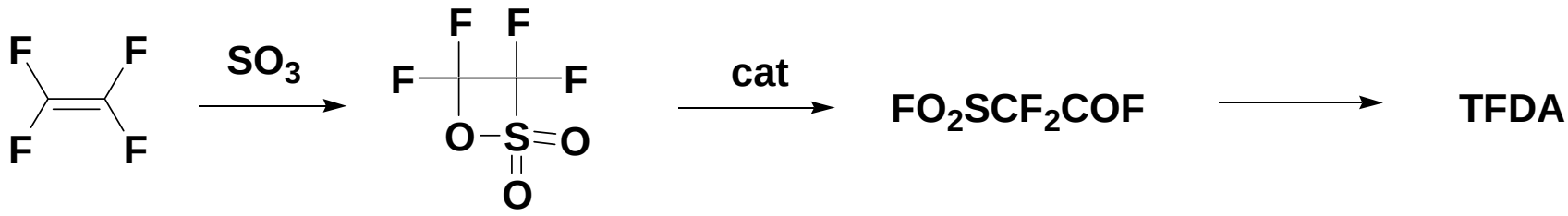
Feng Tian & Jian-Xin Duan, et al, *Org. Syn*. 2003, *80*, 172
J. Fluorine Chem. 2004, *125*, 459

Mechanism for difluorocarbene generation

$$FSO_2CF_2CO_2TMS + F^-(cat) \longrightarrow FSO_2CF_2CO_2^- + TMSF$$

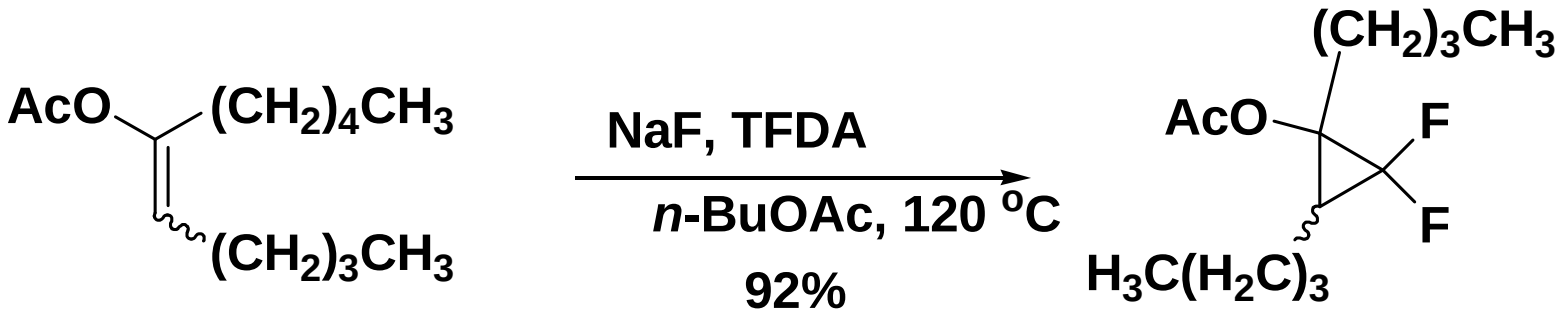
$$FSO_2CF_2CO_2^- \longrightarrow :CF_2 + CO_2 + SO_2 + F^-$$

TFDA is ultimately derived from TFE via the sultone

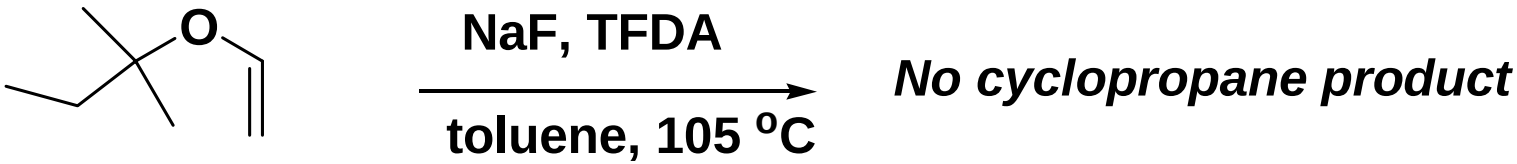


There can be a problem with TFDA when dealing with "acid-sensitive" substrates

Enol acetates are fine:

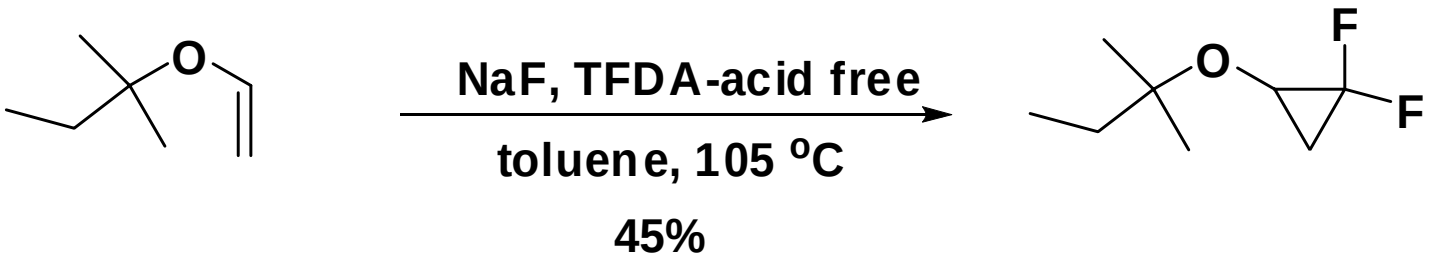


But some enol ethers can be a problem:



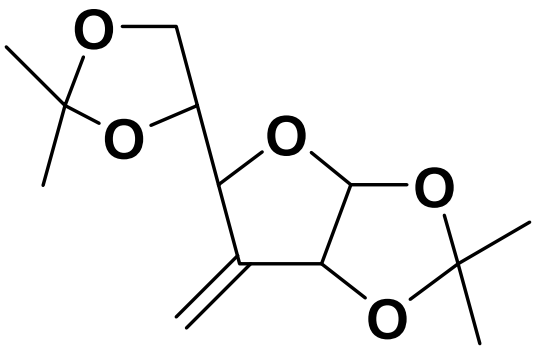
$FSO_2CF_2CO_2TMS$ + $FSO_2CF_2CO_2H$ (2 - 3 % impurity)

Using acid-free TFDA:



Xiaohong Cai

Applying acid-free TFDA to highly acid-sensitive compounds

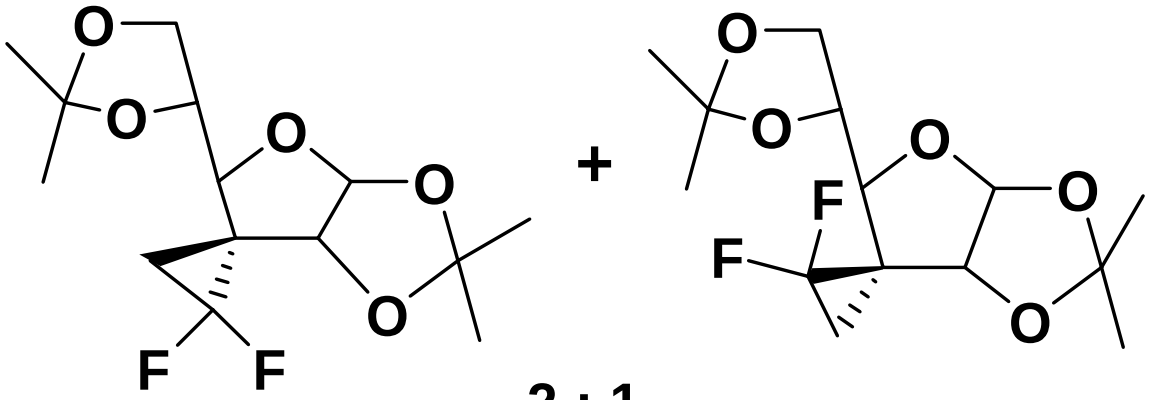


deoxyglucofuranose derivative

NaF, TFDA (acid-free)

