Literature Report 7

Asymmetric silver-catalysed intermolecular bromotrifluoromethoxylation of alkenes with a new trifluoromethoxylation reagent

Reporter: **Huan-Ping Xie**

Checker: **Xiao-Yong Zhai**

Date: **2018/09/17**

Guo, S.; Cong, F.; Guo, R.; Wang, L.; Tang, P. *Nat. Chem*. **2017**, *9*, 546.

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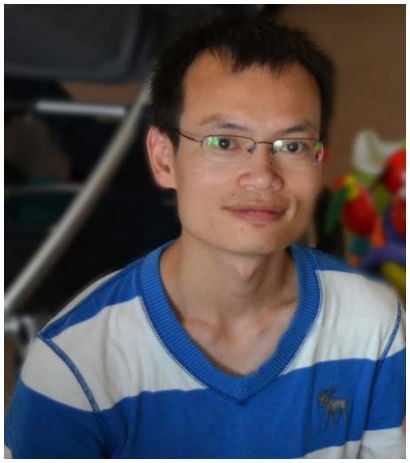
Biography



Pingping Tang

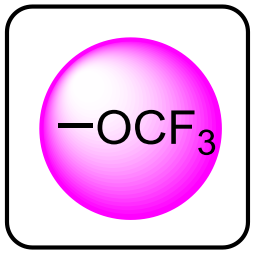
Areas of interest:

- **Total synthesis of bioactive natural product and methodology development**
- **Fluorination chemistry**

Research experience:

- **2012 - Present** Professor, Nankai University.
- **2008 - 2012** Postdoctoral associate, Harvard University (Prof. Tobias Ritter);
- **2007 - 2008** Assistant researcher, SIOC;
- **2002 - 2007** Ph.D., SIOC. (Prof. Biao Yu);
- **1998 - 2002** B.S., Nankai University;

Introduction



- Strong Electron-Withdrawing Effect
- High Lipophilicity

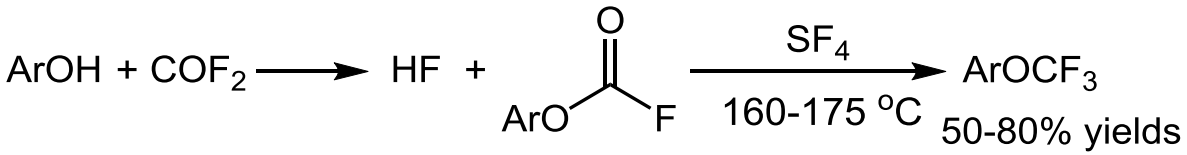
OCF_3 (1.04) > CF_3 (0.88) > CH_3 (0.52) > OCH_3 (-0.02)

Challenges:

- Reversible decomposition of trifluoromethoxide anion
- β-Fluoride elimination from transition-metal–trifluoromethoxide complexes

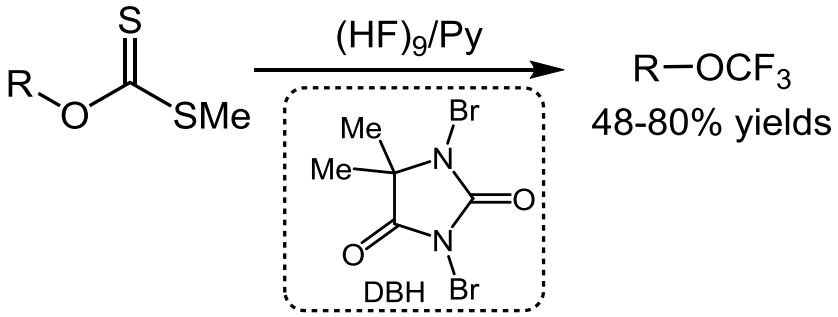
Introduction

- **Deoxyfluorination of fluoroformates**



Sheppard, W. *et al. J. Org. Chem*. **1964**, *29*, 1.

