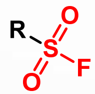
Sulfur Fluoride Exchange (SuFEx)



Reporter: Changxu Zhong

Supervisor: Dr. Ping Lu

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1. Ethenesulfonyl Fluoride
2. $F\text{-}SO_2^+$ Donors
3. Fluorosulfates & Sulfonyl Fluorides
4. SuFEx Based Application

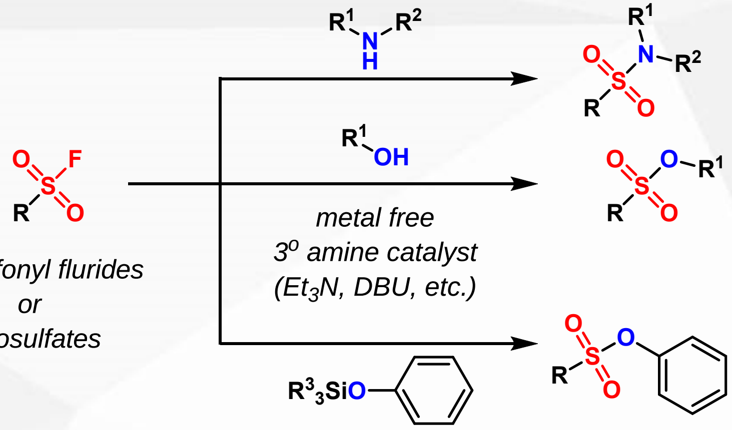
Summary

Summary & Perspective

Introduction

1. SuFEx

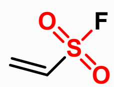
Sulfur Fluoride Exchange



eg. sulfonyl flurides
or
florosulfates

Modular SuFEx Hubs

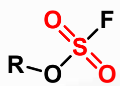
Originally reported by Hedrick in 1953



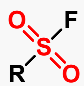
Ethenesulfonyl Fluoride
(ESF)

Sulfuryl Fluoride
(SO_2F_2)

Originally reported by Lebeau in 1901



Fluorosulfates
($ROSO_2F$)



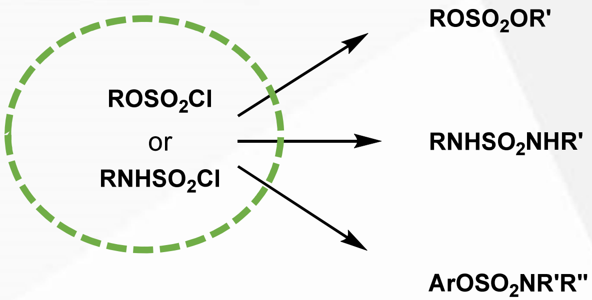
Sulfonyl Fluorides
(RSO_2F)

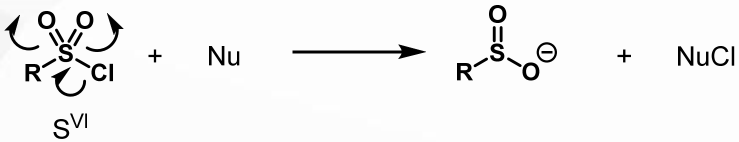
etc.

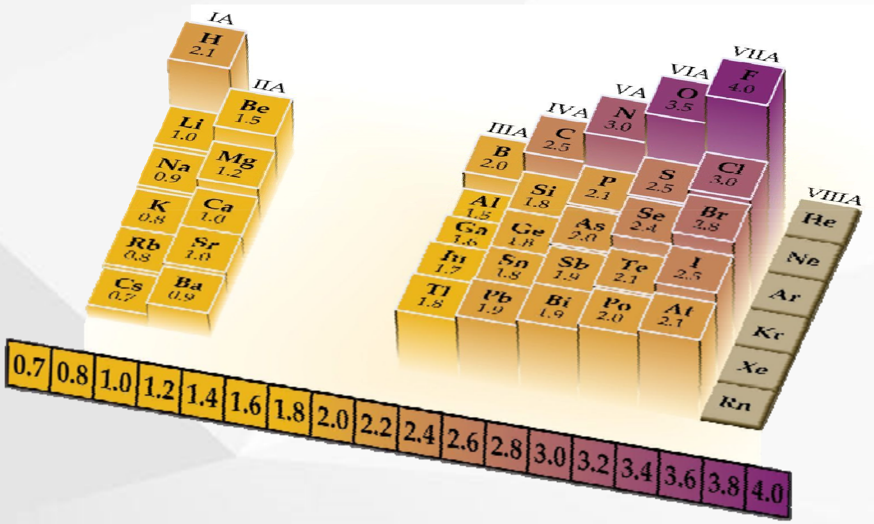
Sharpless, K. B.* *Angew. Chem. Int. Ed.* **2014**, *53*, 2-21.

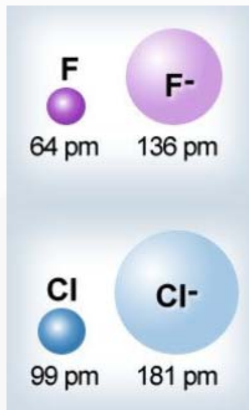
Reactivity between RSO_2Cl & RSO_2F

***Not reliable connective units* for the fast assembly of sophisticated molecules**









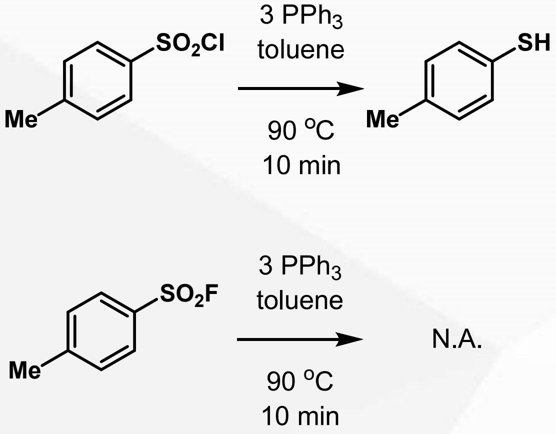
S-F bond strength

SO_2F_2 (90.5±4.3 kcal mol^{-1})

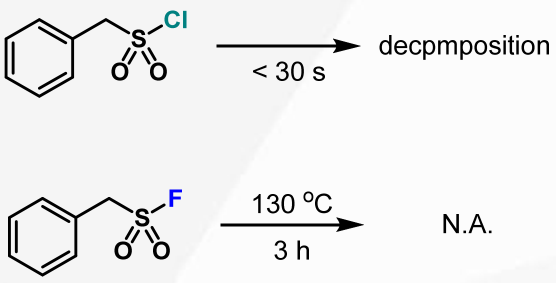
SO_2Cl_2 (46±4 kcal mol^{-1})

Reactivity between RSO_2Cl & RSO_2F

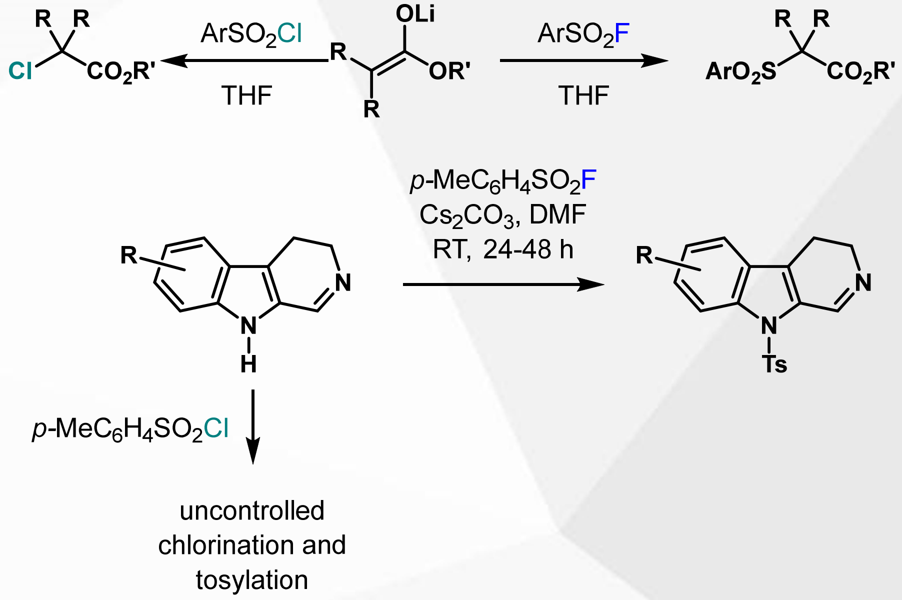
1) Resistance to reduction



2) Thermodynamic stability



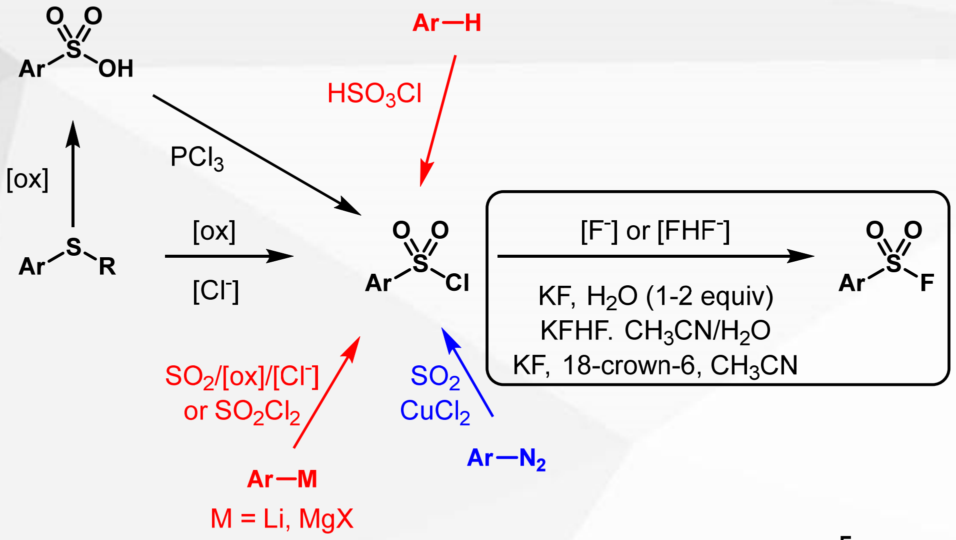
3) Exclusive reaction at sulfur

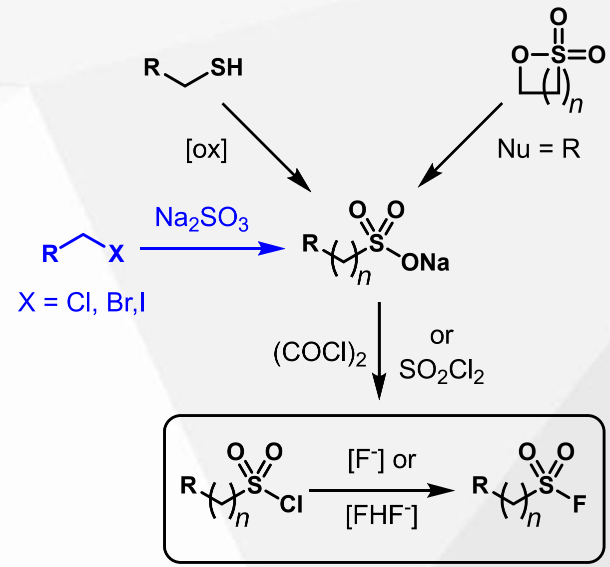


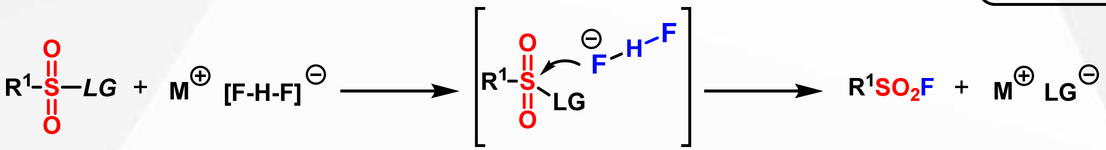
Mendoza, J. S.* *J. Org. Chem.* **1990**, *55*, 1125-1126.