benzene, 80 °C, 3h

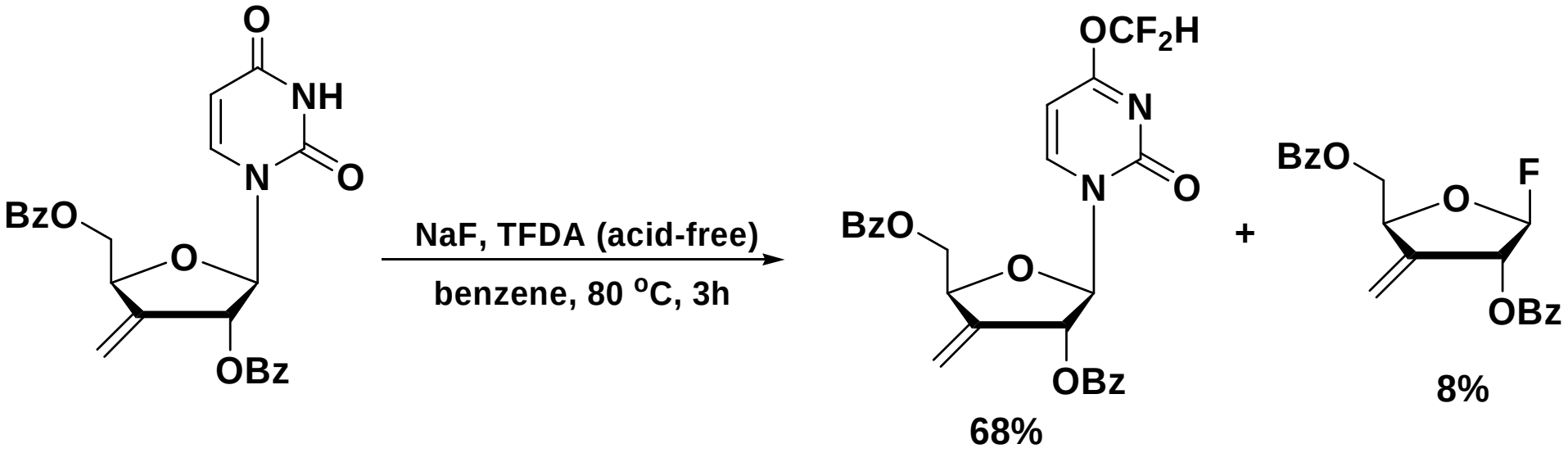
20%



2 : 1

Prof. Stan Wnuk (FIU), Rapp, Cai

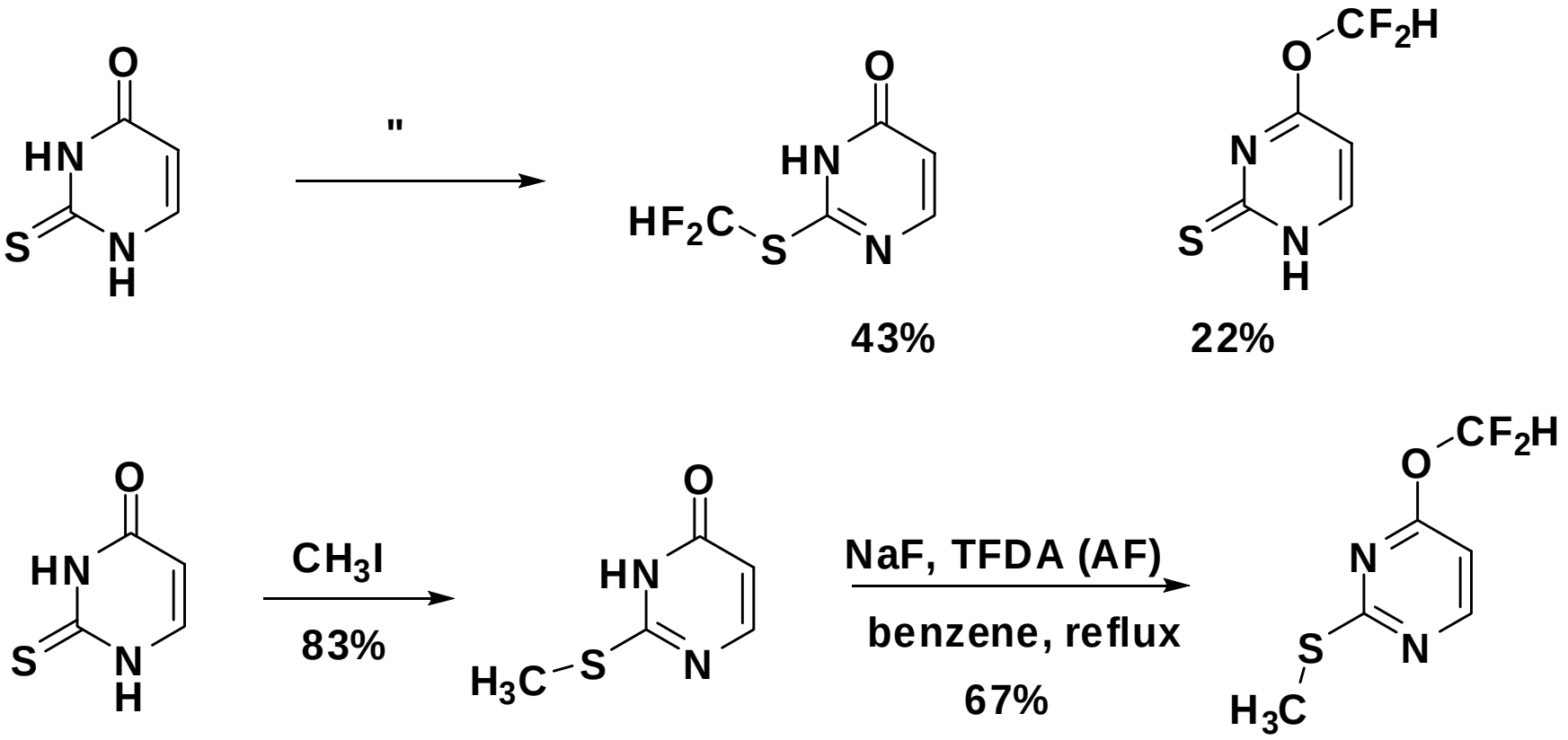
A common alternative fate for the CF_2:



Nucleoside analogue

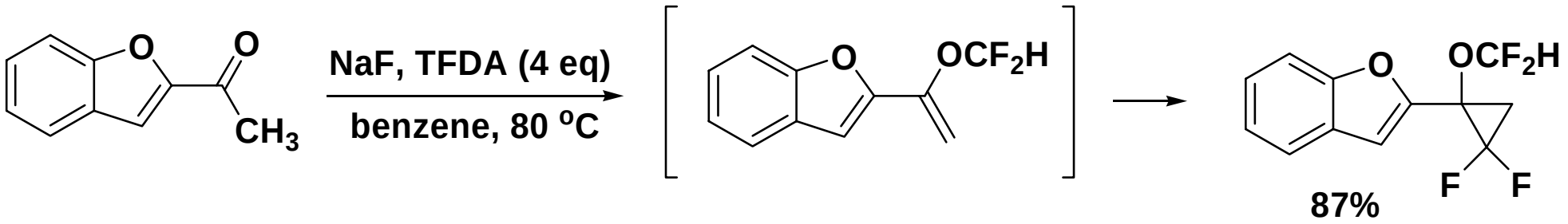
Rapp, Cai, Wnuk

Simpler examples of this chemistry

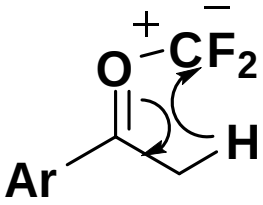


Cai & Xu

Reactions of TFDA with ketones



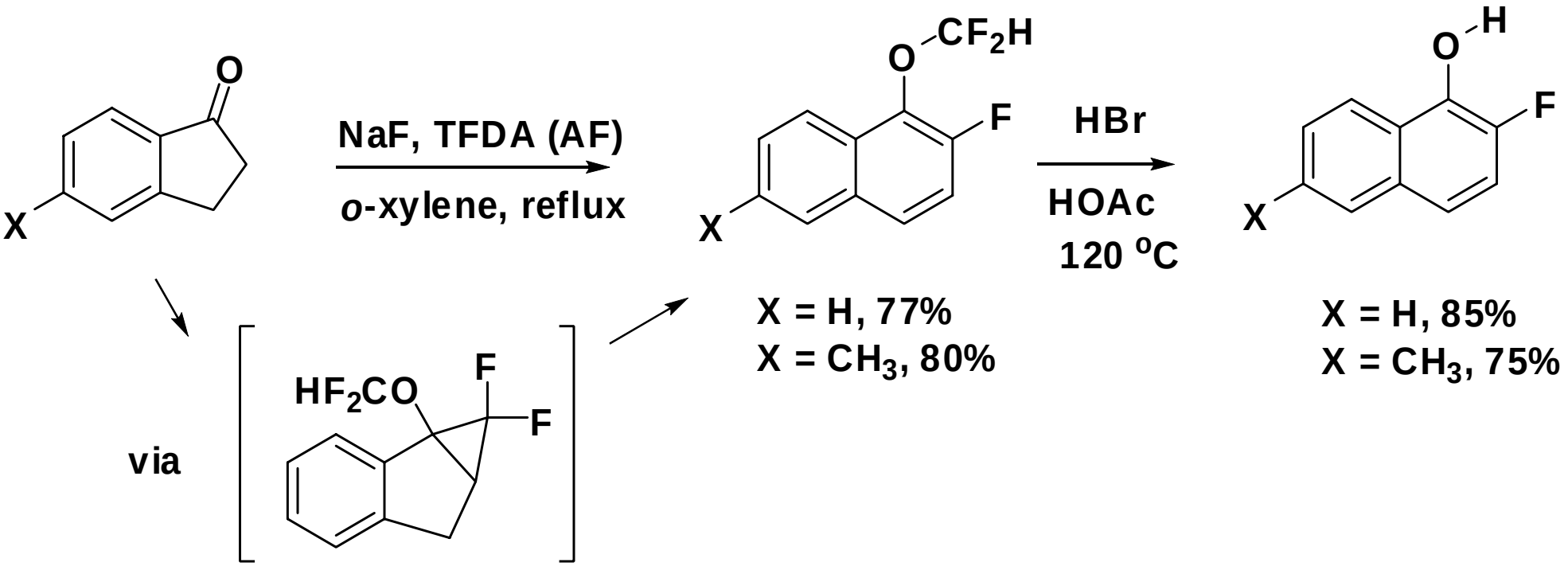
via



Many examples

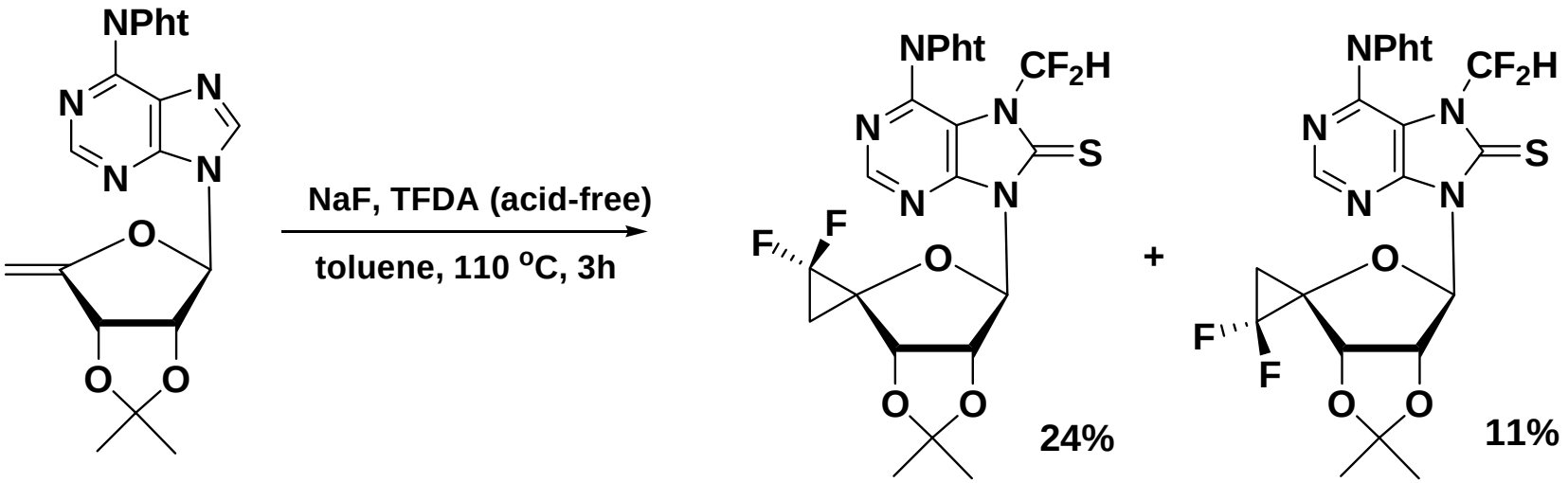
Cai, Zhai, Ghiviriga, Abboud & Dolbier, *JOC,* 2004, *69*, 4210

Can be used for a fluoronaphthalene synthesis



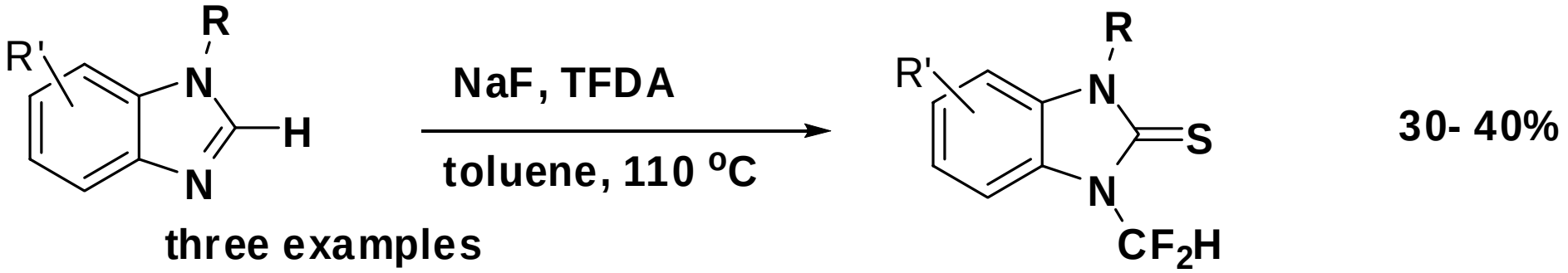
Wu, Cai & Dolbier, *J. Fluorine Chem.* 2005, *126*, 479

An unexpected result

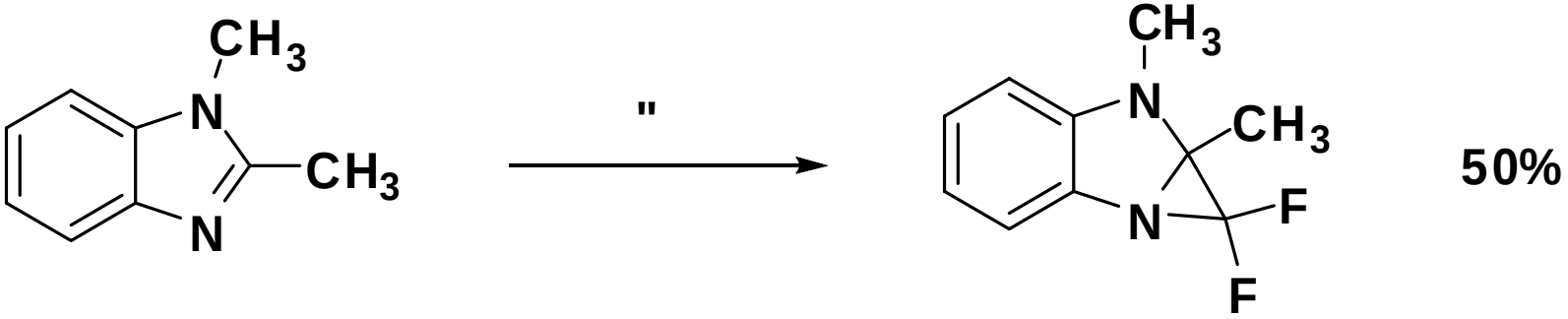


Rapp, Wnuk, & Xu

This seems to be a general reaction, which should have broad application in heterocyclic systems