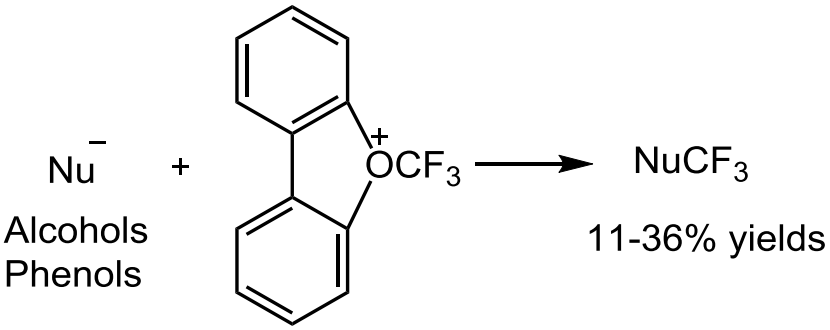
- **Oxidative Desulfurization-Fluorination**



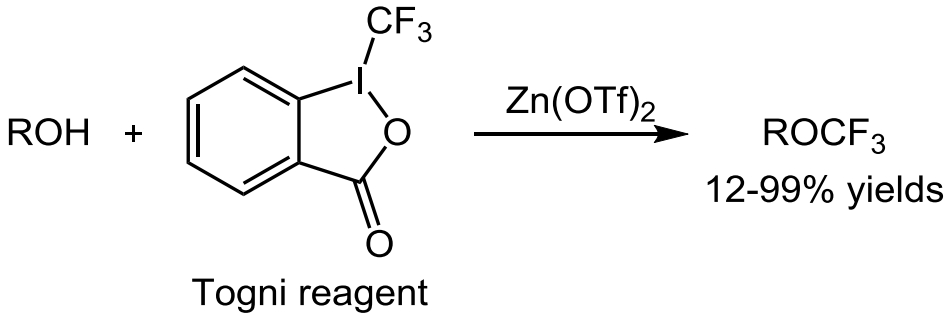
Hiyama, T. *et al. Tetrahedron Lett*. **1992**, *33*, 4173.