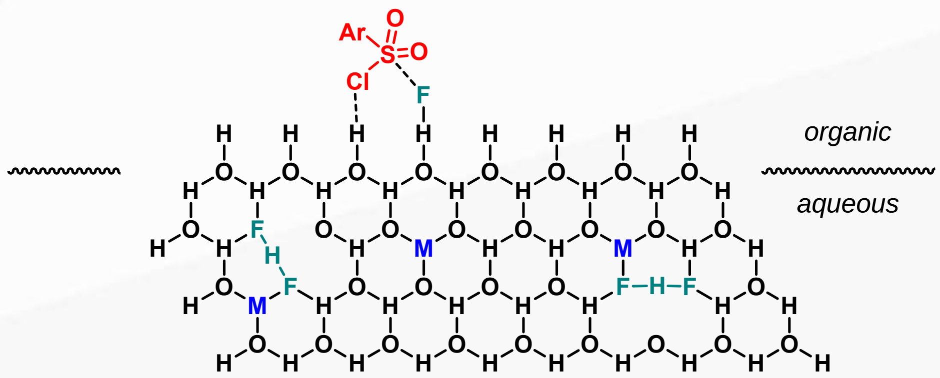
Jacobsen, E. N.* *J. Am. Chem. Soc.* **2013**, *135*, 1891-1894.

General synthesis of sulfonyl fluorides









Kessler, R. J.* *J. Am. Chem. Soc.* **1992**, *114*, 2419-2428.

Marcus, R. A.* *J. Am. Chem. Soc.* **2007**, *129*, 5492-5502.

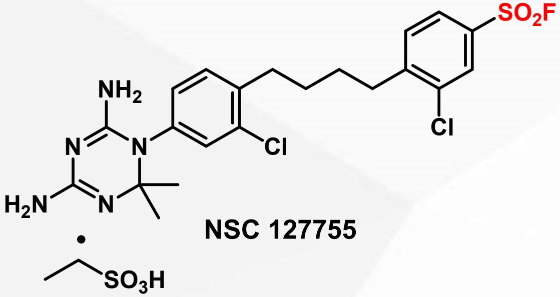
Marcus, R. A.* *Phys. Chem. Chem. Phys.* **2011**, *13*, 5388-5393.

Implications for drug discovery

SO_2F modified noncovalent inhibitor analogues

1. **SO_2F-bearing compound**
2. **Enzyme**
3. **Covalent bond**

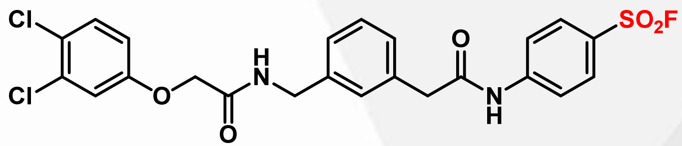
DHFR inhibitor



NSC 127755

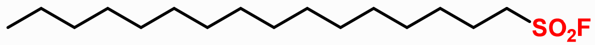
B. R. Baker

α-Chymotrypsin inhibitors



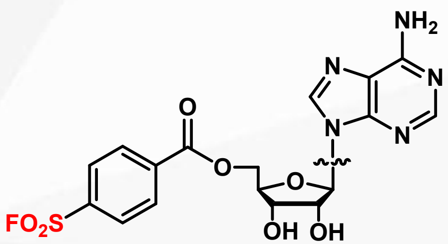
B. R. Baker

FAAH, LPL

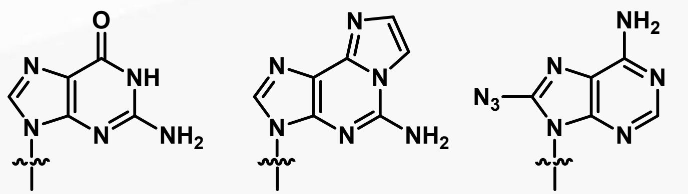


G. Kokotos

Purine Nucleotide Based Probes



5'-FSBA



R. F. Colman

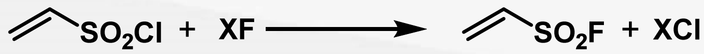
Baker, R. B.* *Acc. Chem. Res.* **1969**, *2*, 129-136.

Modular SuFEx Hubs and Applications

2.1 Ethenesulfonyl Fluoride

ESF

Hedrick 1953

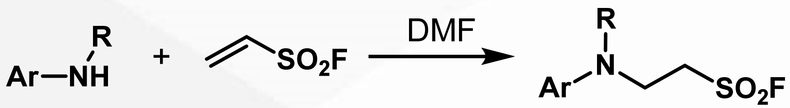


$X = NH_4^+$, Alkali metal, Alkaline earth metal

**Strong Michael acceptor
as well as
Diels–Alder dienophile**

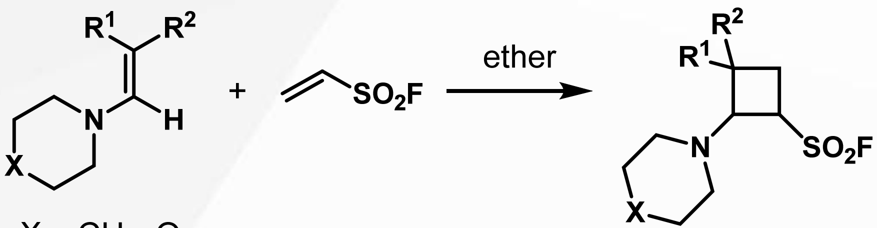
Krutak 1979

Michael addition



up to 93% yield

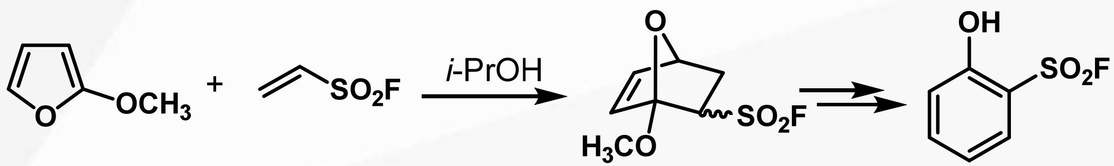
[2+2]

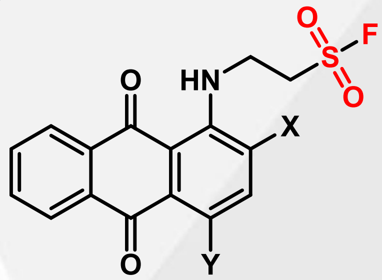


X = CH_2, O

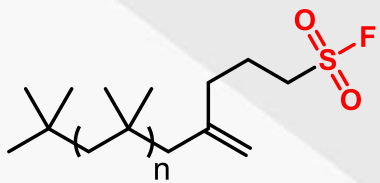
up to 100% yield

[4+2]





dyestuff
(Eastman Kodak)



lubricant oil additive
(Chevron)

Hedrick, R. M. *US Pat.* 2653973, **1953**.

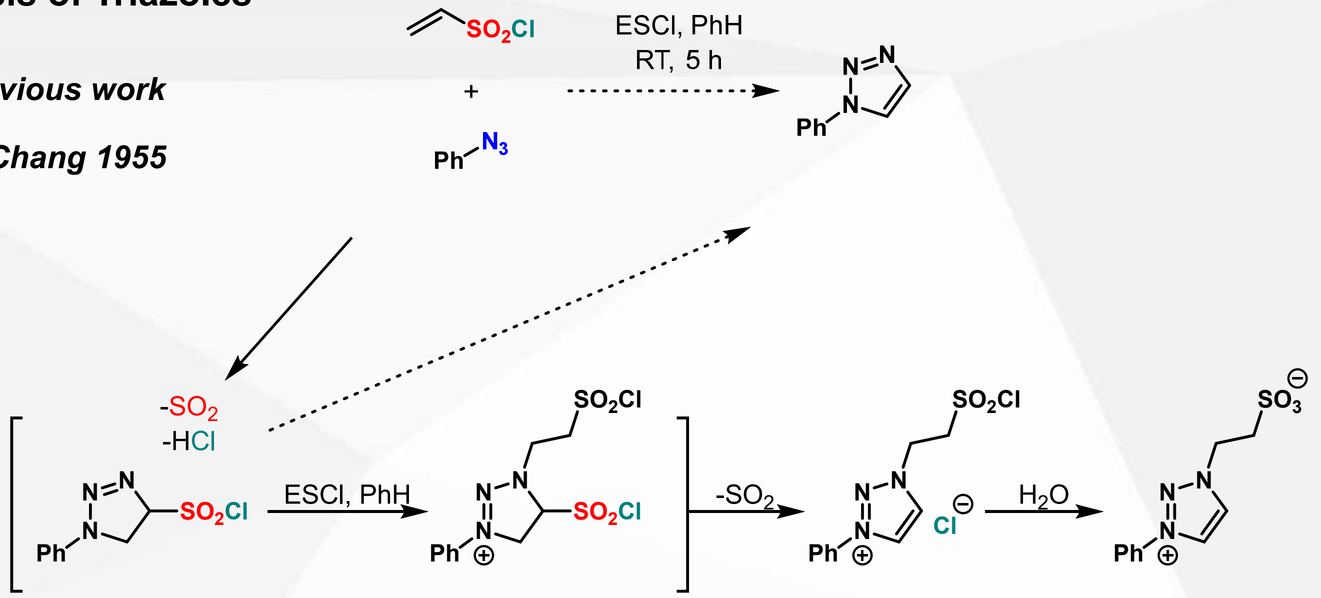
Krutak, J. J.*; Hyatt, J. A.* *J. Org. Chem.* **1979**, *44*, 3847-3858.

ESF

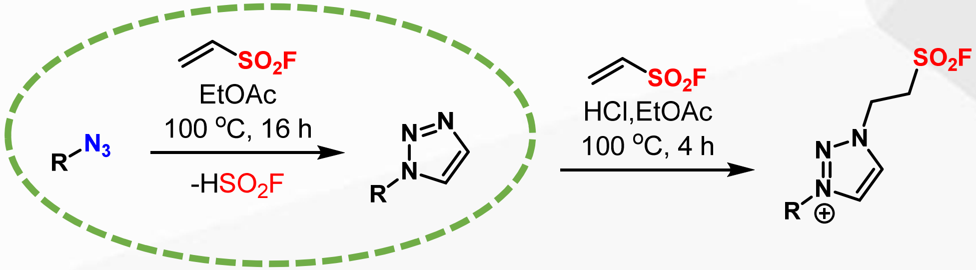
Synthesis of Triazoles

Previous work

Chang 1955



Dong 2020



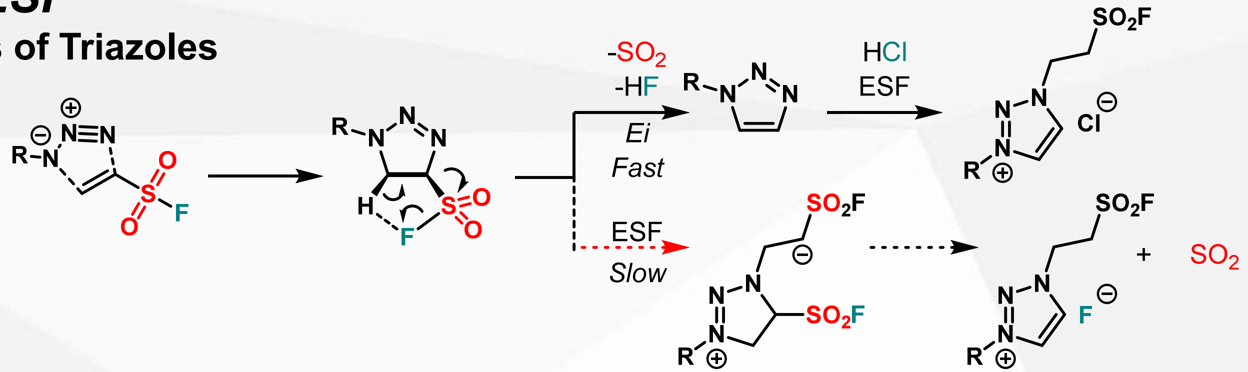
Chang, P. K.* *J. Am. Chem. Soc.* **1955**, *77*, 6532–6540.

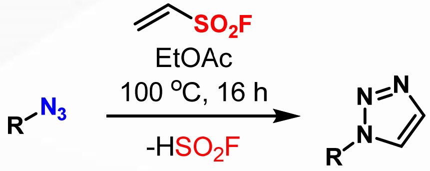
Dong, J.* *Angew. Chem. Int. Ed.* **2020**, *59*, 1181-1186.