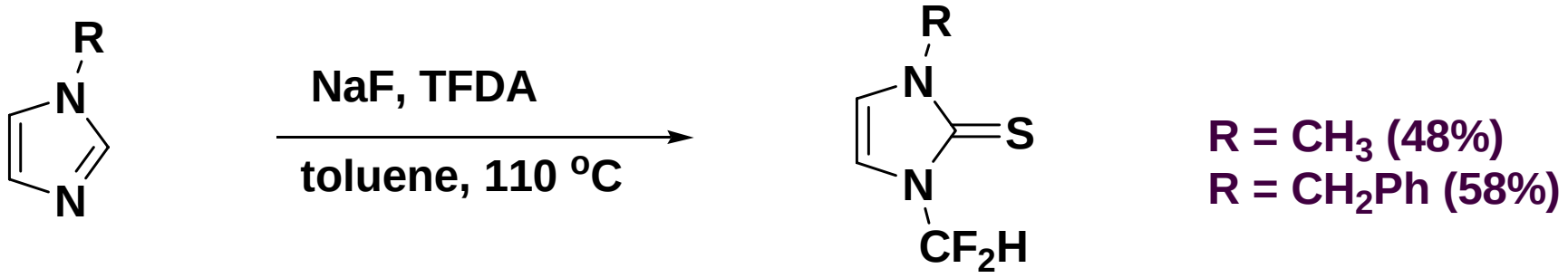


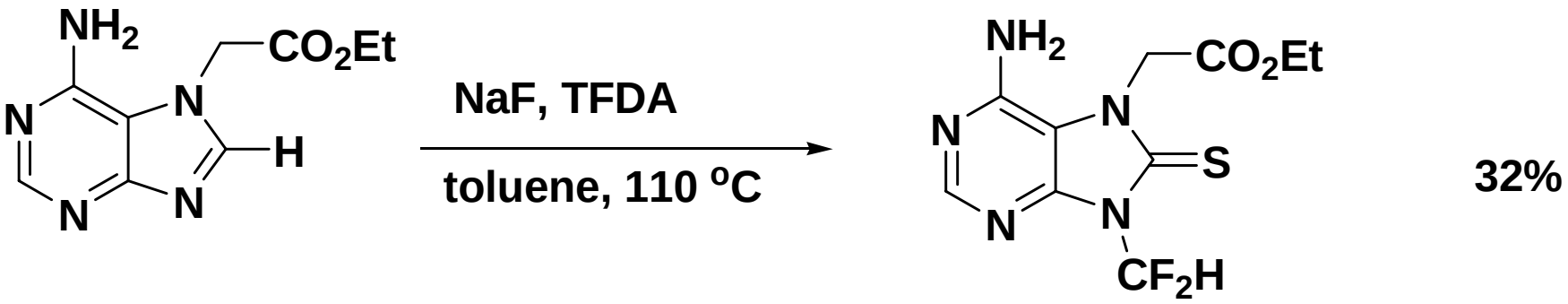
three examples

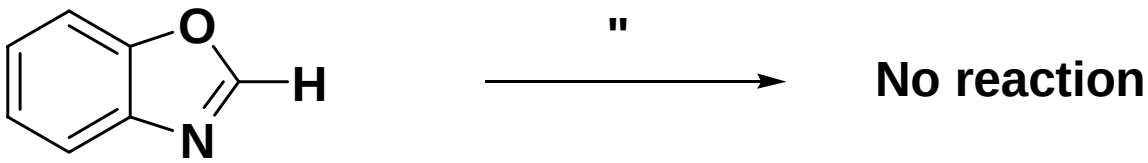


Xu

Most recent results:

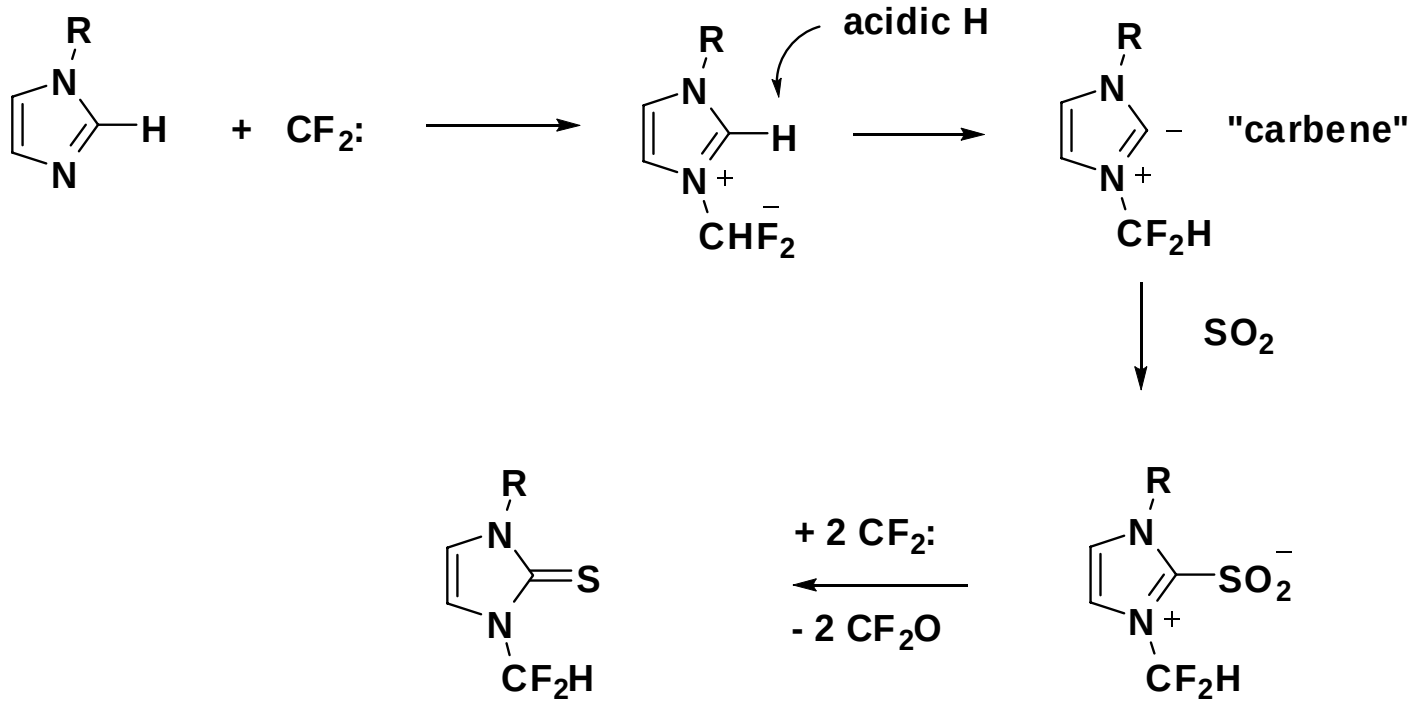






Xu

Possible mechanism:



The Pentafluorosulfanyl substituent

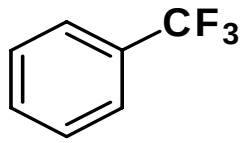
SF_5 versus CF_3

Electronegativity

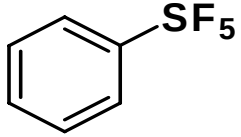
Hammett Sigma Constants

	σ_m	σ_p
SF_5	0.61	0.68
CF_3	0.41	0.53

Dipole moments, μ

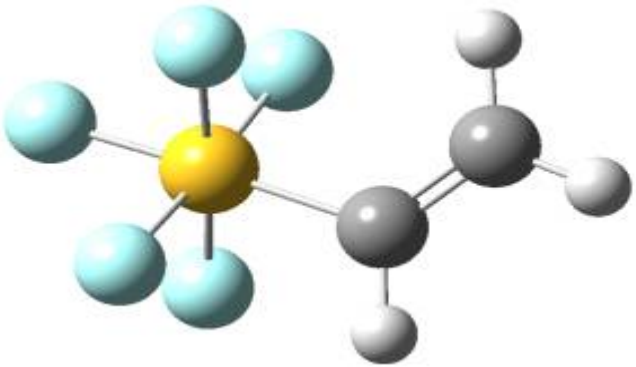


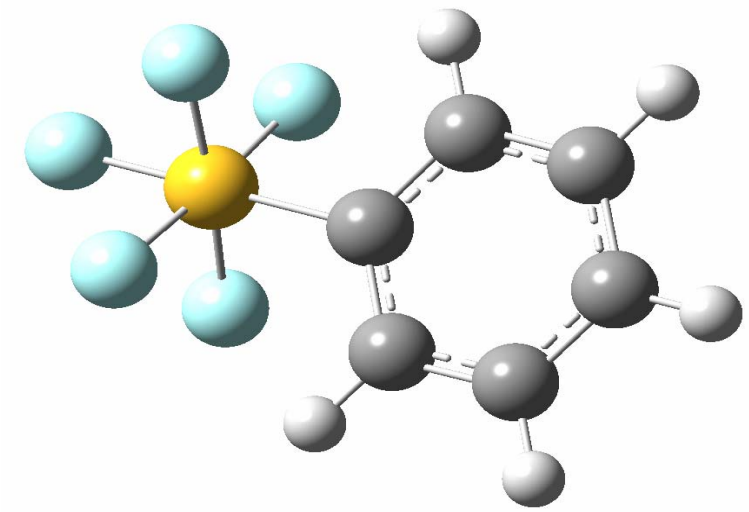
2.60 D



3.44 D

Size of SF_5 group





carbon – sulfur bond lengths

1.844 Å

1.798 Å

MP2(Full)/6-31G(d) structures of SF_5 ethylene and SF_5 benzene

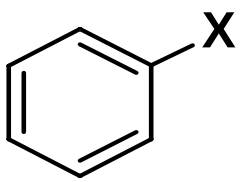
[Dr. Thomas Miller, USAF, private communication]

Impact on Lipophilicity

The hydrophobic character of substituents is measured via their partition coefficients, P_X

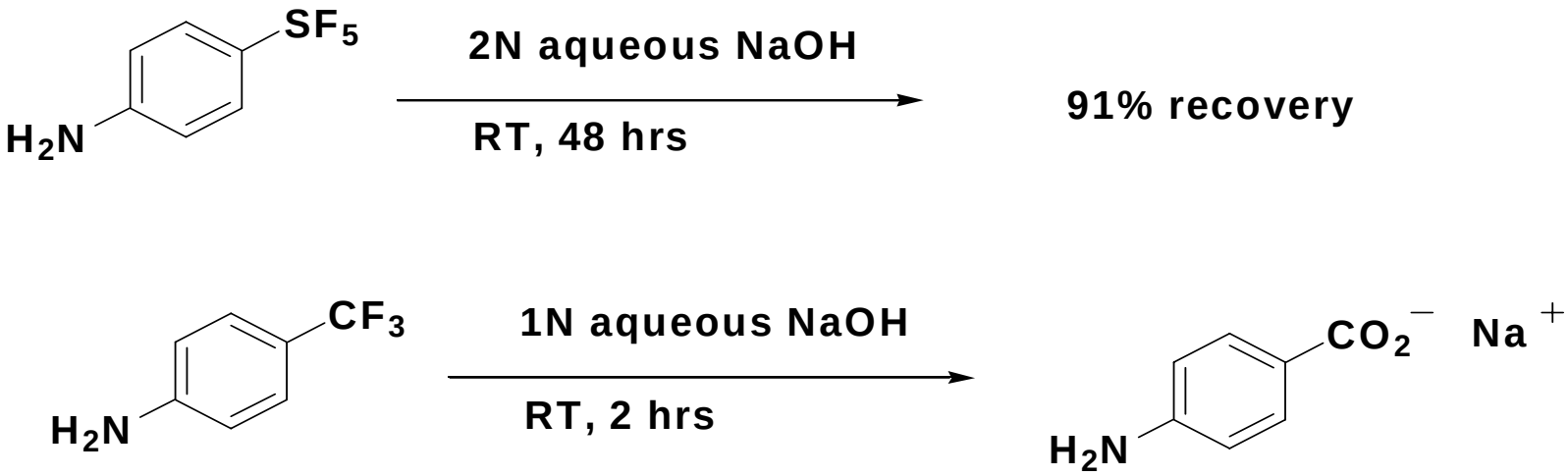
Relative hydrophobicities are reported as their π values:

$$\pi_X = \log P_X - \log P_H$$



X = F	0.14
X = CF_3	0.88
X = OCF_3	1.04
X = SF_5	1.23

Chemical Stability



Bowden, Comina, Greenhall, Kariuki, Loveday & Philp
Tetrahedron 2000, *56*, 3309-3408 (F2 Chemicals)

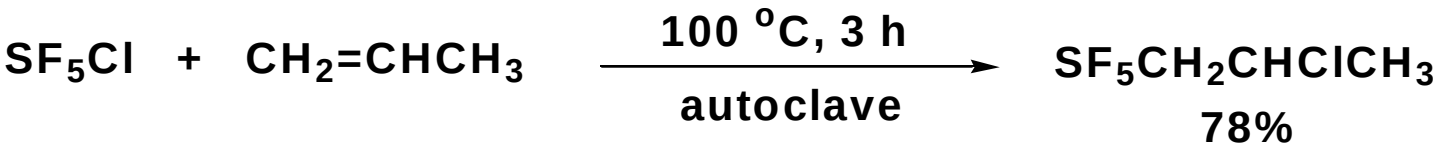
Thermal Stability, etc.