Introduction

- **Electrophilic trifluoromethylation of hydroxyl groups**

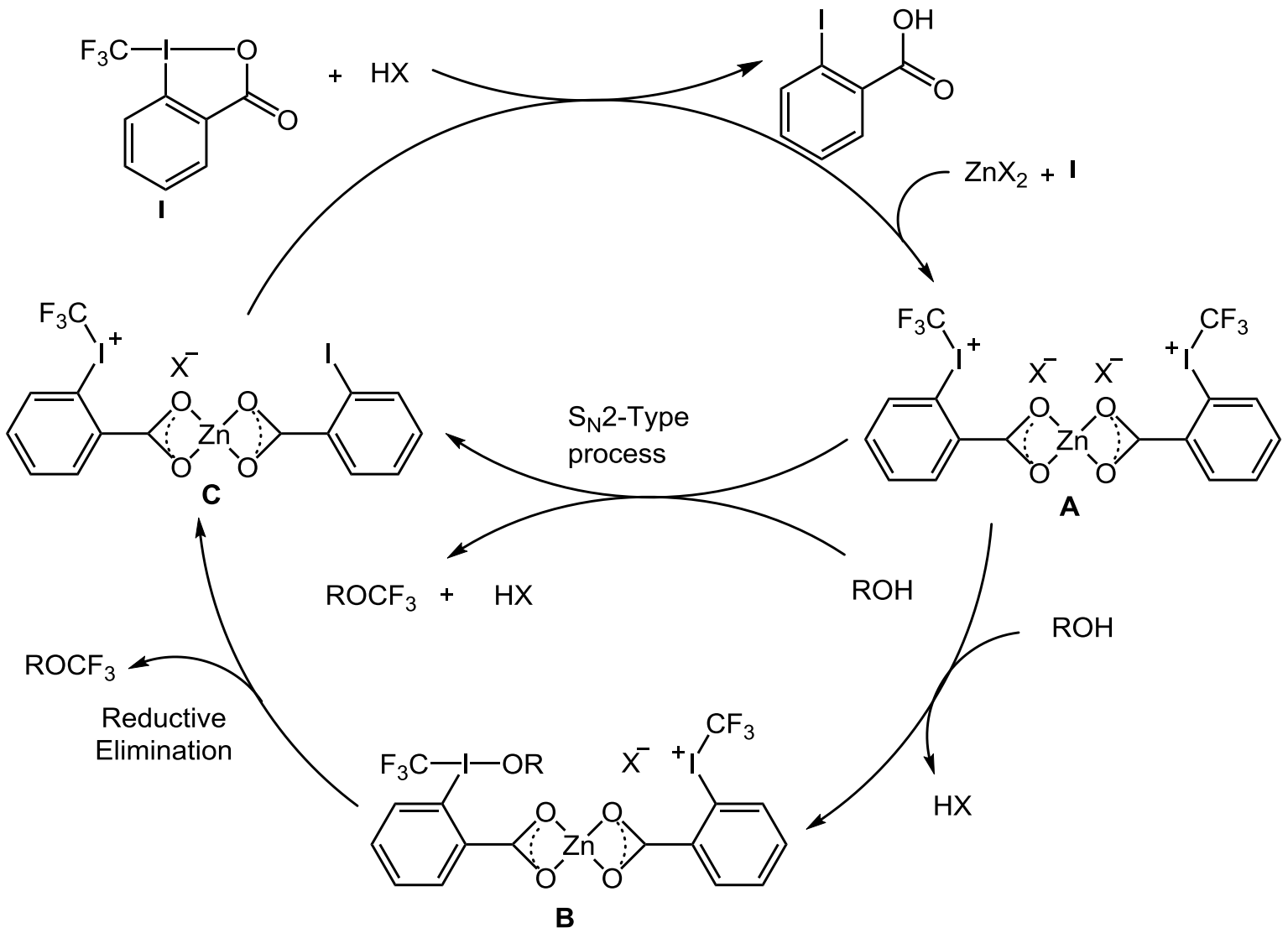


Umemoto, T. *et al. J. Org. Chem.* **2007**, *72*, 6905.



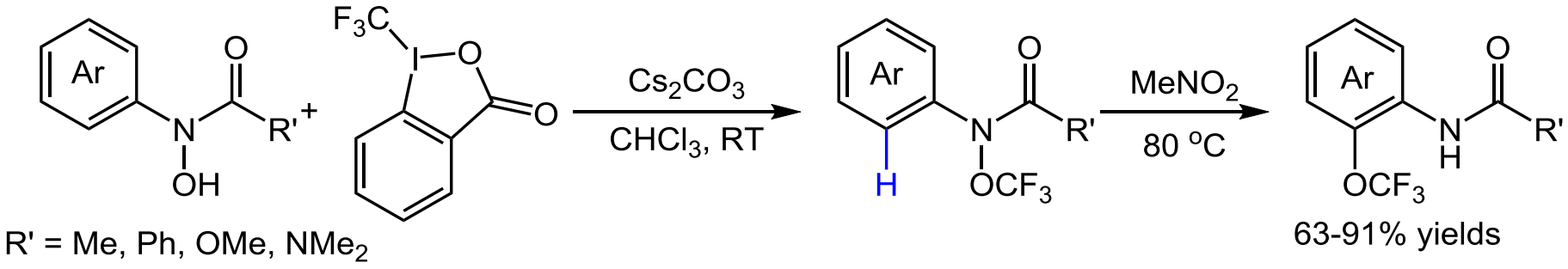
Togni, A. *et al. Angew. Chem. Int. Ed*. **2009**, *48*, 4332.