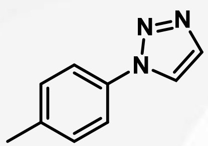
2.1 Ethenesulfonyl Fluoride

ESF

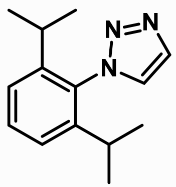
Synthesis of Triazoles



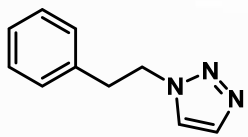




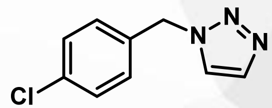
98%



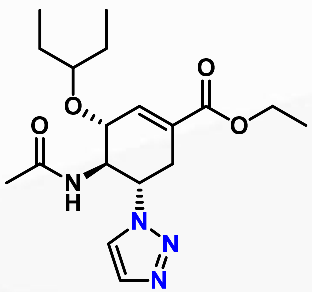
90%



92%



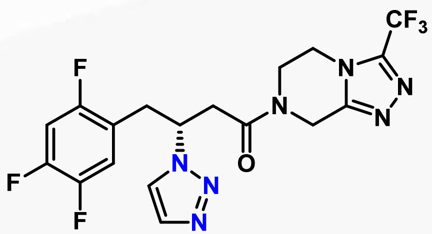
90%



81%

Parent drug = Oseltamivir

(Tamiflu®, anti-viral)



72%

Parent drug = Sitagliptin

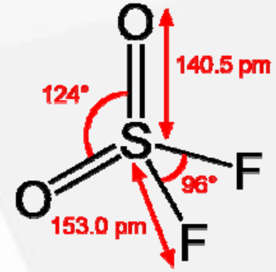
(anti-diabetic)

SO_2F_2 (Sulfuryl Fluoride) :

Hydrogen Bonding as Mediator

Lebeau, P 1901

$$SO_2 + F_2 \longrightarrow SO_2F_2$$



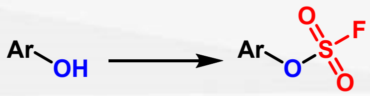
molecular weight	102.1 g mol $^{-1}$
density (25 ^{o}C, 1 atm)	4.18 mg mL^{-1} (air: 1.18 mg mL^{-1})
boiling point	-55 ^{o}C
vapor pressure	1611.47 kPa at 20 ^{o}C
odor	odorless
appearance	colorless gas
flammability	non-flammable
solubility (25 ^{o}C, g L^{-1})	water: 0.75, DCE: 25, MeOH: 33, EtOAc: 59, acetone: 71

stable up to 400 ^{o}C

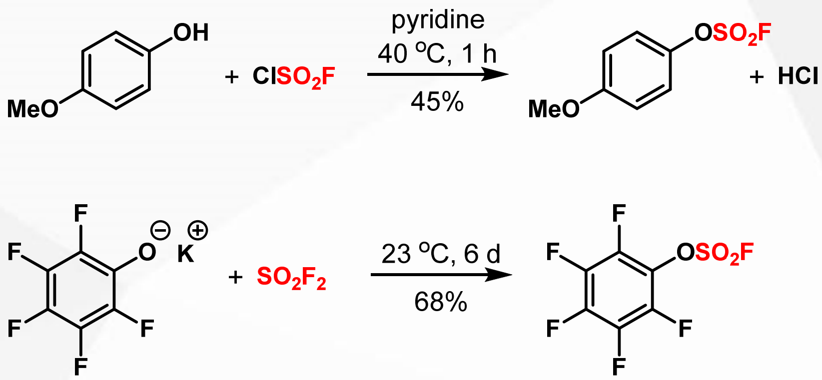
Lebeau, P.* *Compt. Rend.* **1901**, *132*, 374.

SO_2F_2

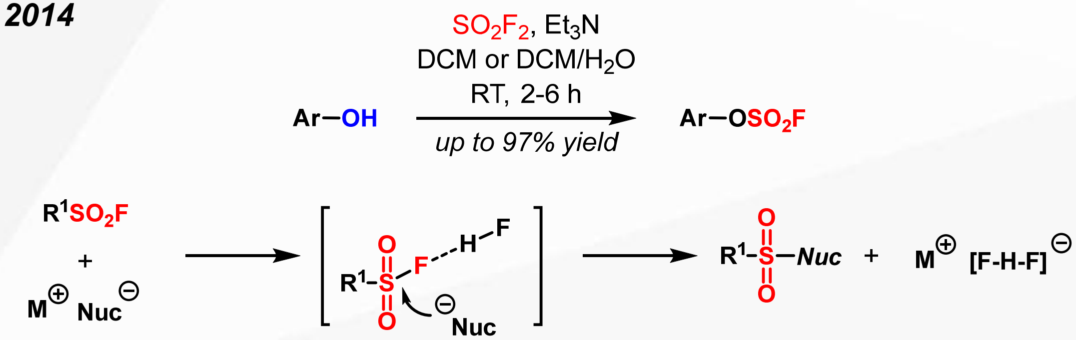
Preparation of Aryl fluorosulfates



Previous works



Sharpless 2014



Coffman, D. D.* *J. Org. Chem.* **1961**, *26*, 4164-4165.

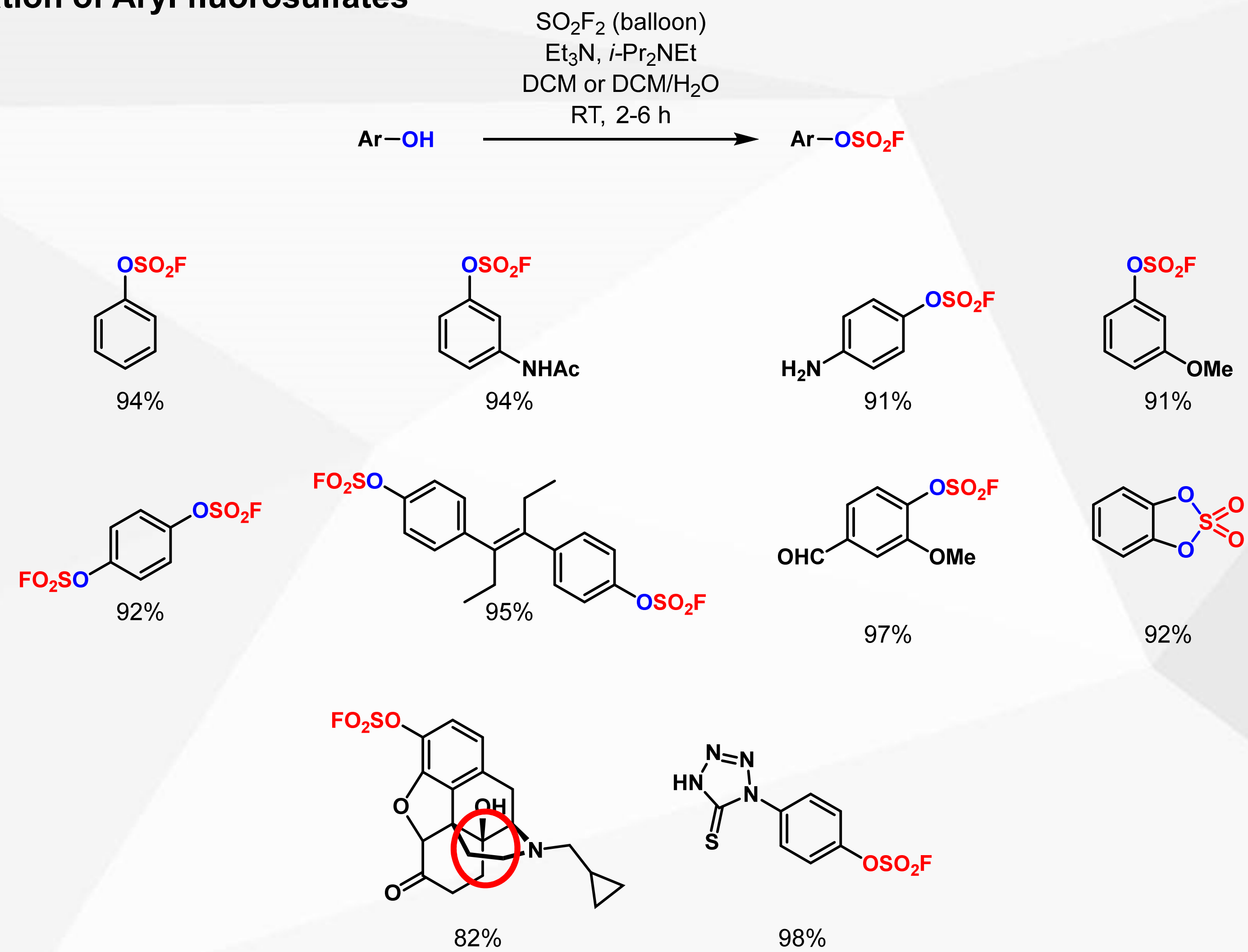
DesMarteau, D. D.* *J. Chem. Eng. Data* **1976**, *21*, 386-387.

Sharpless, K. B.* *Angew. Chem. Int. Ed.* **2014**, *53*, 2-21.

2.2 F-SO_2^+ donor

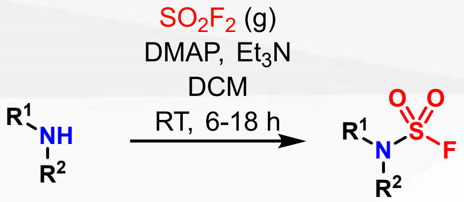
SO_2F_2

Preparation of Aryl fluorosulfates

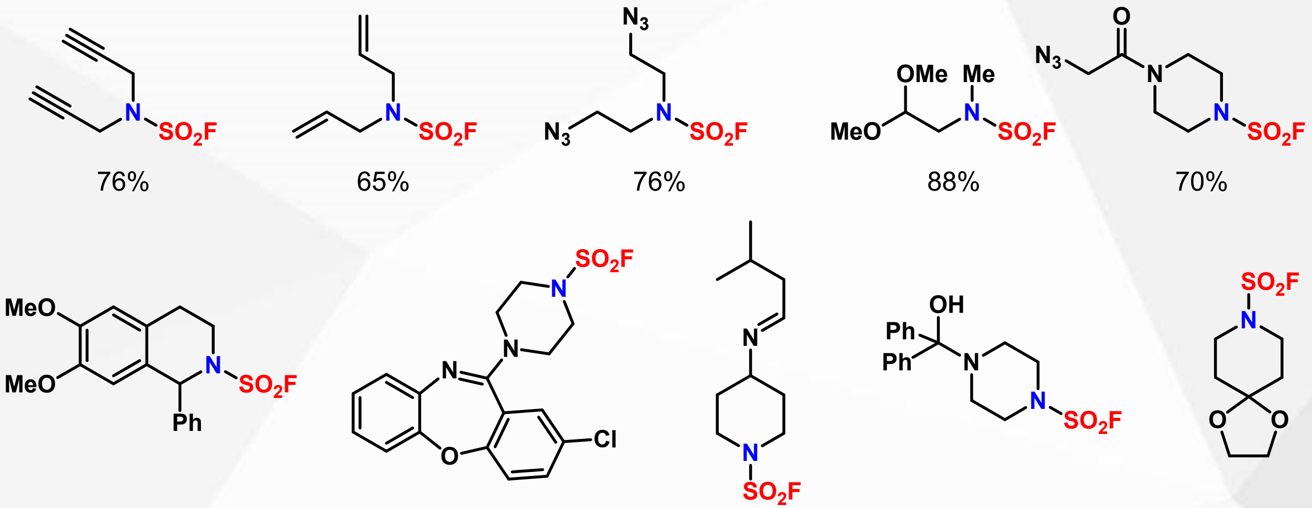


SO_2F_2

Preparation of Sulfamoyl Fluorides
(N-disubstituted)