Previous methods for synthesis of *aliphatic* SF_5 compounds

Using SF_5Cl: bp –21 °C

Major current contributors to this field

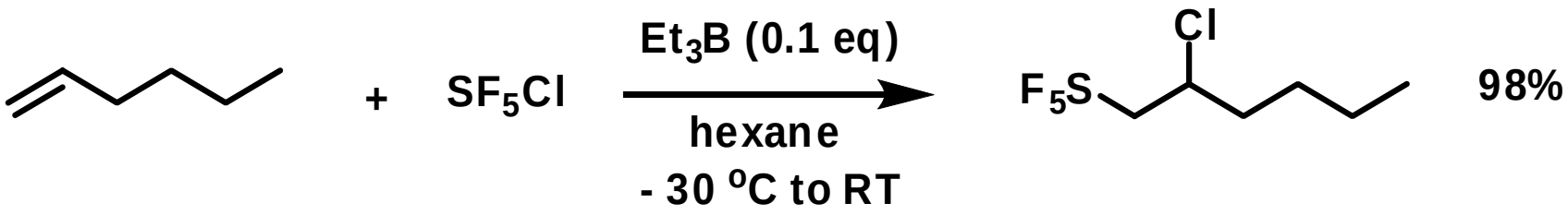
Gard, Thrasher, Seppelt, Shreeve, Brel



Gas phase photolysis gave similar results.

Case, Ray & Roberts, *J. Chem. Soc.* 1961, 2066.

A new method:

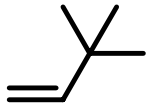


SF_5Cl is strictly a free radical chain reagent!

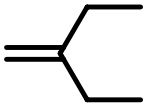
Aït-Mohand and Dolbier, *Org. Lett*. 2002, *4*, 3013-3015
USP 6,919,484 (2005)

Other alkene examples:

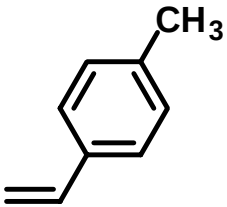
95%



96%

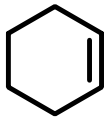


89%



79%

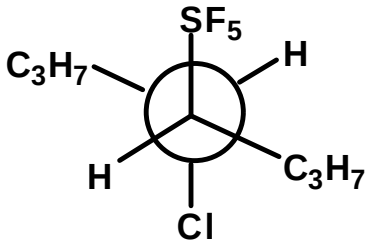
95%



98%

(single diastereomers formed)

presumably:



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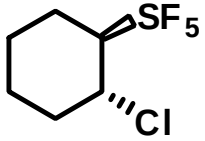
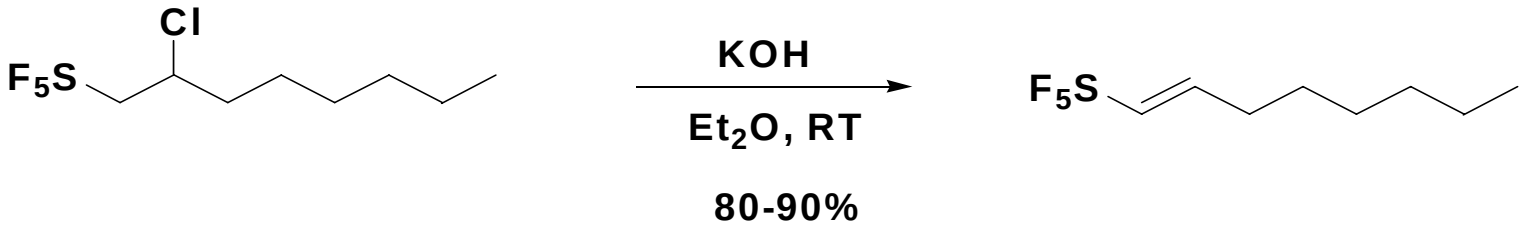
and



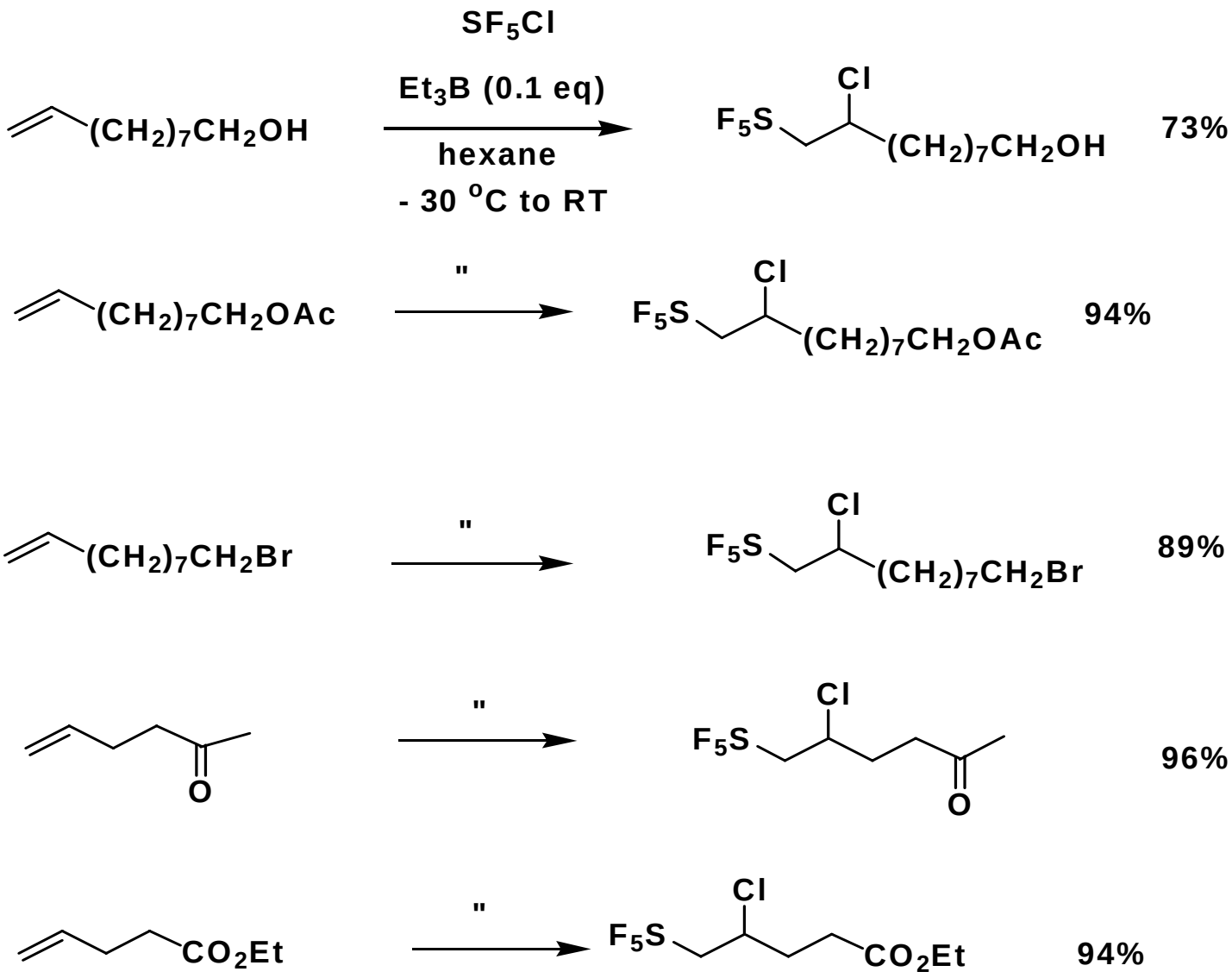
trans

Aït-Mohand and Dolbier
Org. Lett. 2002, *4*, 3013-3015

Typical elimination chemistry:

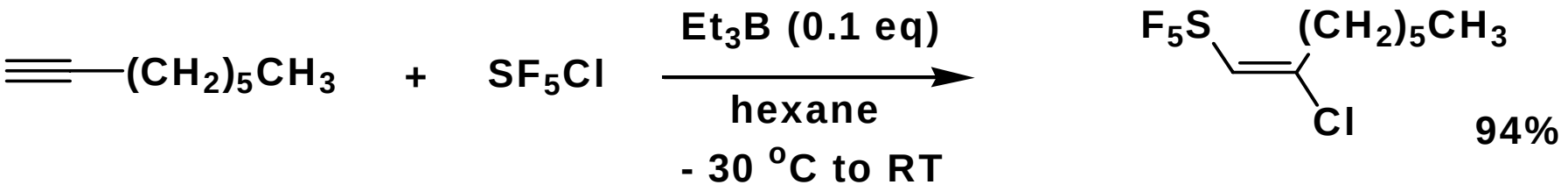


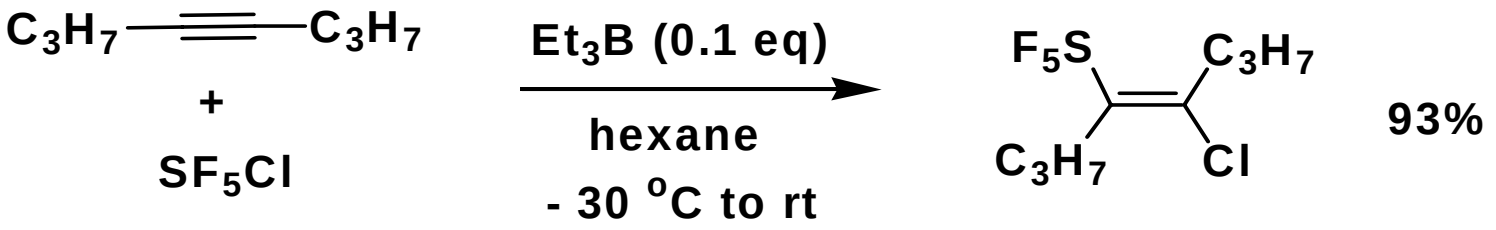
Functional group toleration

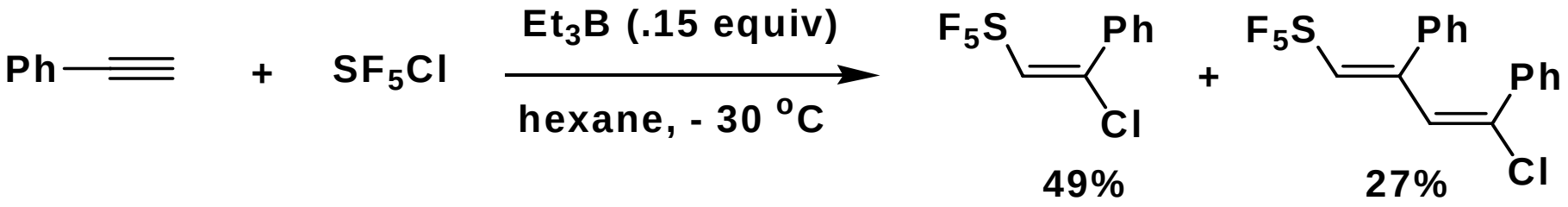


Ait-Mohand

Additions to alkynes:

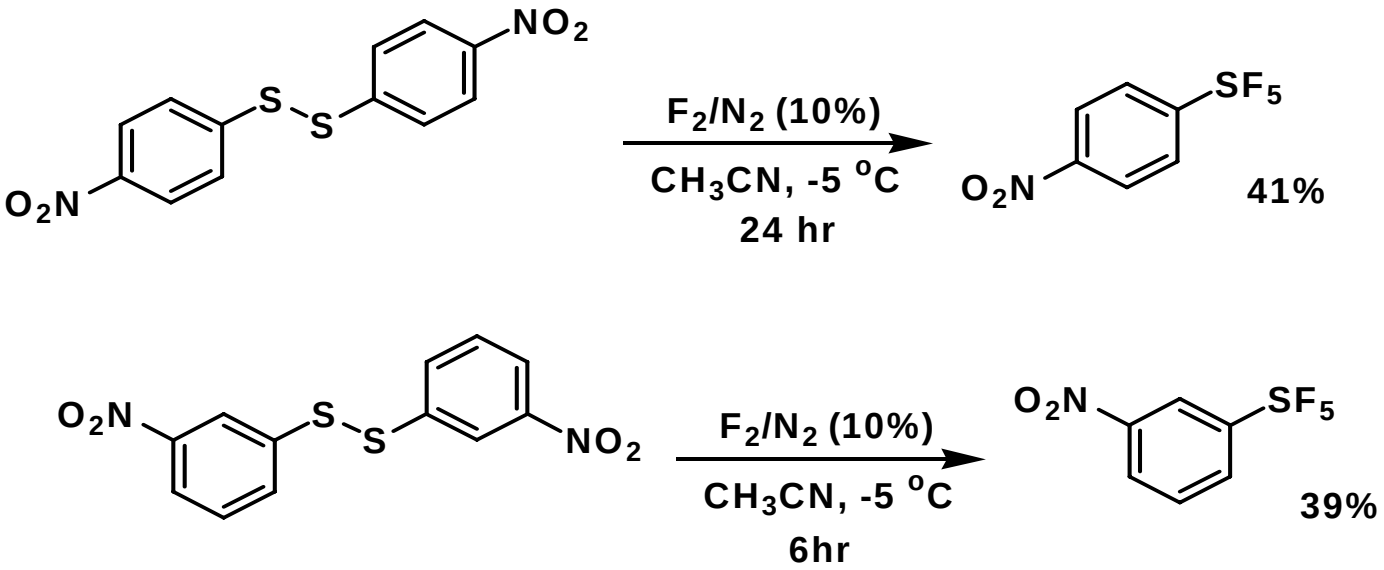






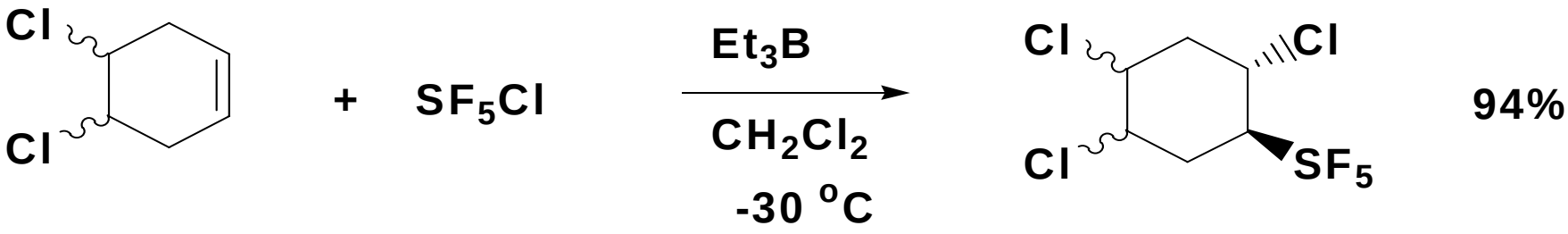
Pentafluorosulfanyl Aromatics

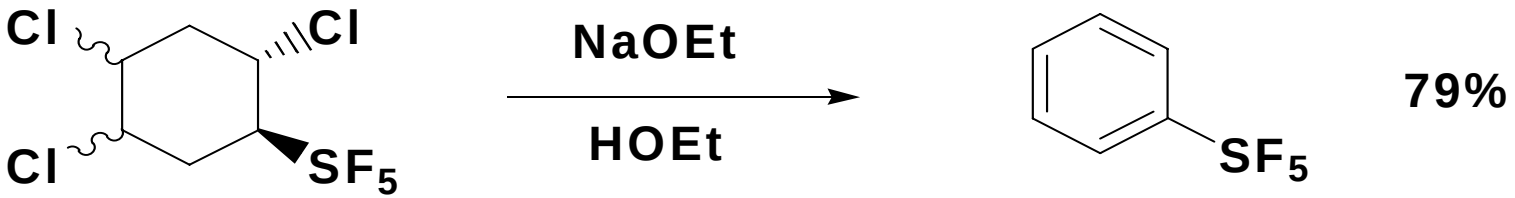
Direct fluorination method:



Bowden, Comina, Greenhall, Kariuki, Loveday & Philp
Tetrahedron 2000, *56*, 3309-3408 (F2 Chemicals)