Introduction



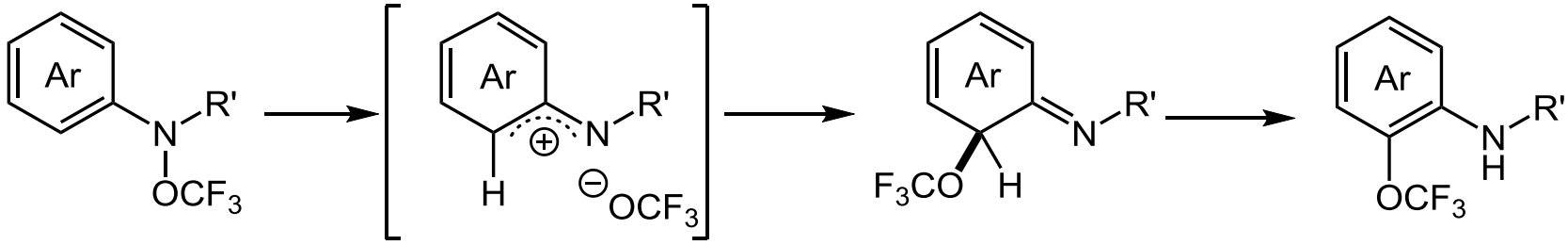
Introduction

- **OCF_3 Migration**



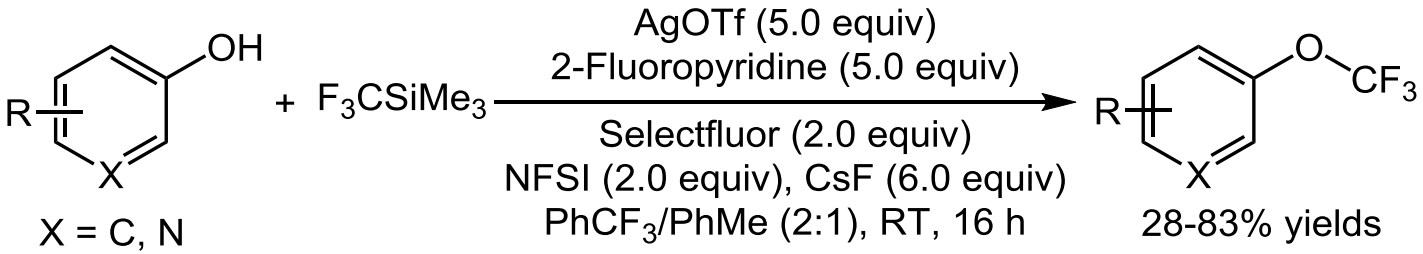
Ngai, M.-Y. *et al. Angew. Chem. Int. Ed*. **2014**, *53*, 14559.

Mechanism: (ion-pair formation)



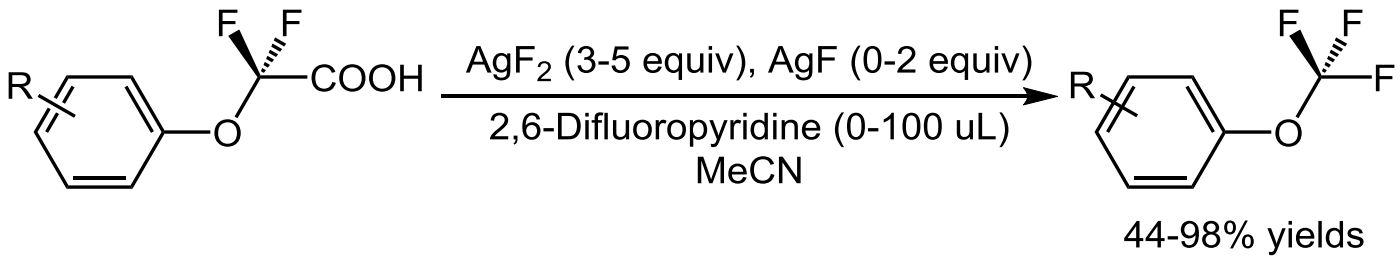
Introduction

- **Oxidative Trifluoromethylation**



Qing, F. *et al. Angew. Chem. Int. Ed*. **2015**, *54*, 11839.