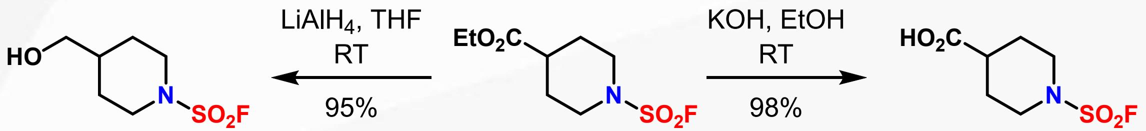


Stable under RT
for more than a week

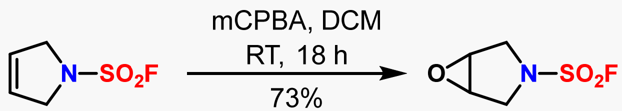


76% 65% 76% 88% 70%

80% 73% 70% 94% 99%

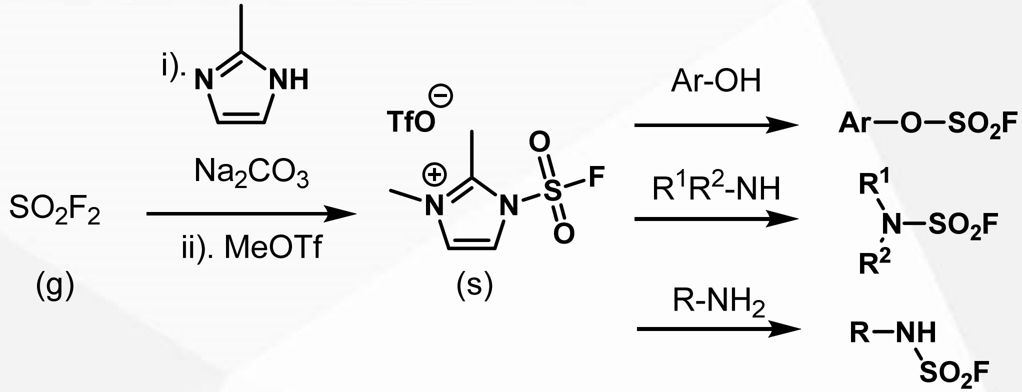


Well tolerance

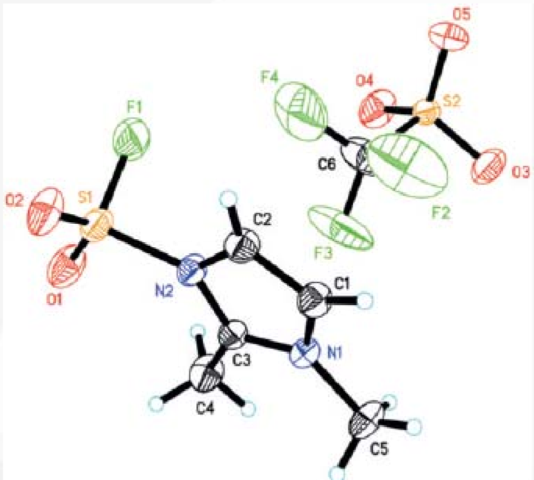


Transformations of the sulfamoyl fluoride moiety

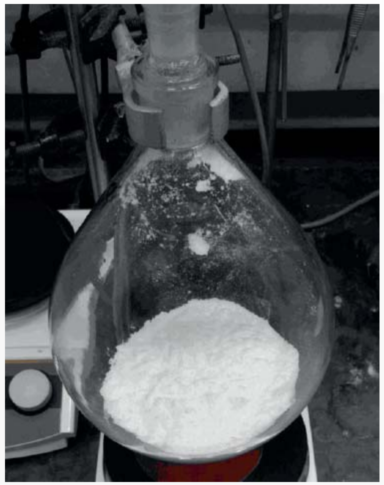
Fluorosulfuryl Imidazolium Salt



·Shelf-stable
·Overwhelming performance with phenols, primary and secondary amines



Single-crystal X-ray diffraction



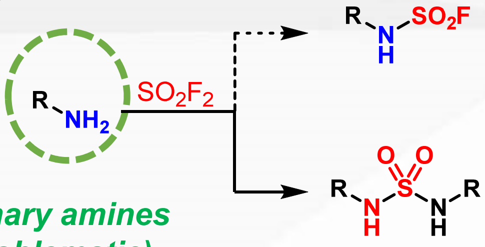
Stable in refrigerator or desiccator

Dong, J.* *Angew. Chem. Int. Ed.* **2018**, *57*, 2605-2610.

Fluorosulfuryl Imidazolium Salt

Preparation of Sulfamoyl Fluorides

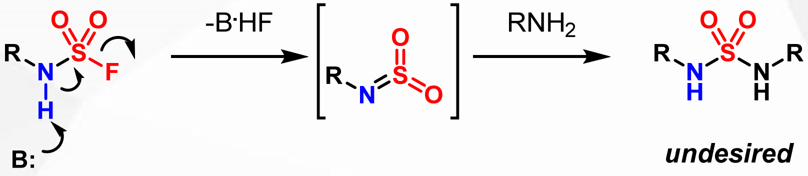
(N-monosubstituted)



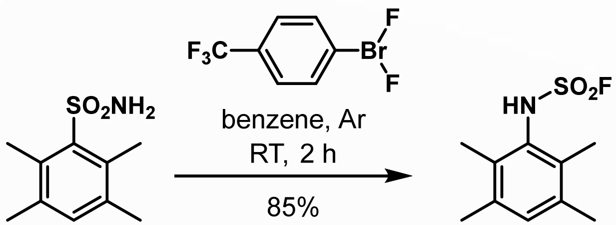
desired

undesired

Primary amines (problematic)

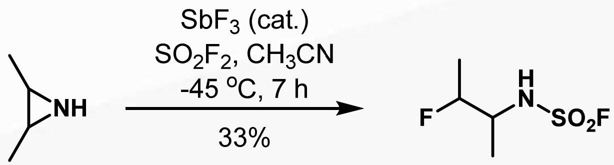


undesired



Hoffmann rearrangement

Indirect approaches



Ring opening

known preparations of N-monosubstituted sulfamoyl fluorides

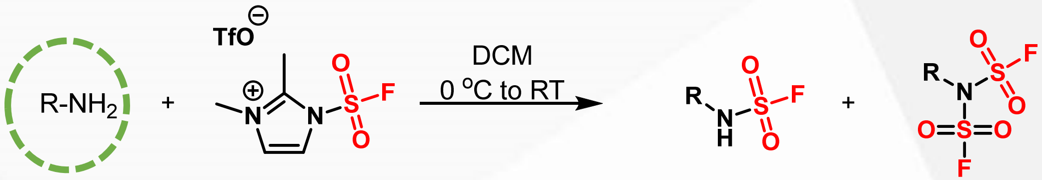
Ochiai, M.* *J. Am. Chem. Soc.* **2009**, *131*, 8392-8393.

Schulze, G.* *Justus Liebigs Ann. Chem.* **1969**, *729*, 40-51.

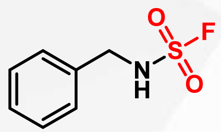
Fluorosulfuryl Imidazolium Salt

Preparation of Sulfamoyl Fluorides

(N-monosubstituted)



Primary amines



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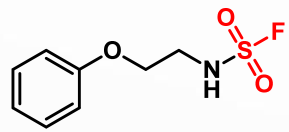

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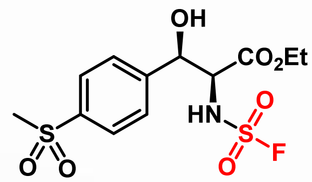

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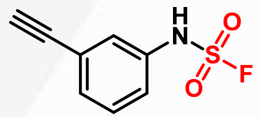
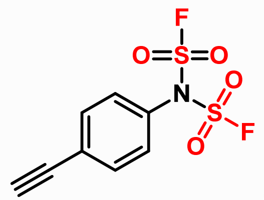
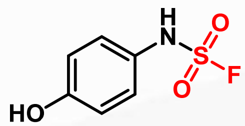


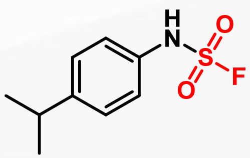
88%



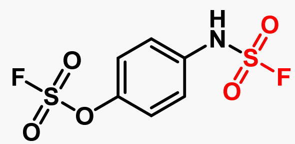
72%



91%



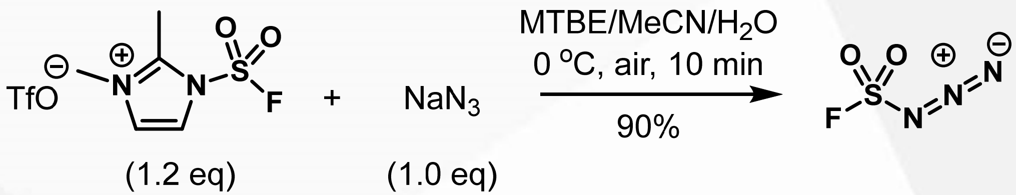
88%



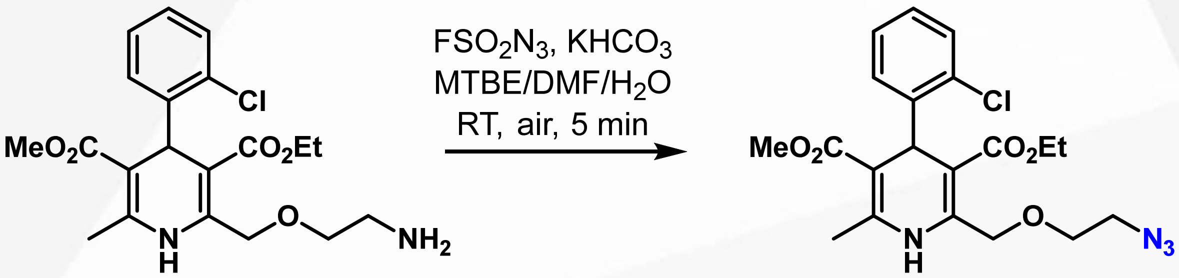
74%

Fluorosulfuryl Imidazolium Salt

Preparation of fluorosulfuryl azide



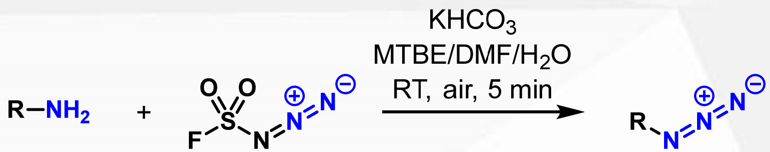
Diazotransfer Reaction

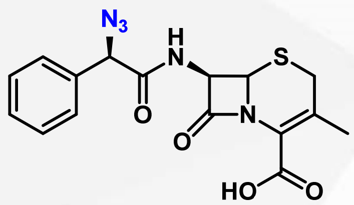


1 mmol: 95% conversion
10 mmol: >99% conversion

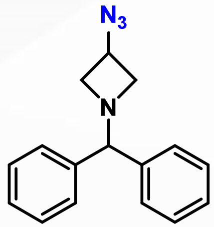
Sharpless, K. B.*, Dong, J.* *Nature* **2019**, *574*, 86–89.