Our synthesis of pentafluorosulfanyl benzene

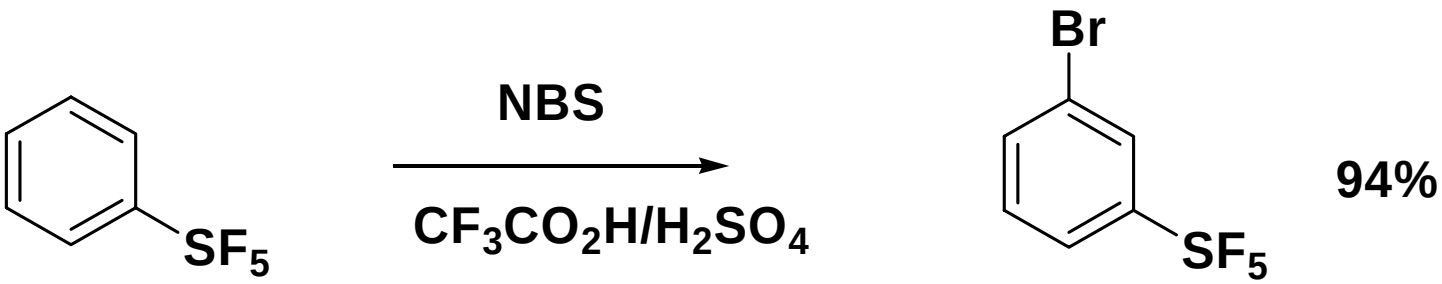


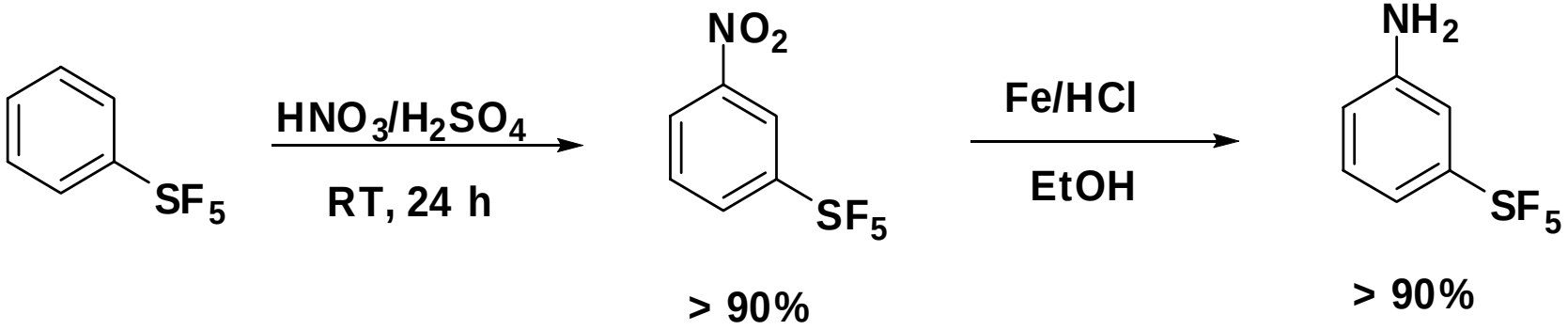


Overall yield: 71%

Tanya Sergeeva

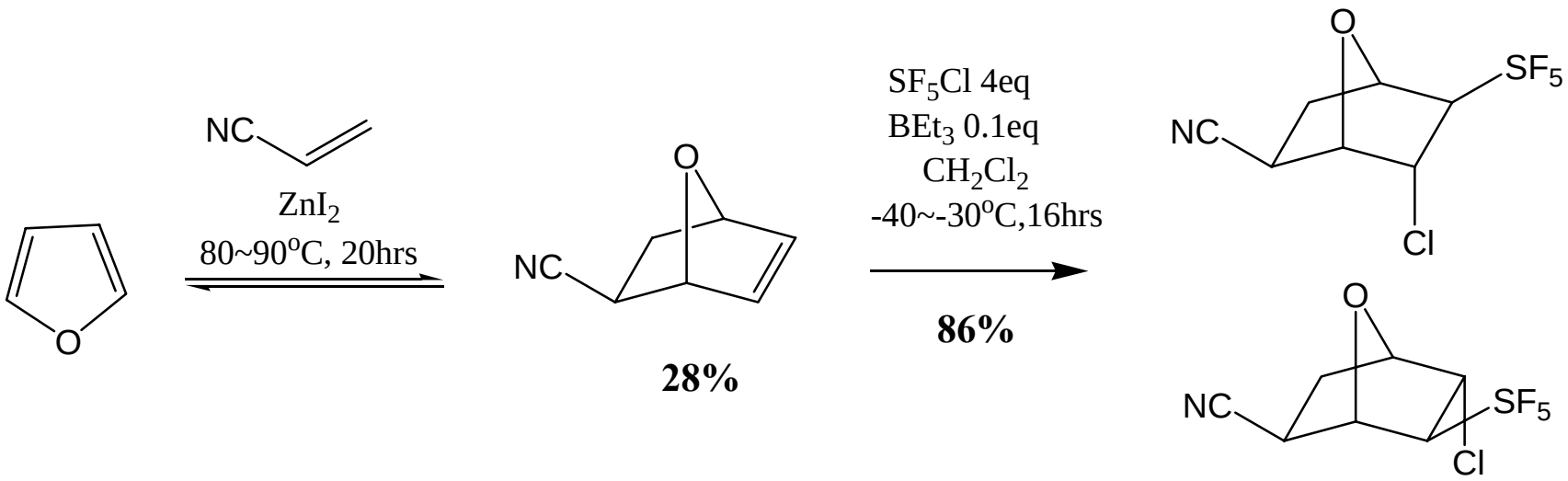
Synthesis of aromatic derivatives





Sergeeva

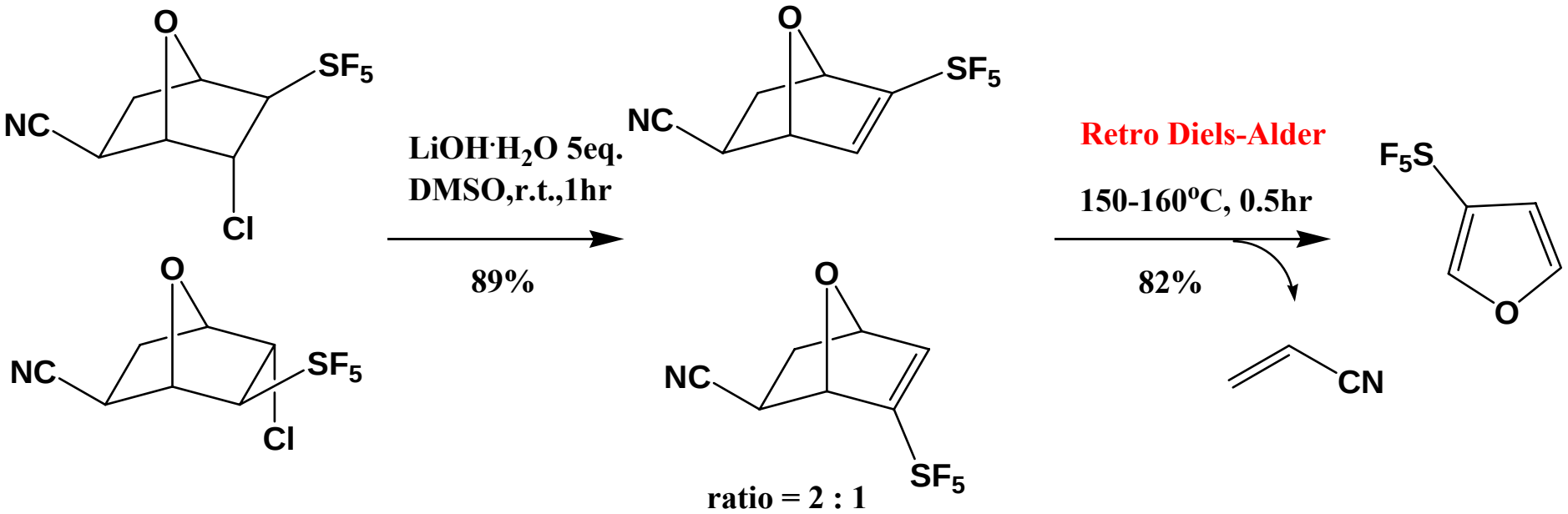
SF_5-Heterocycles, an indirect method



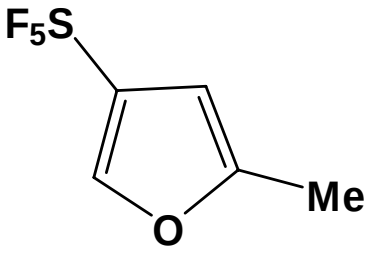
ratio = 2 :1

Many other dienophiles proved unsatisfactory

Akira Mitani

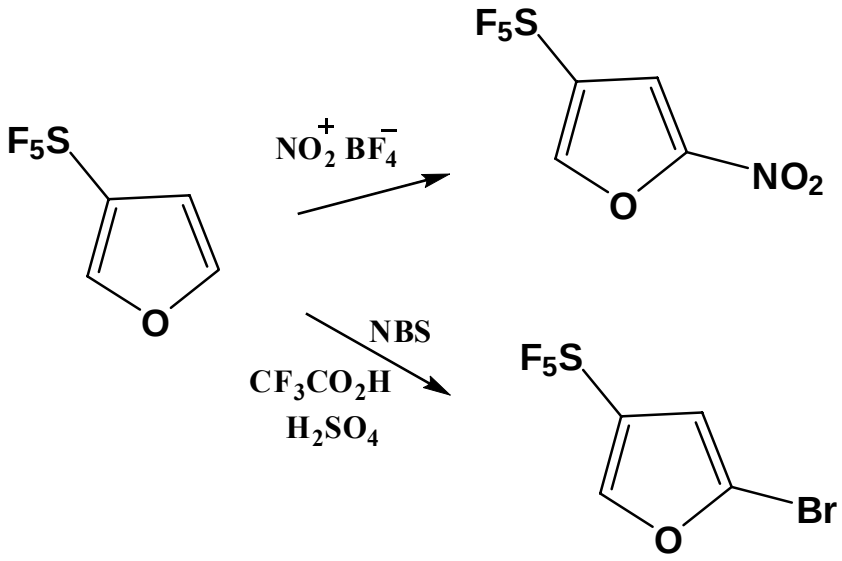


similarly



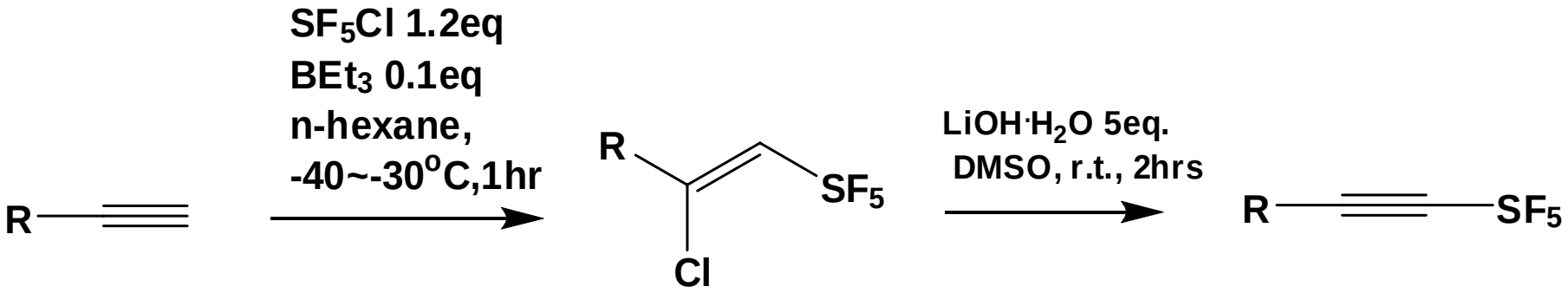
Mitani

Derivativizing reactions:



Mitani

An alternative approach using SF_5-alkynes



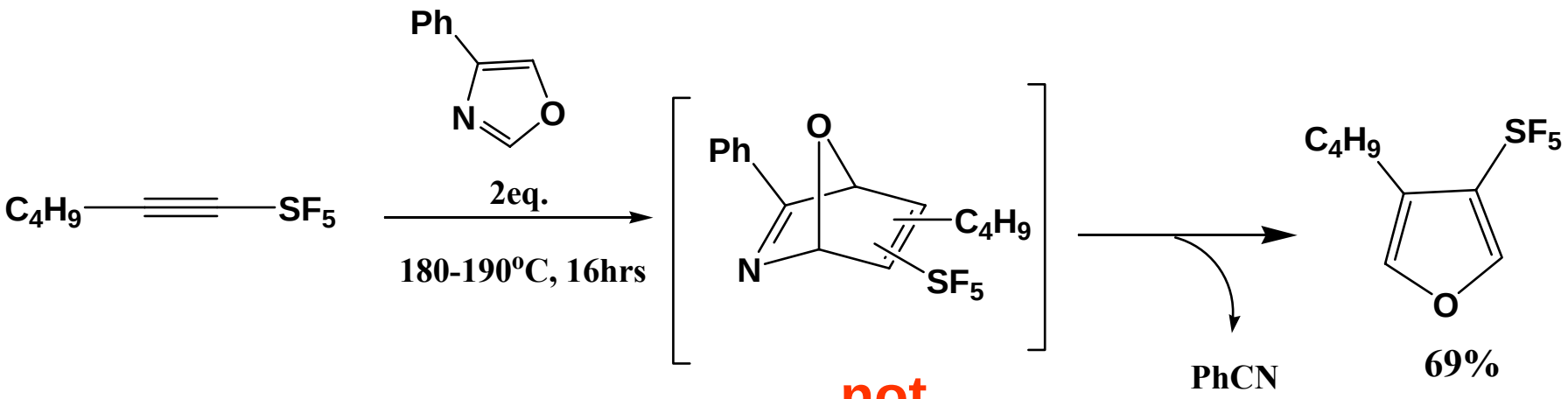
$R=C_4H_9$ 92%

R=Ph 49%

$R=C_4H_9$ 68%

R=Ph 93%

Mitani

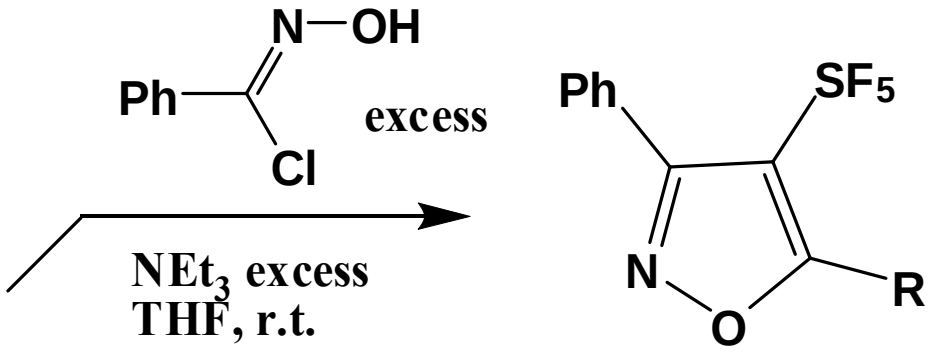


Thiazoles & imidazoles?

Mitani

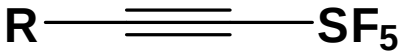
1,3-Dipolar cycloadditions

(nitrile oxides)

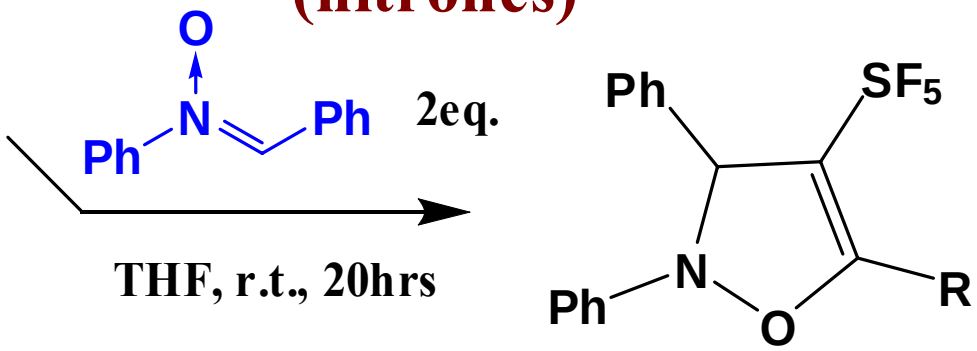


R=C_4H_9 45%

R=Ph 53%



(nitrones)

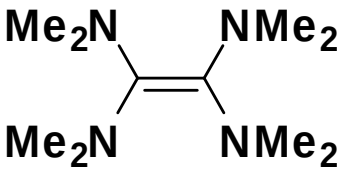


R=C_4H_9 67%

R=Ph 90%

Mitani

TDAE Chemistry

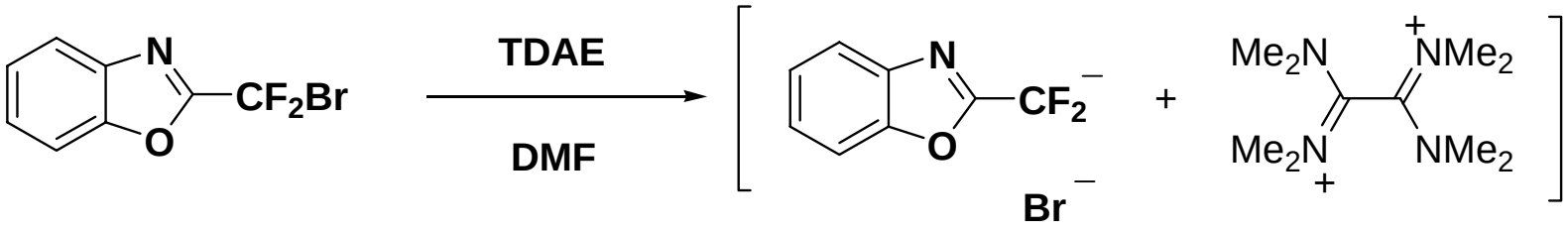


= TDAE (a potent organic reducing agent)

For example:

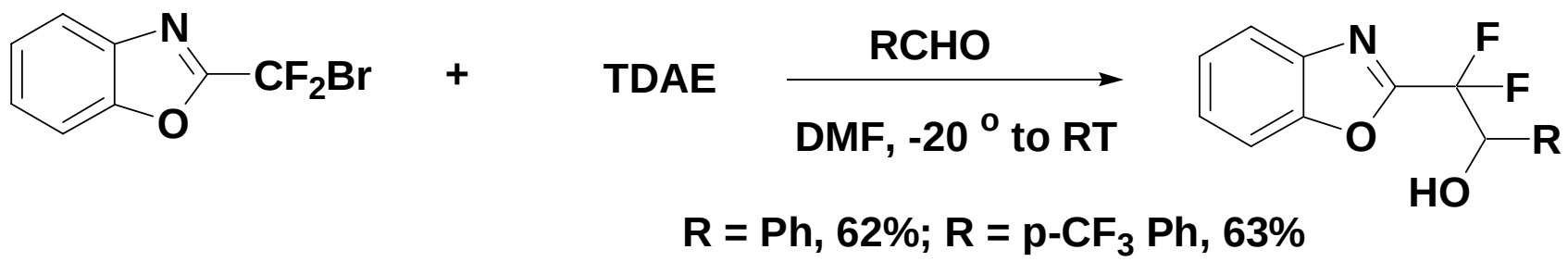
Reduction of bromodifluoromethyl heterocycles