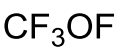
- **Fluorodecarboxylation**



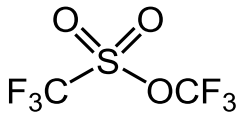
Hartwig, J. F. *et al. Angew. Chem. Int. Ed*. **2016**, *55*, 9758.

Introduction

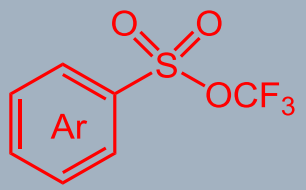
Trifluoromethoxylation reagents:



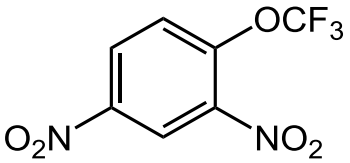
FMT (1948)
Gas, toxic



TFMT (1965)
Volatile liquid, expensive



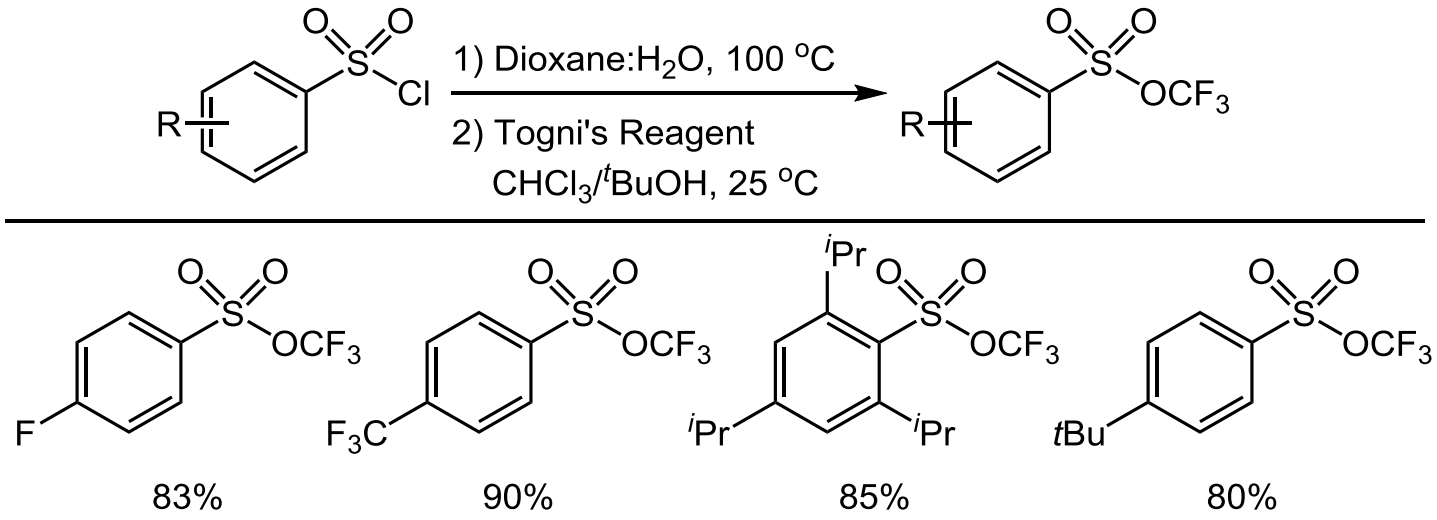
TFMS (2009)
Easily prepared
thermally stable