Fluorosulfuryl Imidazolium Salt

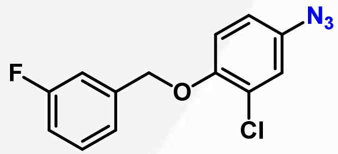




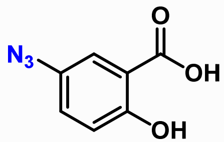
96%



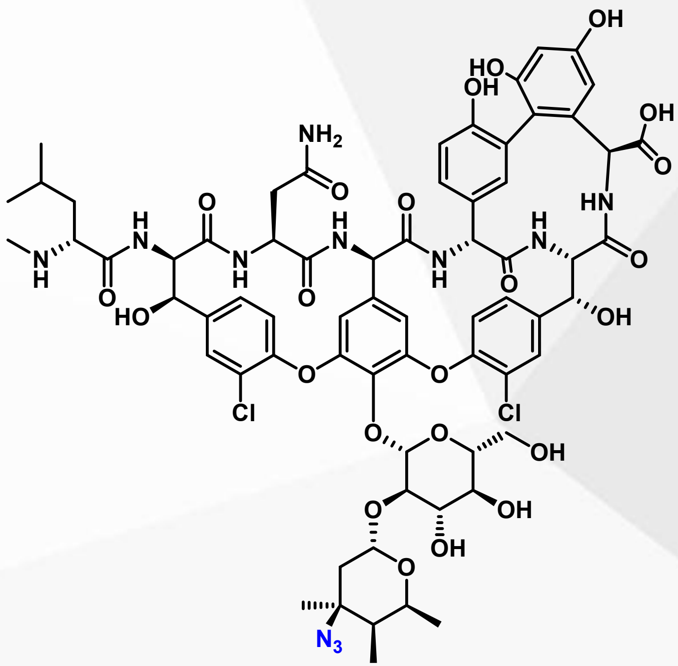
96%



98%



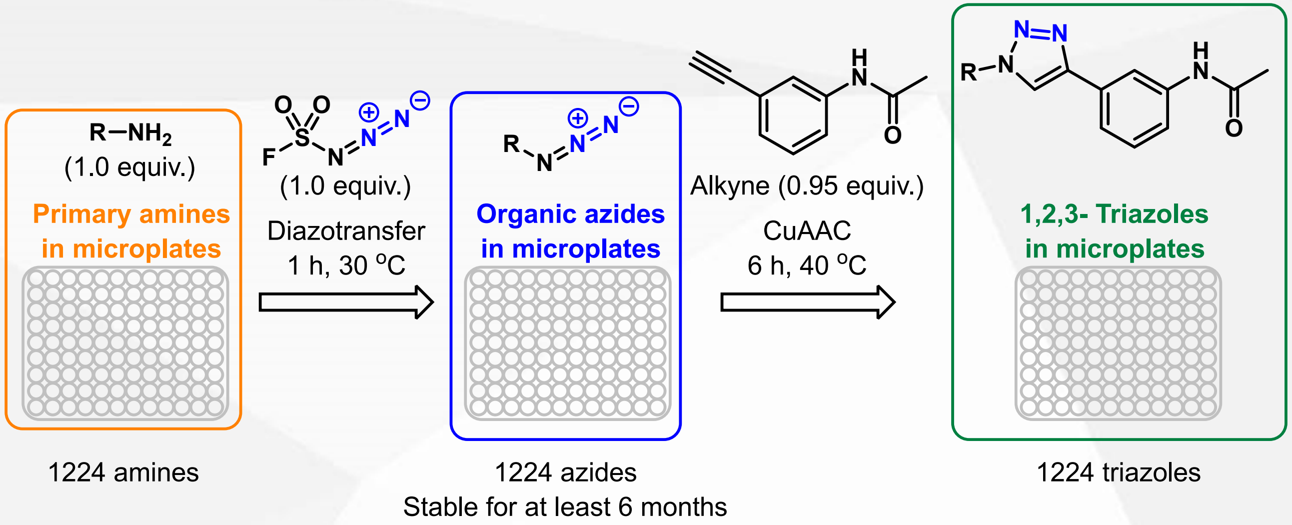
96%



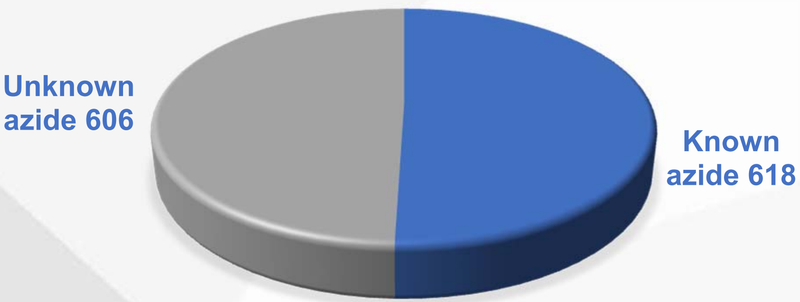
67%

2.2 F-SO_2^+ donor

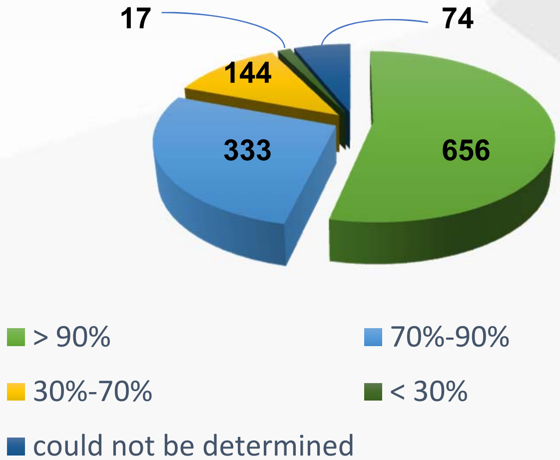
Fluorosulfuryl Imidazolium Salt



Azide library



Conversion of alkyne



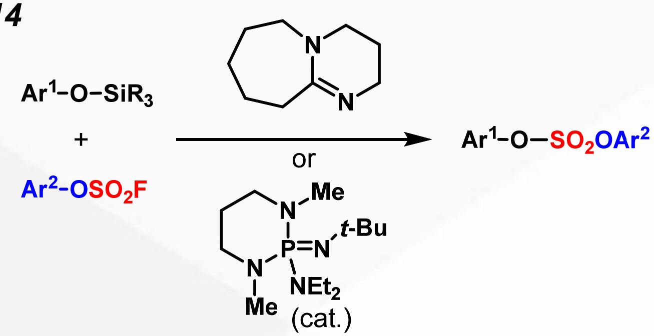
Preparation of Sulfates

Silicon as Mediator

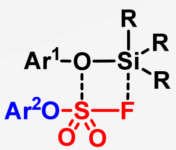
Previous works

$$ROSi(CH_3)_3 + C_6H_5SO_2F \xrightarrow[\text{1 d to 4 wks}]{Et_4NF} ROSO_2C_6H_5$$

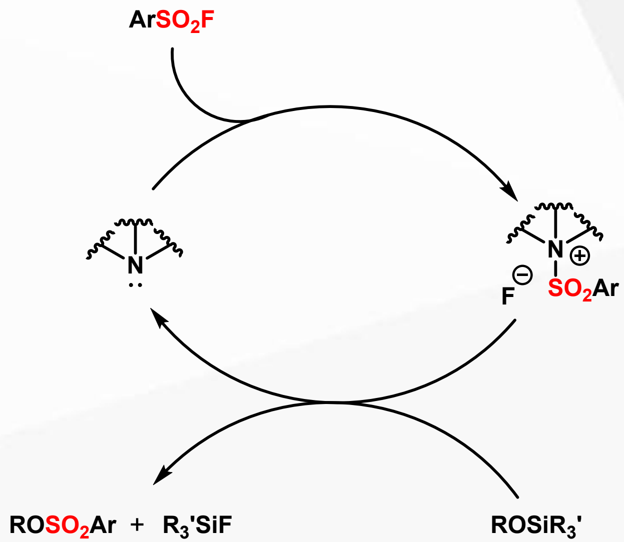
Sharpless 2014



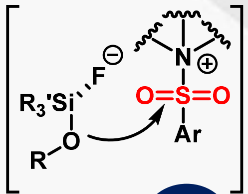
$SiR_3 = SiMe_3$ (< 4 h, RT);
$SiR_3 = SiMe_2tBu$ (4-18 h, RT to 80 °C)



	Bond Strength (KJ/mol)	Bond Length (pm)
H-H	432	74
C-C	346	154
Si-O	**452**	**163**
Si-F	**565**	**160**



Ar = p-MeC_6H_4

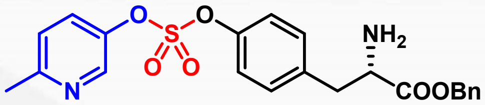


Hall, H. K. J.* *J. Organomet. Chem.* **1976**, *116*, 153-159.

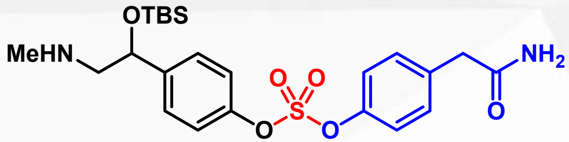
Sharpless, K. B.* *Angew. Chem. Int. Ed.* **2014**, *53*, 2-21.

Levacher, V.* *Synlett* **2007**, 381.