(In situ generation of heterocyclic difluoromethyl anions)

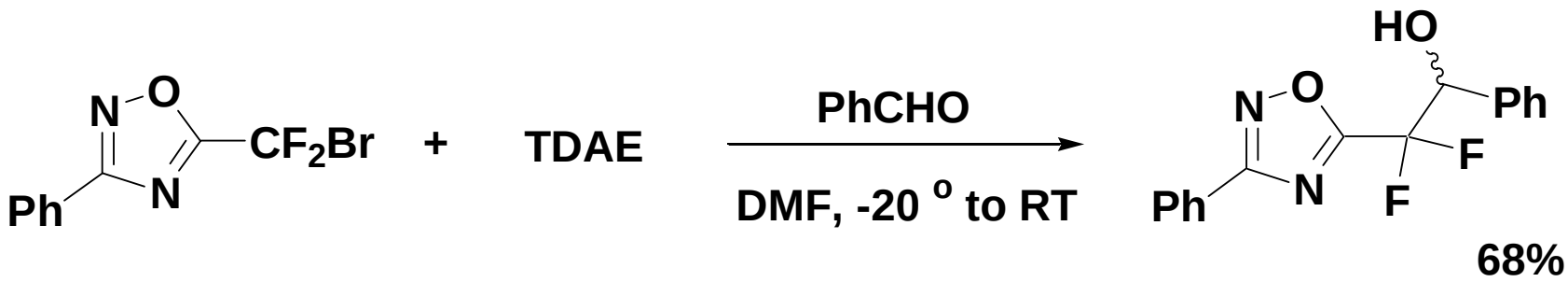


Maurice Médebielle

Reactions of bromodifluoromethyl heterocycles with with aromatic aldehydes – via carbanions generated *in situ*



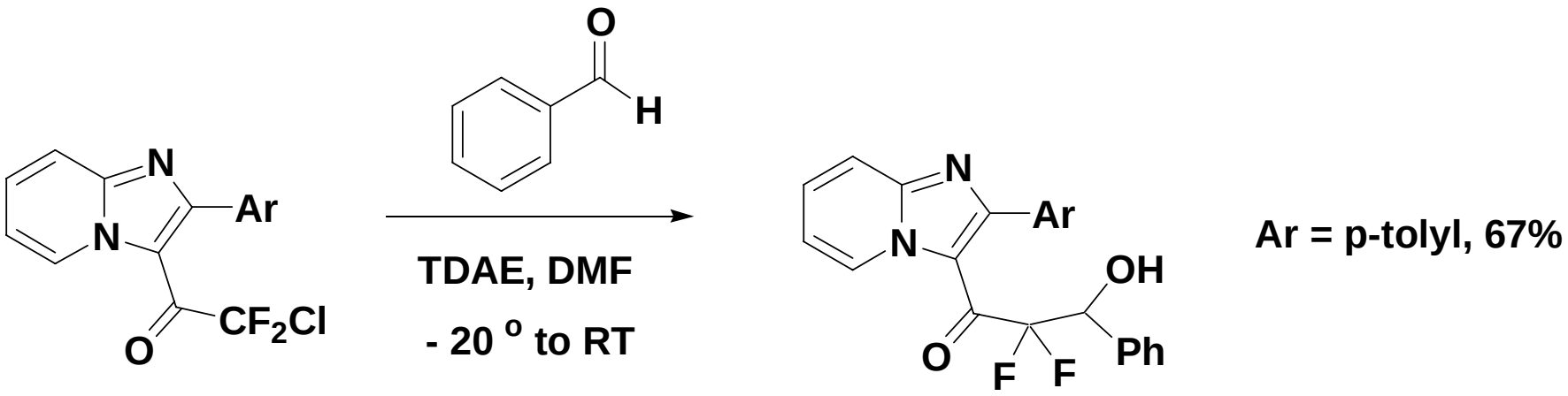
R = Ph, 62%; R = p-CF_3 Ph, 63%



68%

Burkholder, Dolbier & Médebielle, *J. Org. Chem*. 1998, *63*, 5385

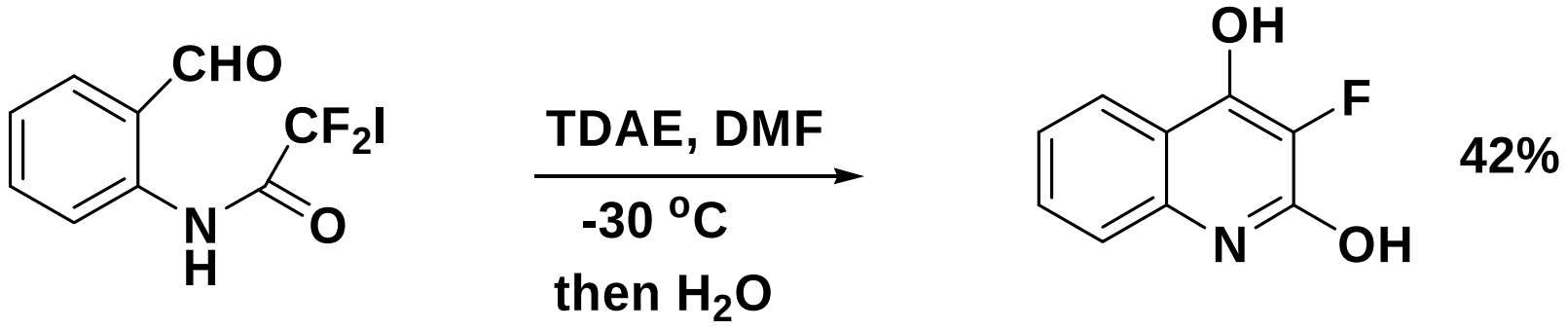
Reactions of chlorodifluoromethyl ketones with aldehydes



Ar = p-tolyl, 67%

Burkholder, Dolbier, Médebielle & Aït-Mohand, *Tetrahedron Lett*. 2001, *42*, 3077

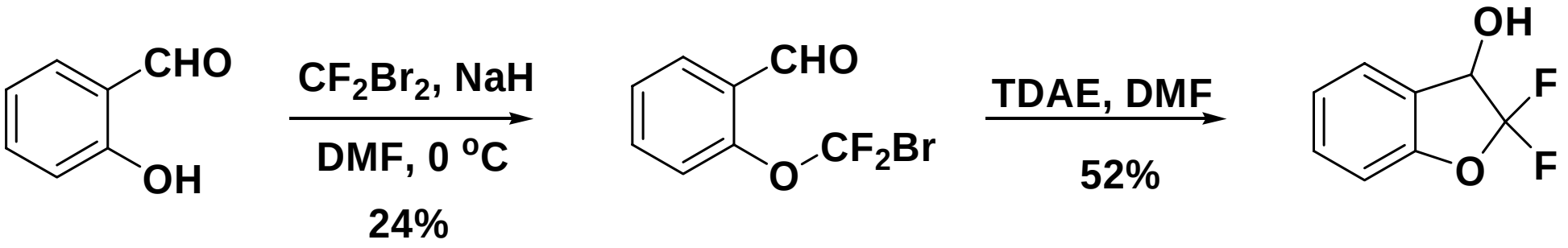
An intramolecular example:



42%

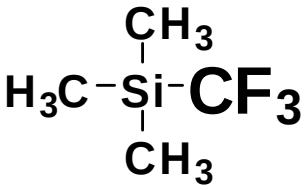
Wei Xu

A related heterocycle-forming reaction



Xu

Nucleophilic trifluoromethylation

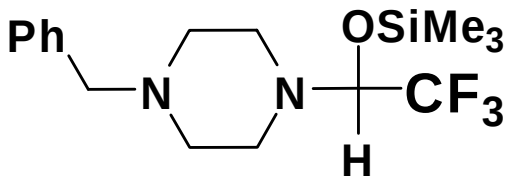


TMS-CF_3

Ruppert's Reagent

Prakash & Yudin (*Chem. Rev.* 1997, *97*, 757-786)

Singh & Shreeve (*Tetrahedron*, 2000, *56*, 7613-7632)



Langlois' reagent

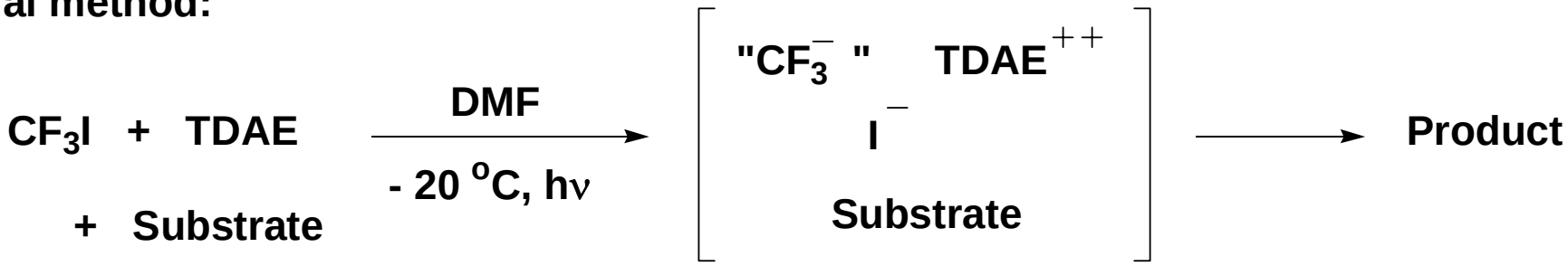
Billard, Langlois & Blond, *Eur. J. Org. Chem*. 2001, 1467

"CF_3ZnI"

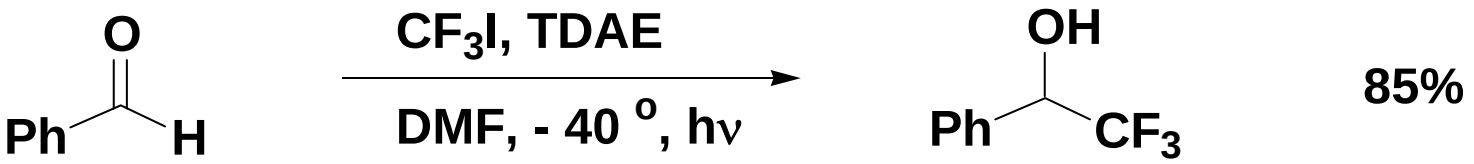
Kitazume & Ishikawa, *J. Am. Chem. Soc*. 1985, *107*, 5186

CF_3I/TDAE – A nucleophilic trifluoromethylating reagent

General method:

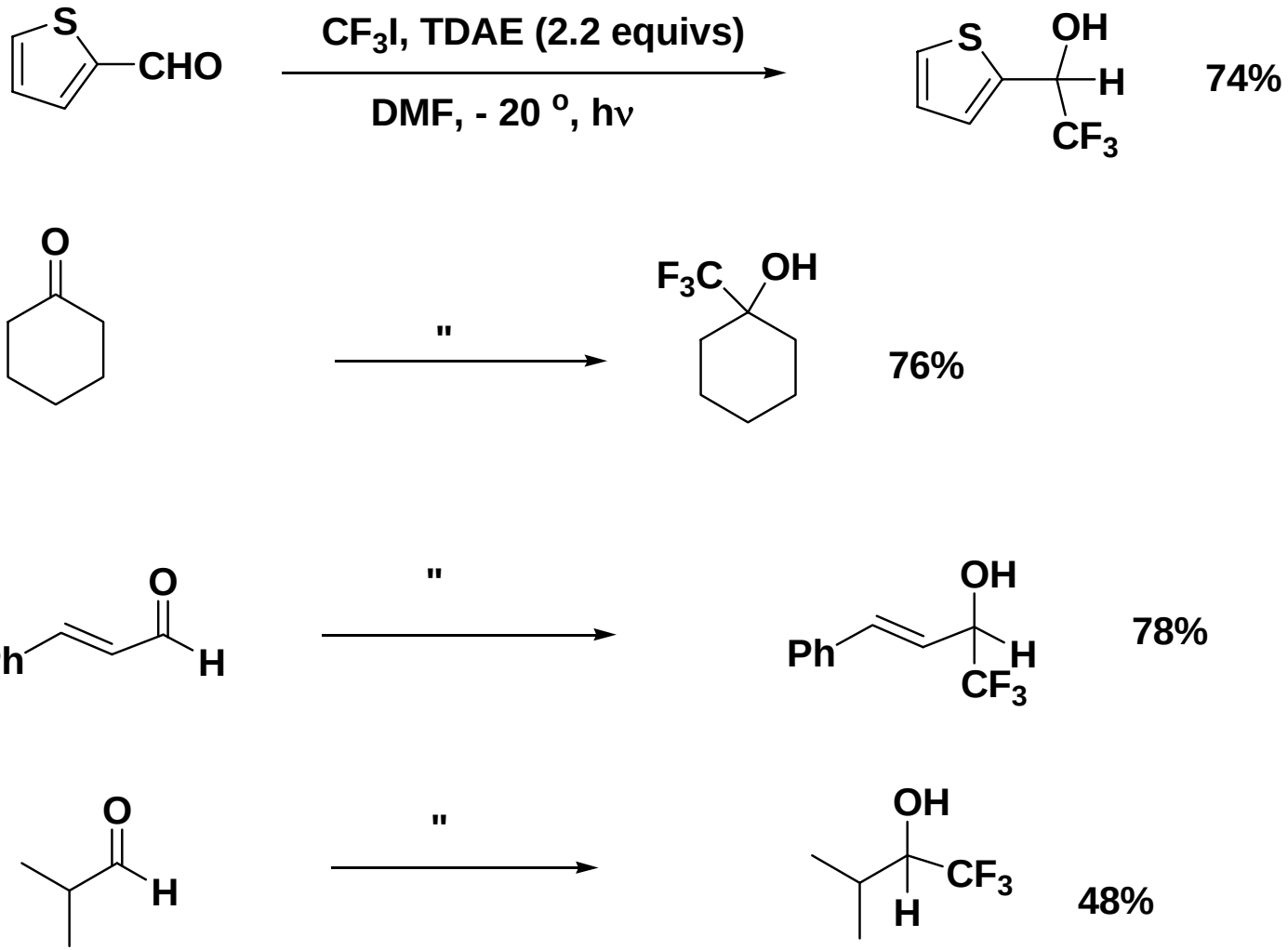


Example:



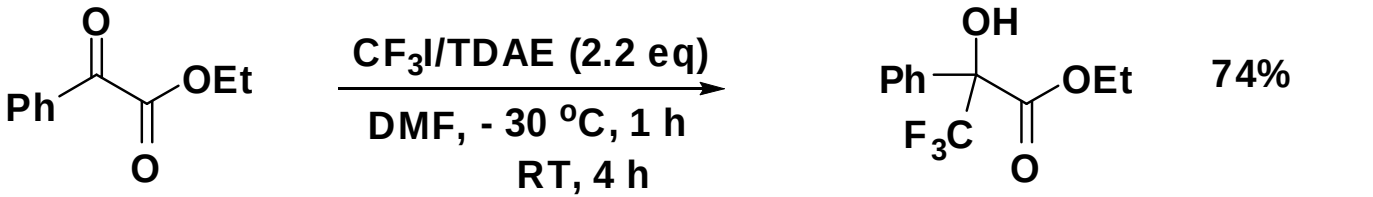
Samia Aït-Mohand

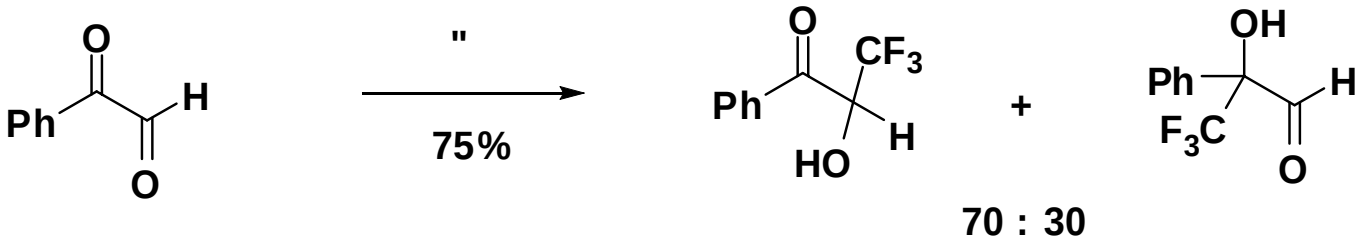
Further aldehyde examples

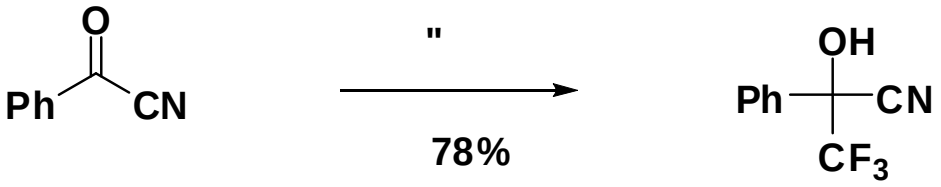


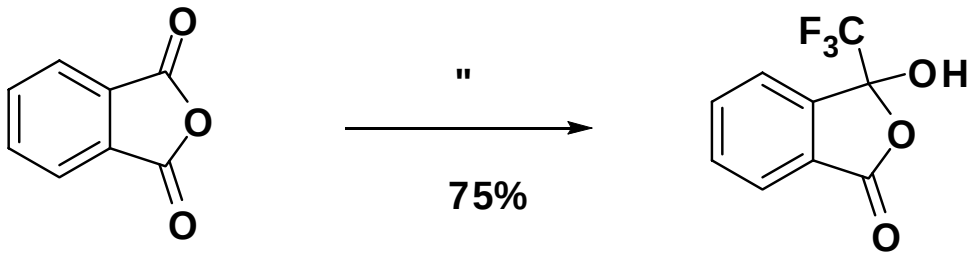
Aït-Mohand, Takechi, Médebielle & Dolbier, *Org. Lett*. 2001, *3*, 4241

Other examples

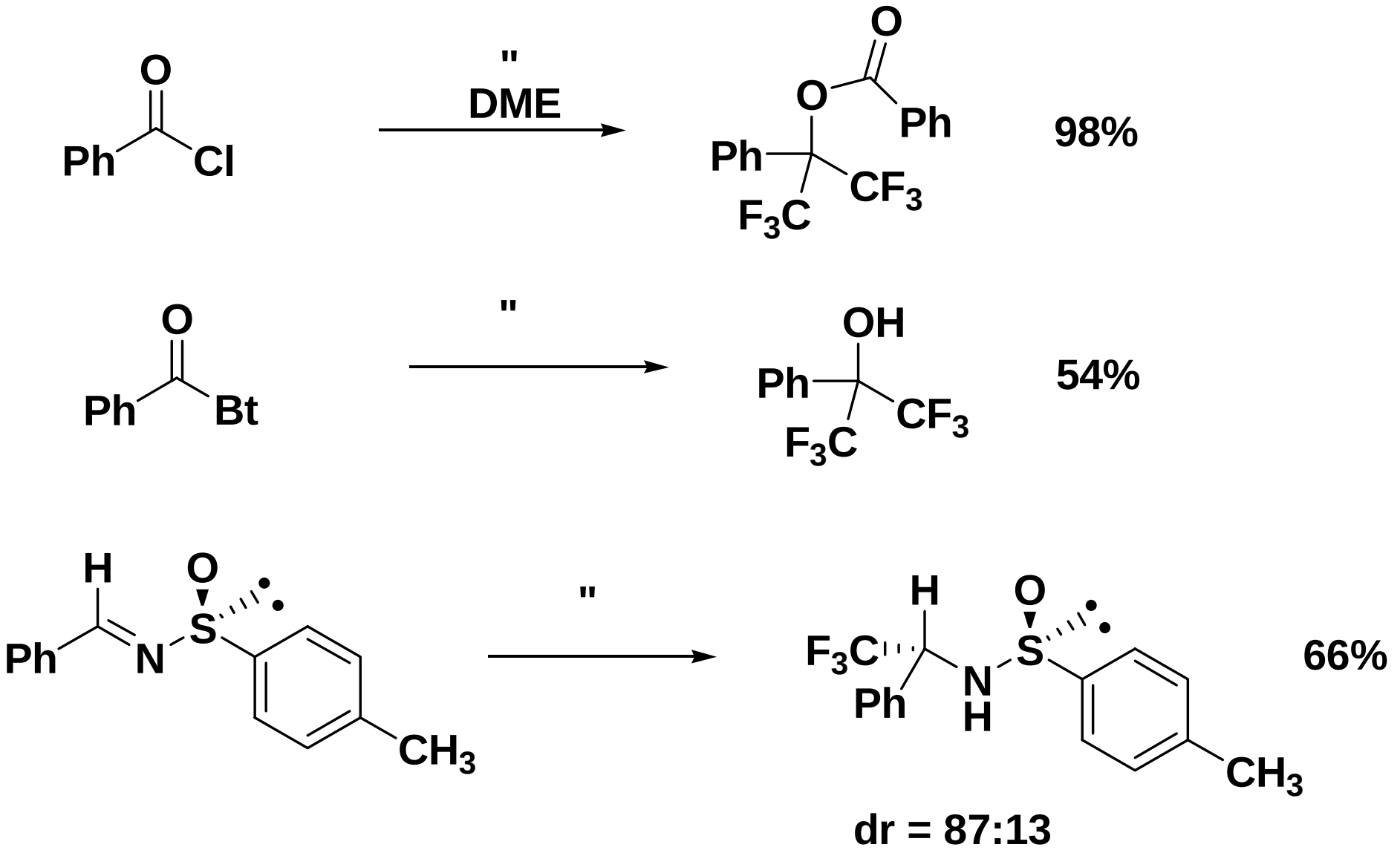






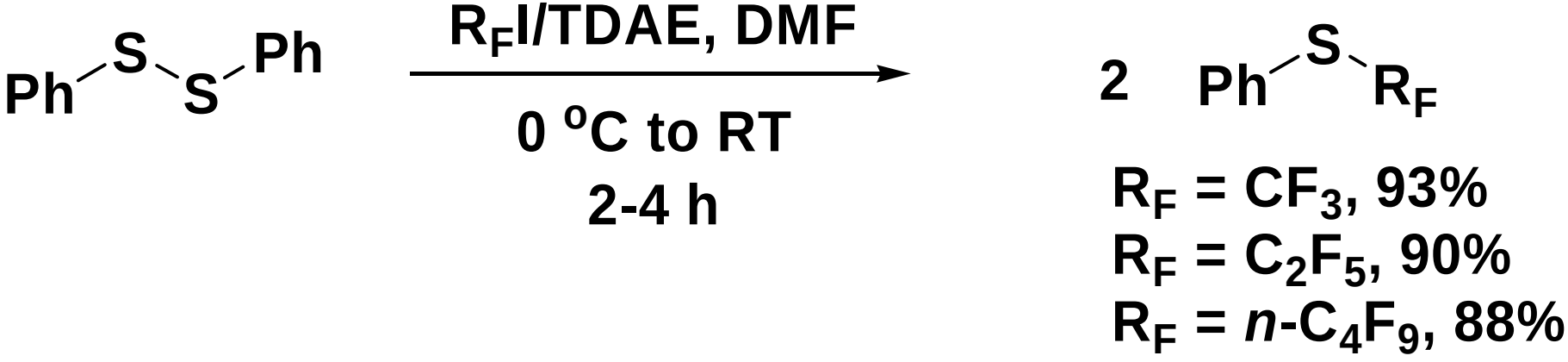


Wei Xu, Takechi, Aït-Mohand


O
Ph
Cl
"
DME
O
O
Ph
Ph
CF3
F3C
98%
O
Ph
Bt
"
OH
Ph
CF3
F3C
54%
H
O
Ph
N
S
CH3
"
H
O
F3C
S
Ph
N
H
CH3
66%
dr = 87:13

Takechi & Xu

Synthesis of aryl and alkyl sulfides



Many examples

Also selenides

Chaya Pooput

Mechanism