DNTFB (2010)
Low reactivity

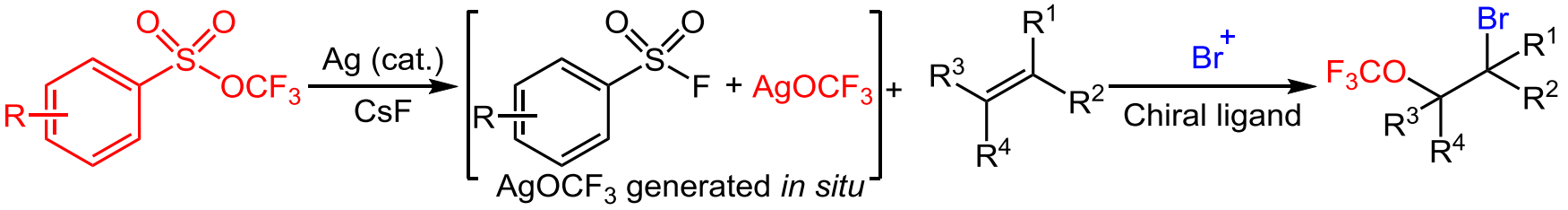
Tang, P. *et al. Nat. Chem*. **2017**, *9*, 546.

Preparation of Trifluoromethyl Arylsulfonate



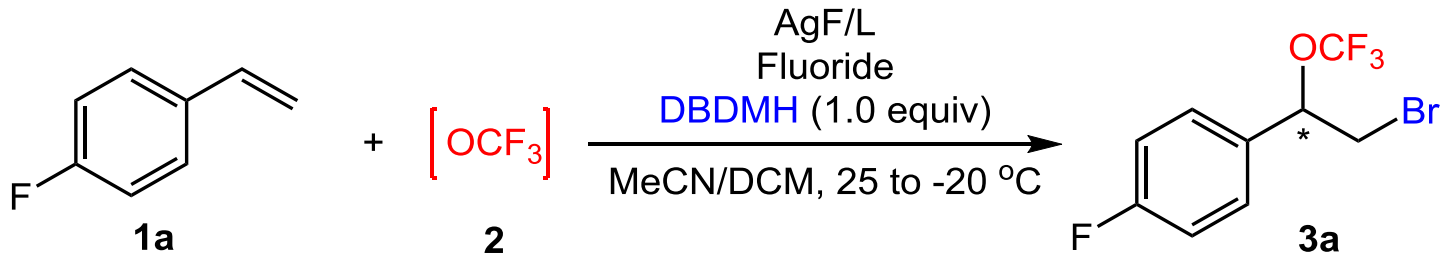
Togni, A. *et al. Chem. Commun*. **2009**, *5993*.

Bromotrifluoromethoxylation of Alkenes



Tang, P. *et al. Nat. Chem*. **2017**, *9*, 546.