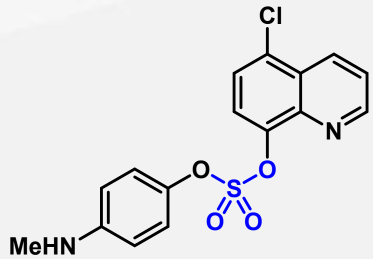
2.3 Fluorosulfates & Sulfonyl Fluorides



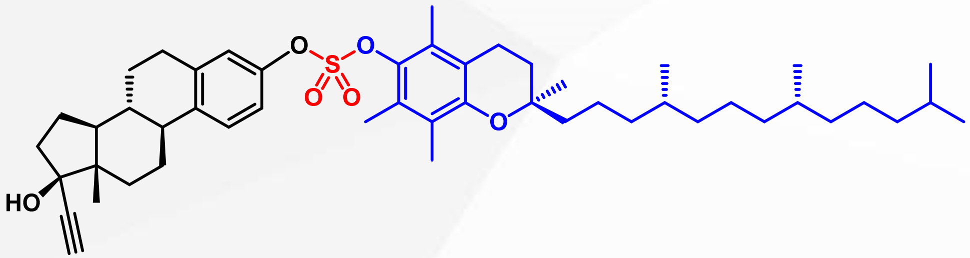
83%



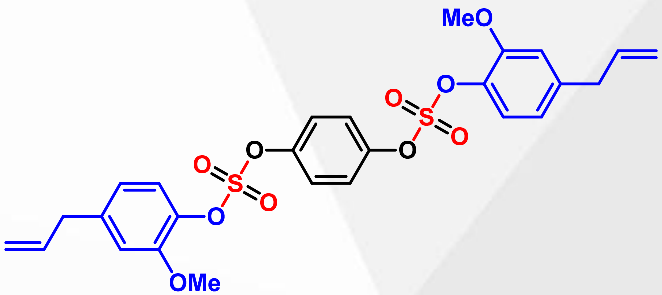
75%



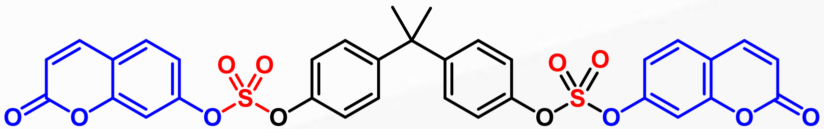
61%



98%



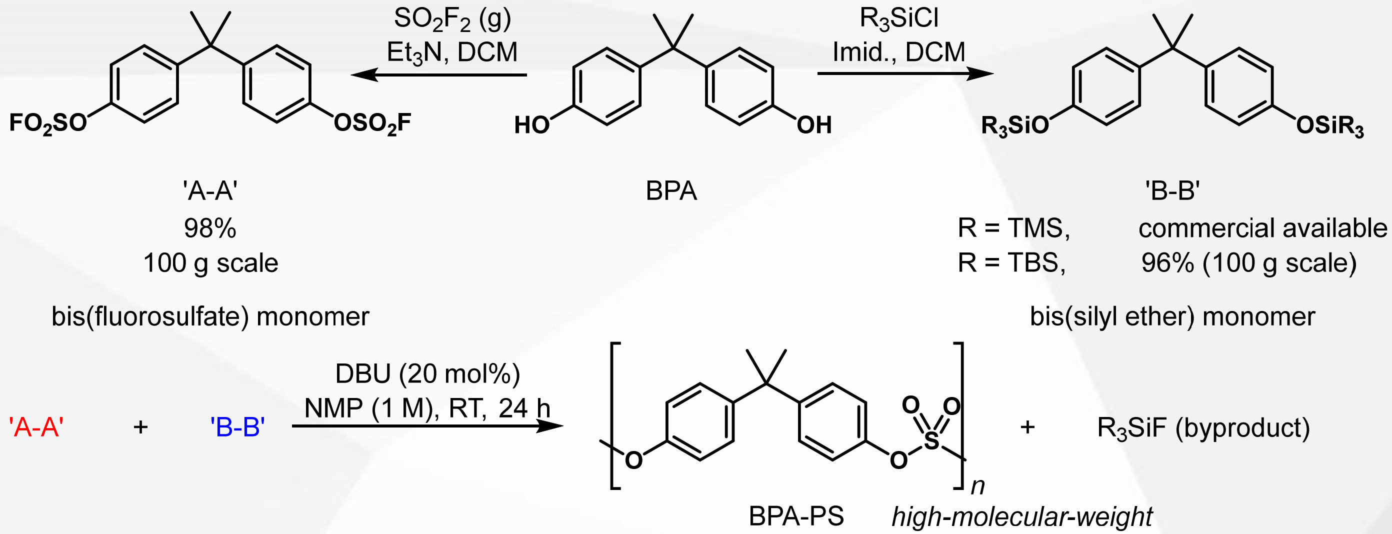
92%



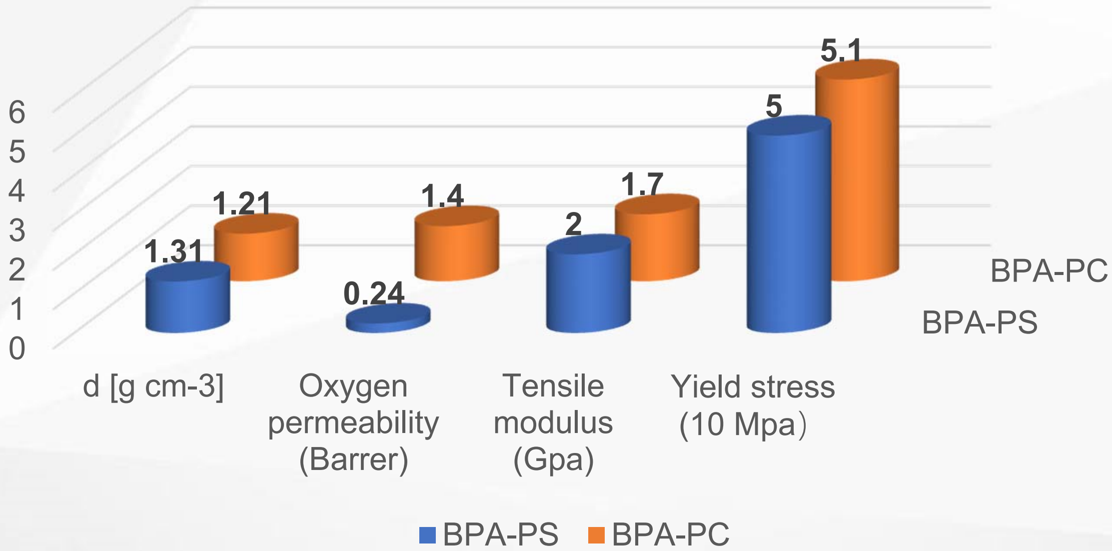
75%

Preparation of Polysulfates

Lewis base-catalyzed

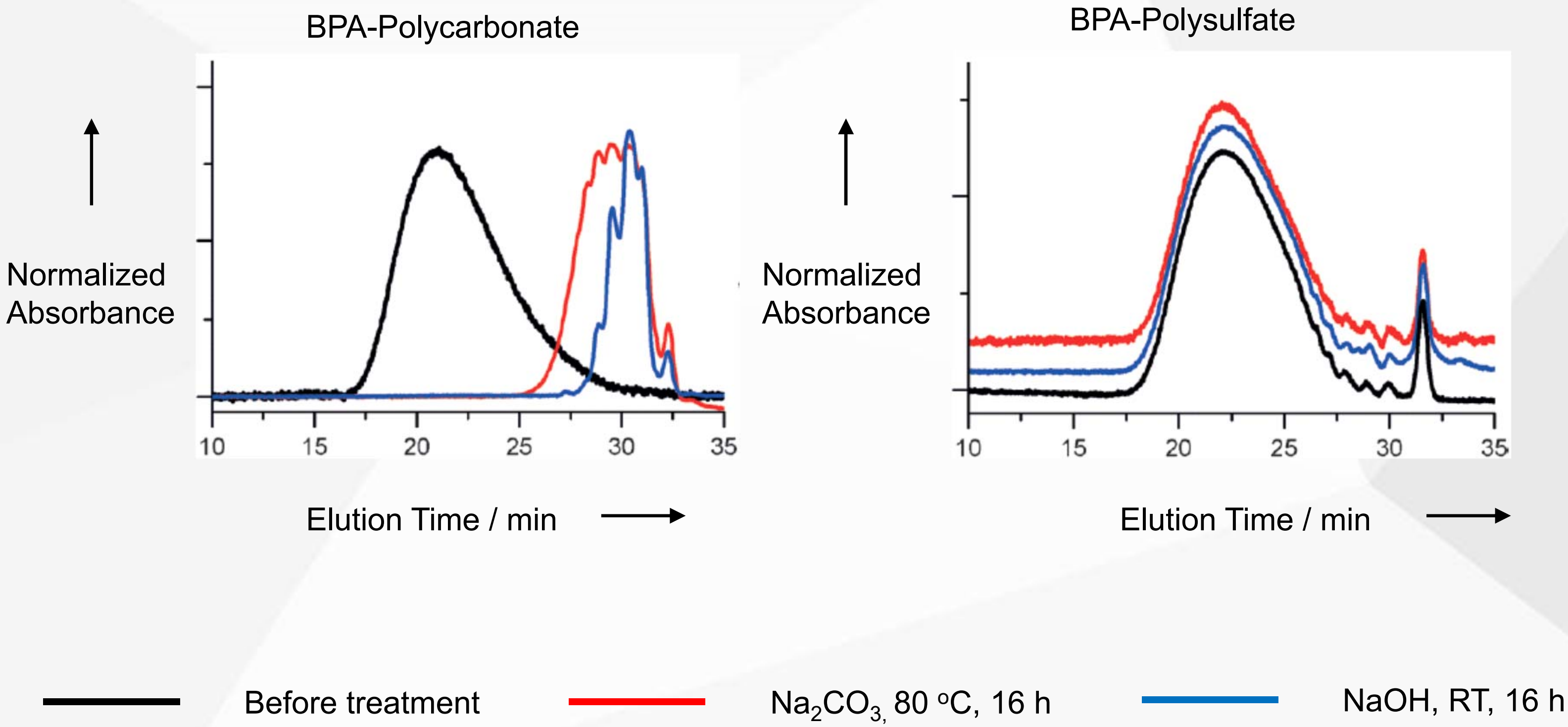


Average measured properties



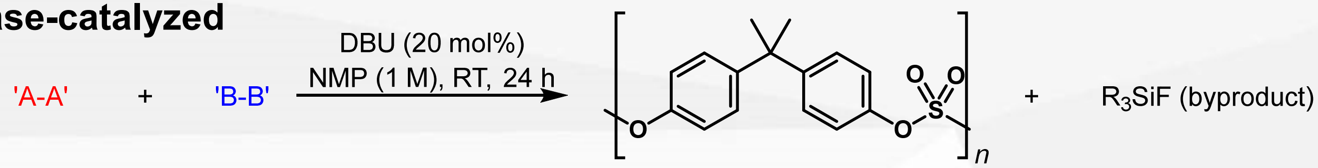
Sharpless, K. B.*; Fokin, V. V.* *Angew. Chem. Int. Ed.* **2014**, *53*, 9466 –9470.

Hydrolytic stability of polysulfate

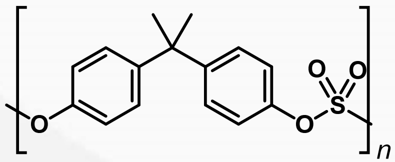


Preparation of Polysulfates

Lewis base-catalyzed

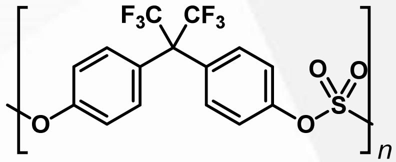


BPA-PS

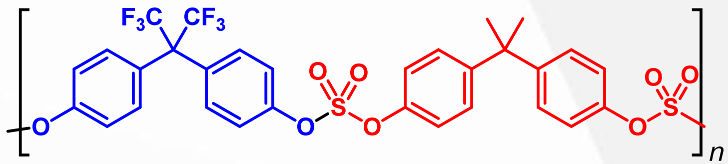


R = TMS, M_n^{ps} = 30.9 kDa, PDI = 1.6

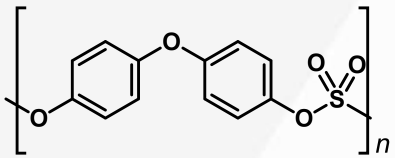
R = TBS, M_n^{ps} = 24.6 kDa, PDI = 1.4



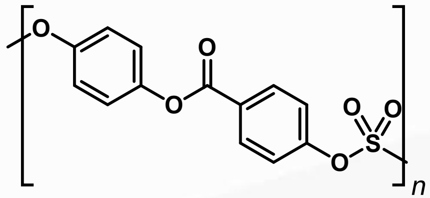
R = TMS, M_n^{ps} = 46.1 kDa, PDI = 1.5



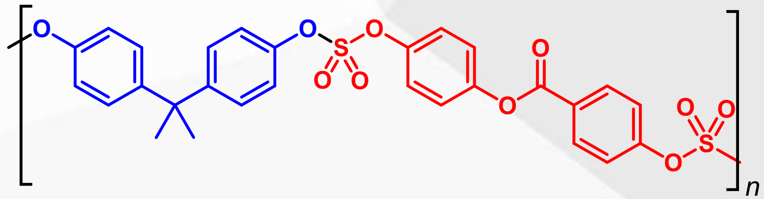
R = TMS, M_n^{ps} = 36.0 kDa, PDI = 1.4



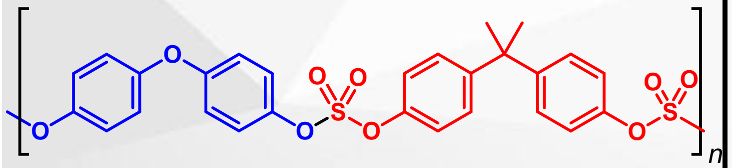
R = TBS, M_n^{ps} = 58.7 kDa, PDI = 1.5



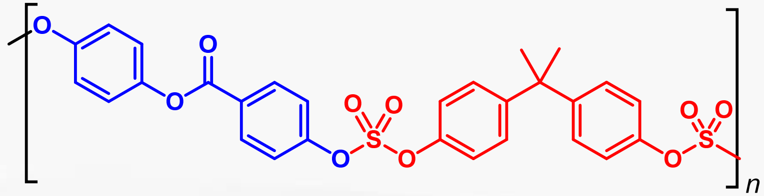
R = TBS, M_n^{ps} = 46.1 kDa, PDI = 1.5



R = TBS, M_n^{ps} = 30.6 kDa, PDI = 1.5



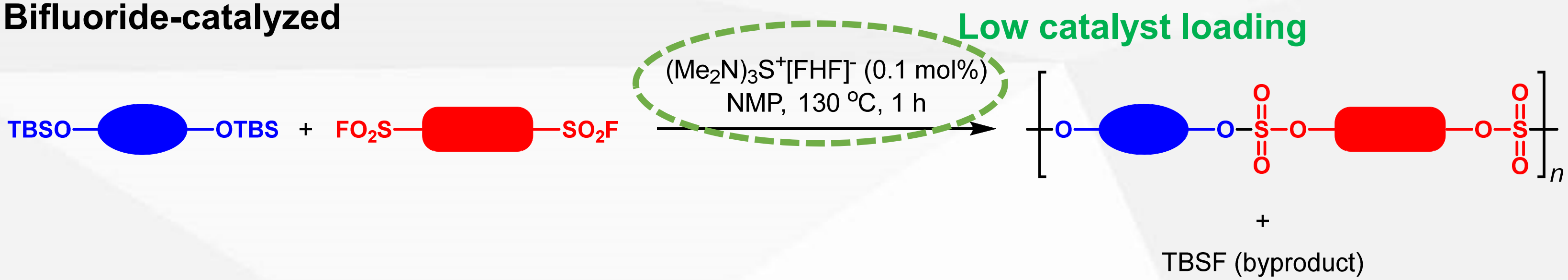
R = TBS, M_n^{ps} = 67.1 kDa, PDI = 1.4

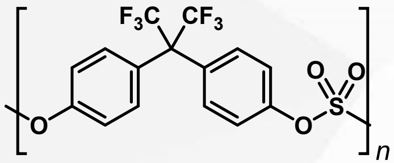


R = TBS, M_n^{ps} = 37.2 kDa, PDI = 1.5

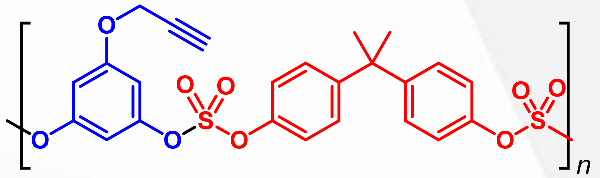
Preparation of Polysulfates

Bifluoride-catalyzed

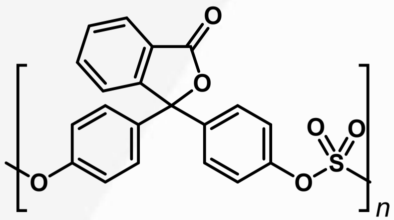




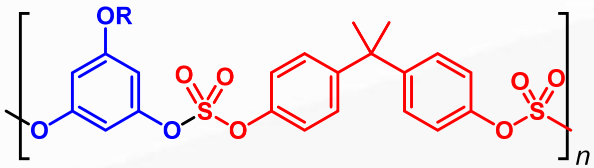
M_n^{ps} = 84 kDa, PDI = 1.6



M_n^{ps} = 16 kDa, PDI = 1.3



M_n^{ps} = 37 kDa, PDI = 1.6



1) BBr_3, DCM
2) SO_2F_2 (g), Et_3N
CH_2Cl_2

(R = Me)
M_n^{ps} = 33 kDa, PDI = 1.5

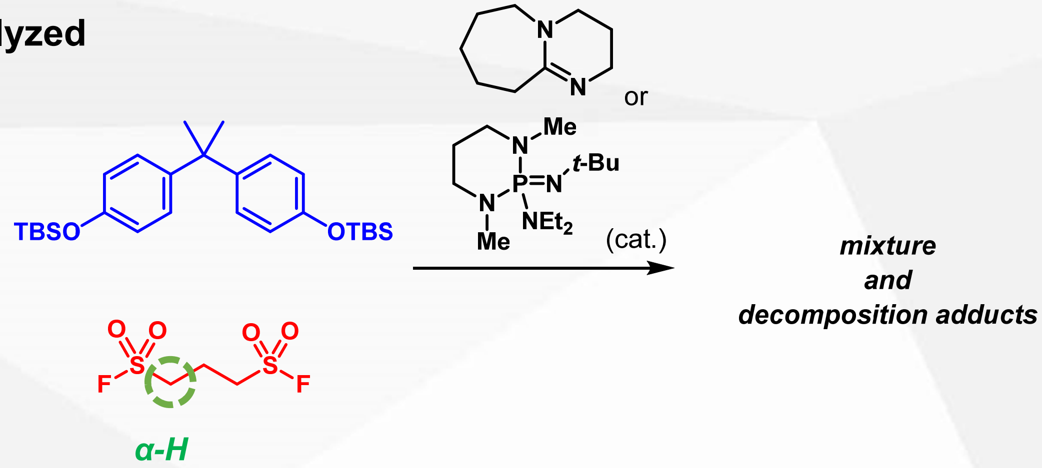
(R = SO_2F)
M_n^{ps} = 38 kDa, PDI = 1.9