Reaction Optimization

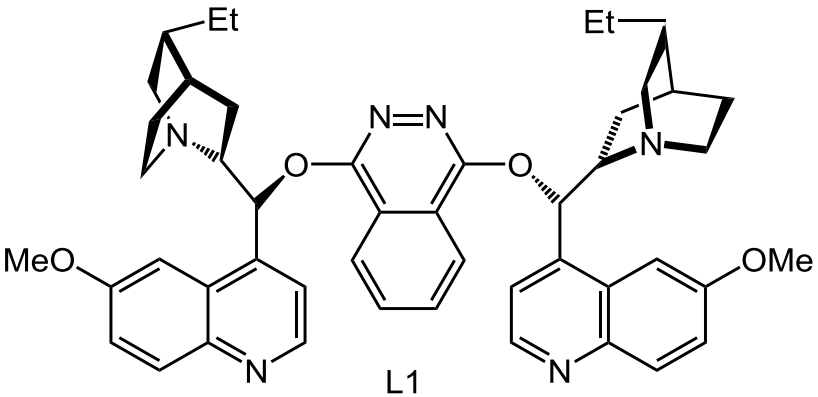


1a + [OCF$_3$] **2** → **3a**

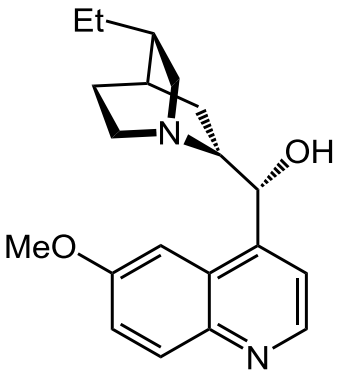
Entry[a]	[OCF$_3$]	Fluoride	L	Yield (**3a**, %)[b]	e.r.[c]
1	**2a**	NaF	L1	93	90:10
2	**2a**	KF	L1	98	91:9
3	**2a**	CsF	L1	98	91.5:8.5
4	**2b**	CsF	L1	97	90:10
5	**2c**	CsF	L1	75	91.5:8.5
6	**2d**	CsF	L1	94	90:10
7	**2a**	CsF	L2	70	22.5:77.5
8	**2a**	CsF	L3	54	52:48
9	**2a**	CsF	L4	0	--

[a] Reaction conditions: styrene **1a** (1.0 equiv.), **2** (3.0 equiv.), AgF (30 mol%), chiral ligand (10 mol%), DBDMH (1.0 equiv.), fluoride ion (2.0 equiv.), 2:1 (v:v) MeCN/DCM, N_2 atmosphere, 25 to −20 °C. [b] Yields were determined by ^{19}F NMR with benzotrifluoride as a standard. [c] The enantiomeric ratios (e.r.) were determined by chiral GC analysis.