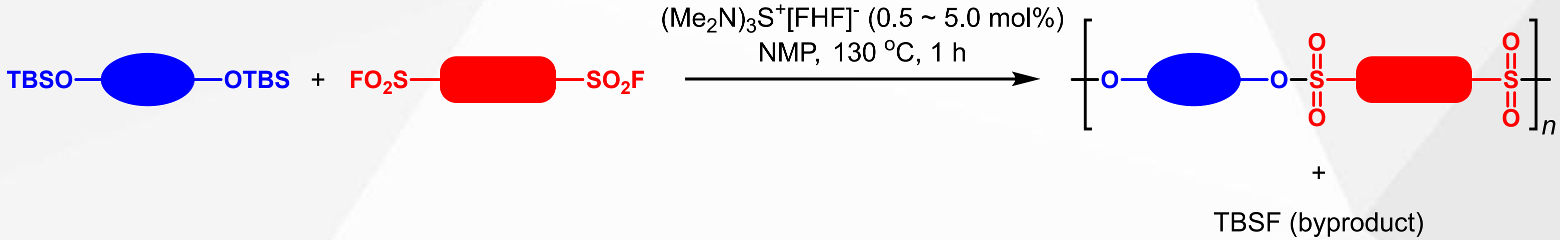
Dong, J.*; Wu, P.*; Sharpless, K. B.* *Nat. Chem.* **2017**, *9*, 1083-1088.

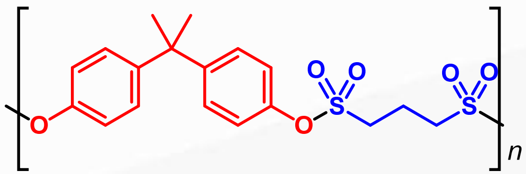
Preparation of Polysulfates

Lewis base-catalyzed

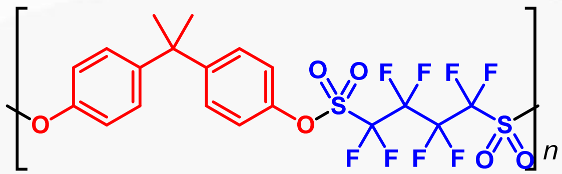
Previous work:







M_n^{ps} = 23 kDa, PDI = 1.3

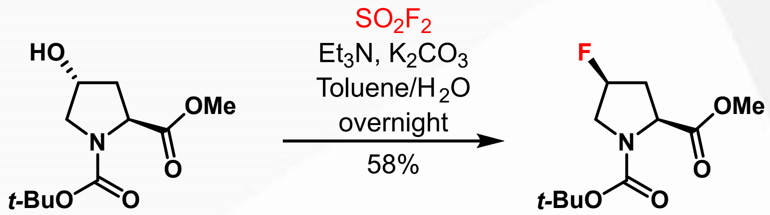


M_n^{ps} = 23 kDa, PDI = 1.3

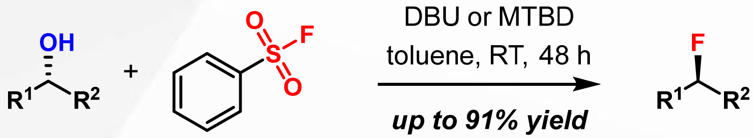
Functional Reagents

Deoxyfluorination reagent

Central Glass 2014

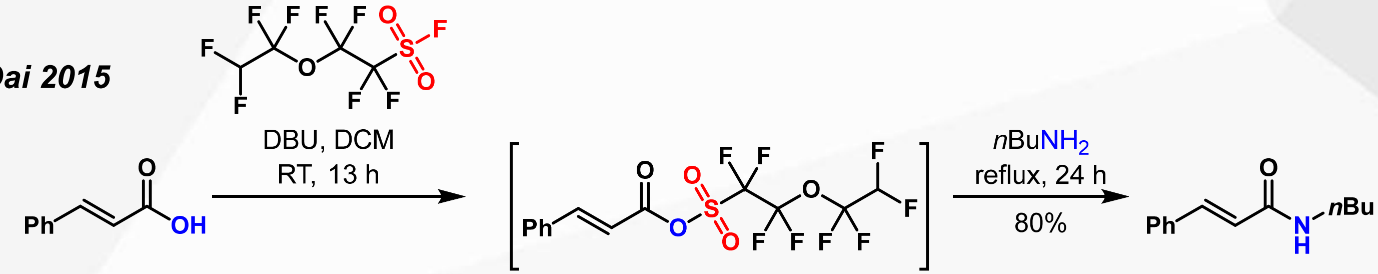


Doyle 2015



Coupling reagent

Dai 2015

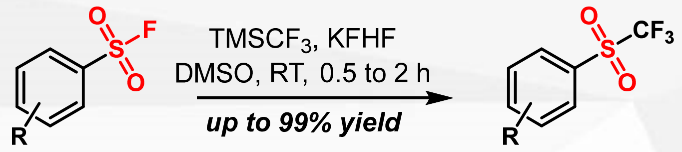


Central Glass Company, *US Pat.* 8835669B2, **2014**.

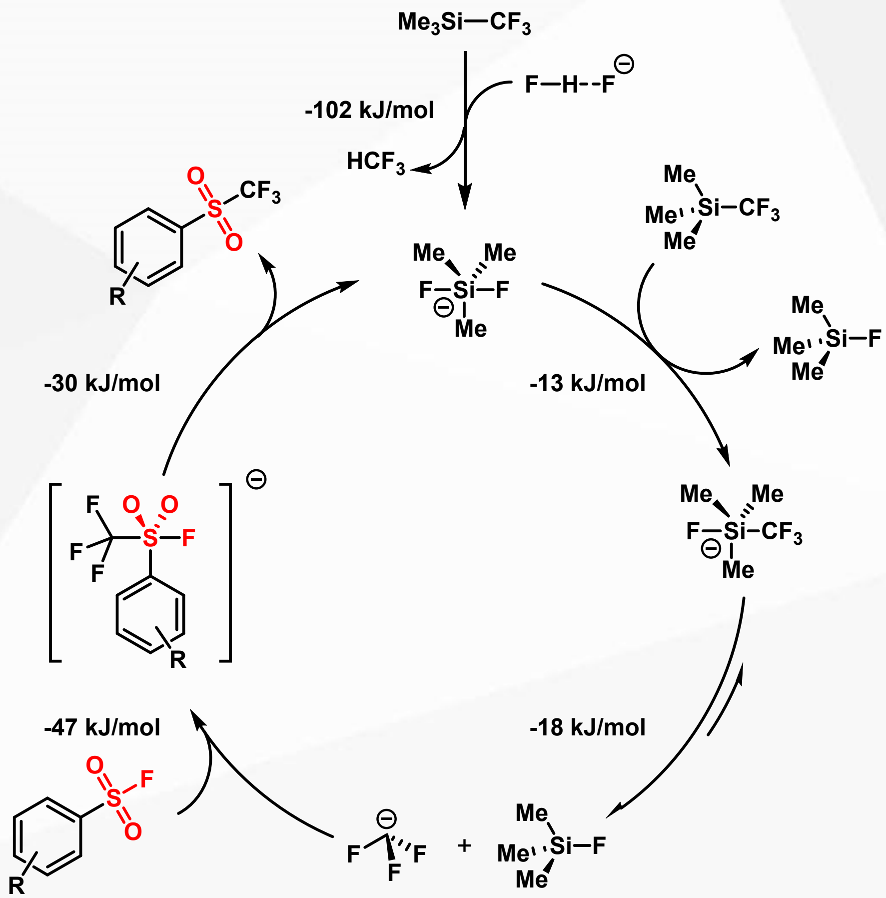
Doyle, A. G.* J. Am. Chem. Soc. **2015**, *137*, 9571-9574.

Dai, Y.* *Tetrahedron Lett.* **2009**, *50*, 2727-2729.

SuFEx Trifluoromethylation



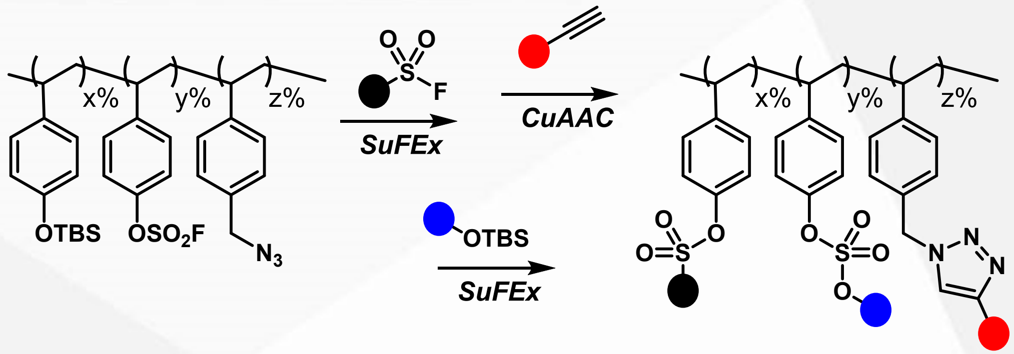
Moses 2019



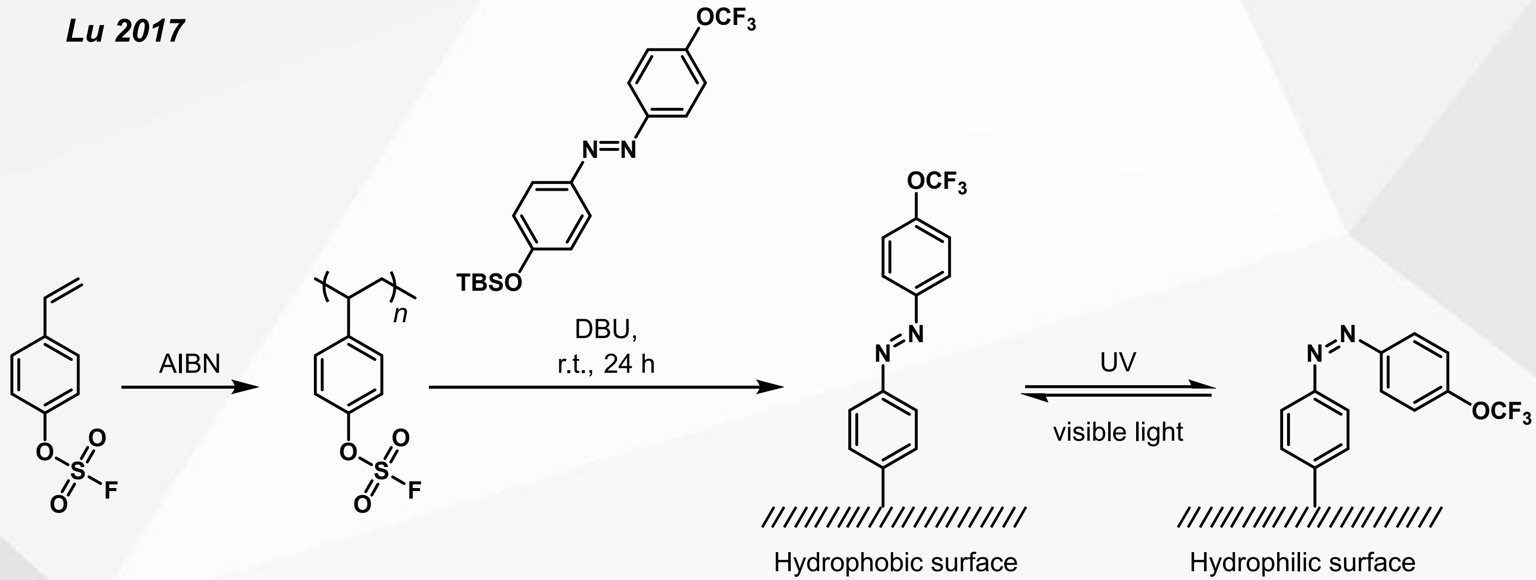
Moses, J. E.* *Angew. Chem. Int. Ed.* **2019**, *58*, 4552-4556.

Polymer modification

Fokin 2016



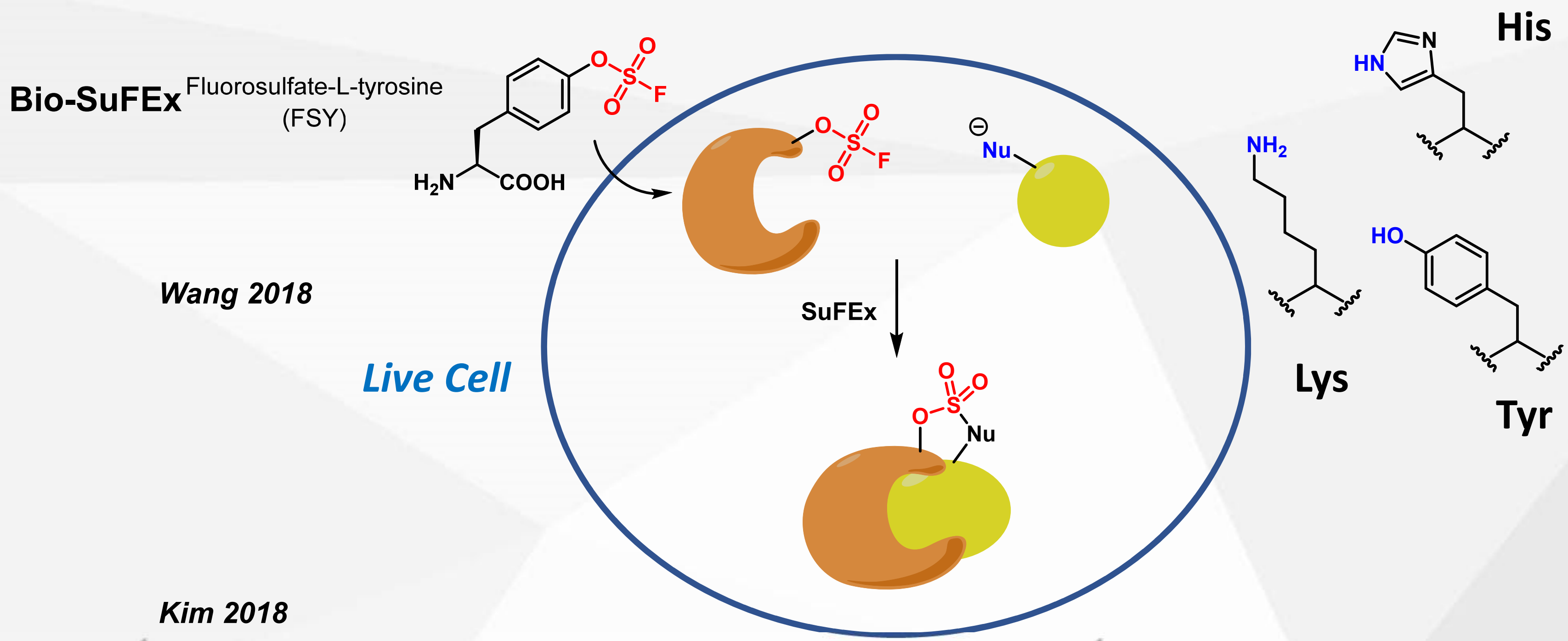
Lu 2017



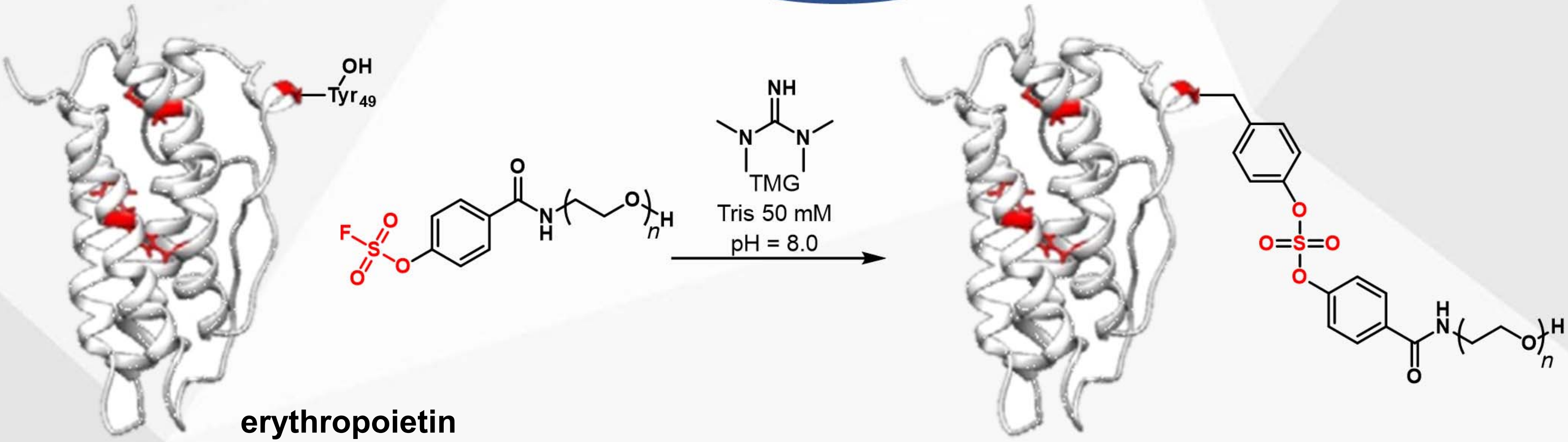
Fokin, V. V. * *Macromolecules*, **2016**, *49*, 4473-4479.

Lu, J. * *Chem. Eur. J.* **2017**, *23*, 14712-14717.

2.4 SuFEx based application



Kim 2018

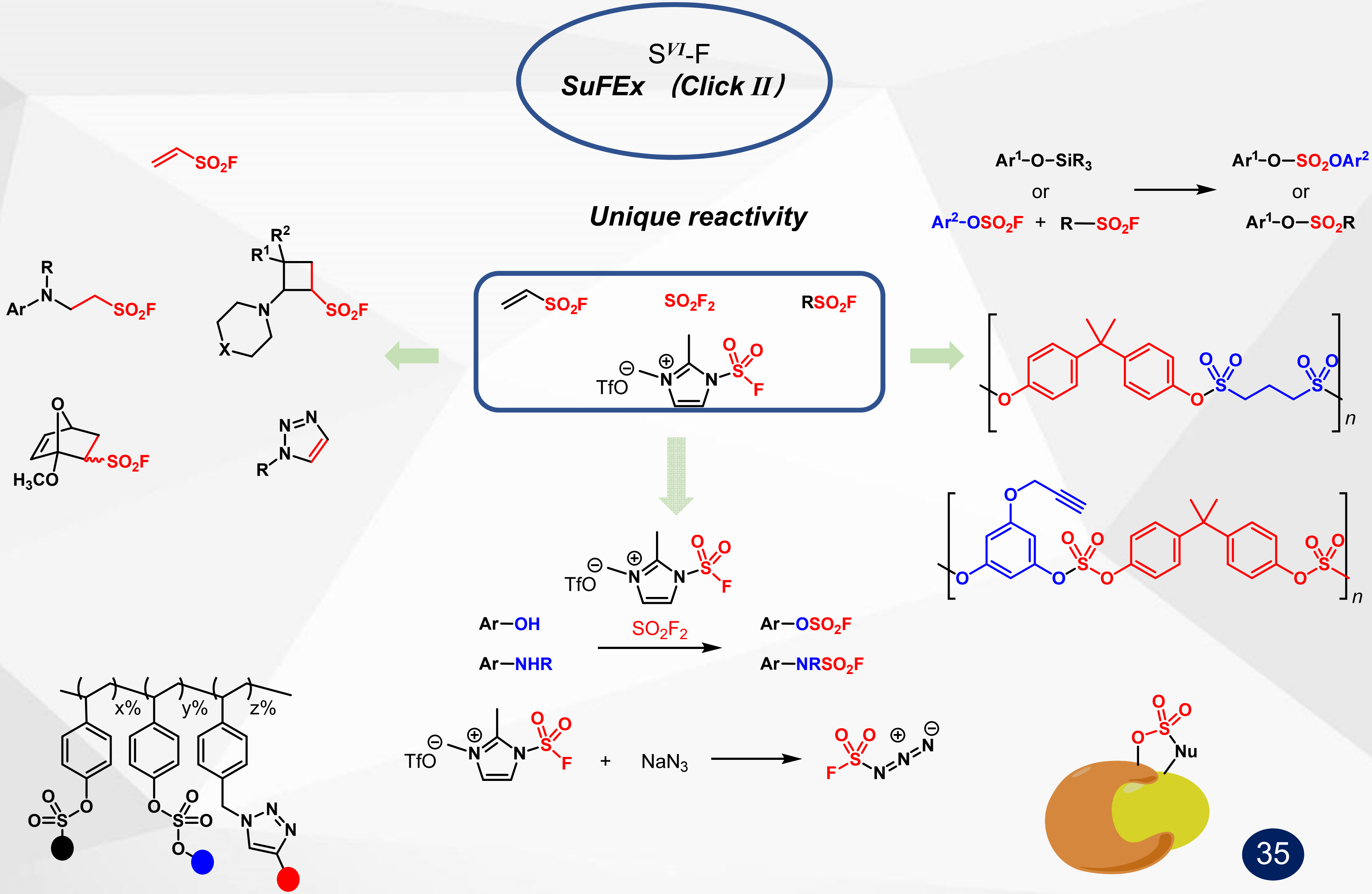


Wang, L.* *J. Am. Chem. Soc.* **2018**, *140*, 4995-4999.

Kim, B. M.* *Chem. Eur. J.* **2018**, *24*, 10948-10952.

Summary

Summary

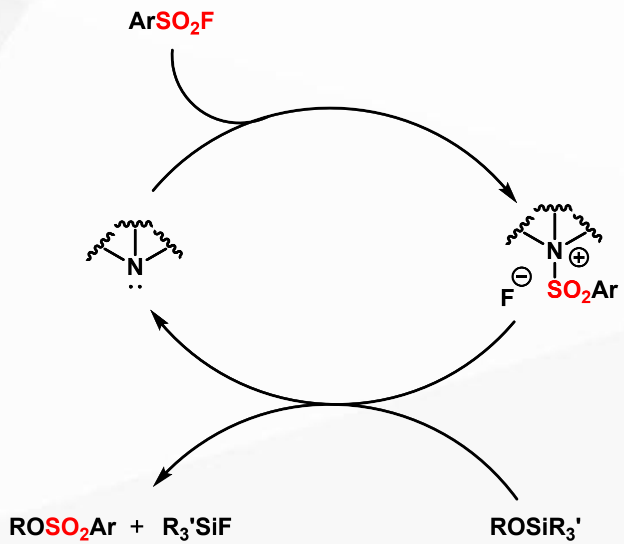


S^VI-F
SuFEx (Click II)
Unique reactivity
SO2F
SO2F2
RSO2F
TfO
Ar1-O-SiR3
or
Ar2-OSO2F + R—SO2F
Ar1-O—SO2OAr2
or
Ar1-O—SO2R
Ar—OH
Ar—NHR
SO2F2
Ar—OSO2F
Ar—NRSO2F
NaN3
x%
y%
z%
H3CO
Nu
n

Challenge:

A deeper understanding of the finer details of SuFEx catalysis will hopefully

Etc.



Thanks for your attention~