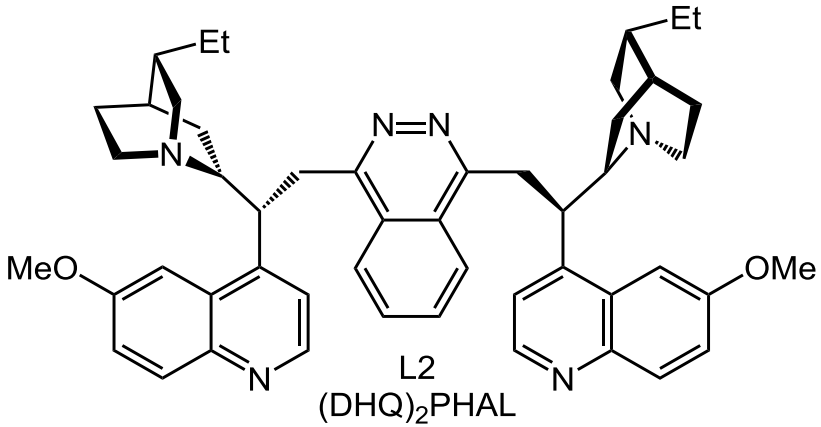
Reaction Optimization



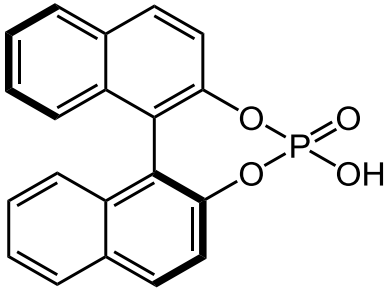
L1
$(DHQD)_2PHAL$



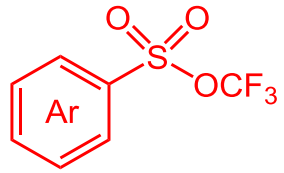
L3



L2
$(DHQ)_2PHAL$

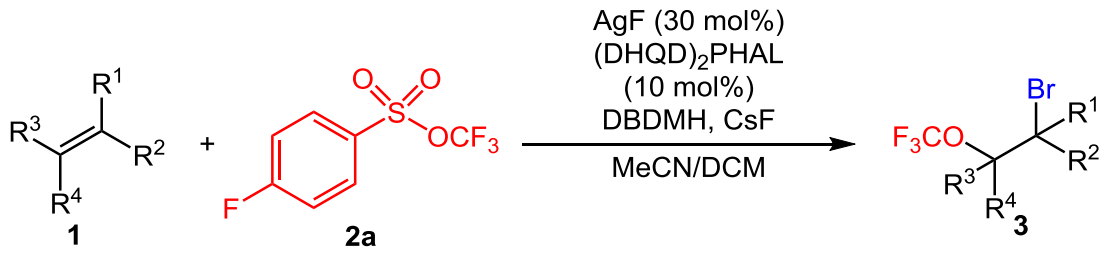


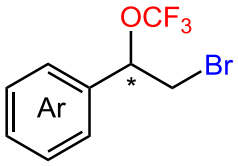
L4



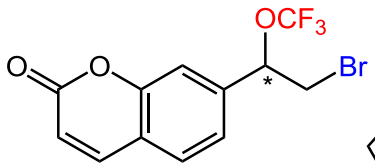
2a Ar = 4-FC_6H_4
2b Ar = C_6H_5
2c Ar = 4-$F_3CC_6H_4$
2d Ar = 2,4,6-$^{i}Pr_3C_6H_2$

Substrate Scope

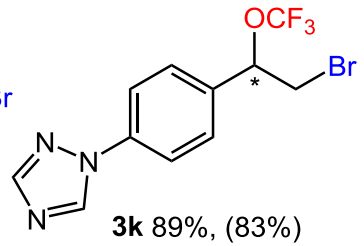




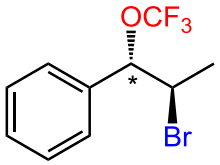
3a Ar = 4-FC_6H_4 83%, (78%)
3b Ar = 4-ClC_6H_4 94%, (84%)
3c Ar = 4-BrC_6H_4 79%, (92%)
3d Ar = 4-IC_6H_4 83%, (80%)
3e Ar = 4-$NO_2C_6H_4$ 59%, (67%)
3f Ar = 4-$F_3COC_6H_4$ 83%, (78%)
3g Ar = C_6H_5 75%, (67%)
3h Ar = 4-^{t}BuC_6H_4 77%, (37%)
3i Ar = Naphthyl 83%, (55%)



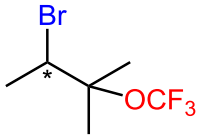
3j 94%, (66%)



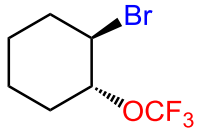
3k 89%, (83%)



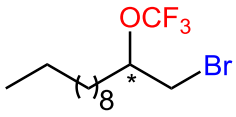
3o 90% (37%)
d.r. > 20:1



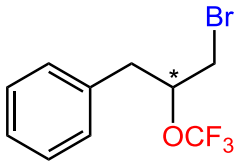
3p 84%



3q 88%

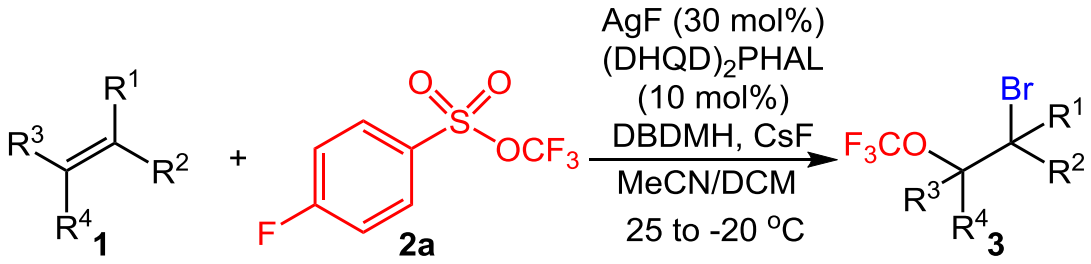


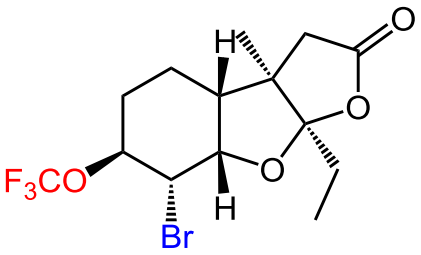
3r 52%, (10%)
r.r. = 4.3:1



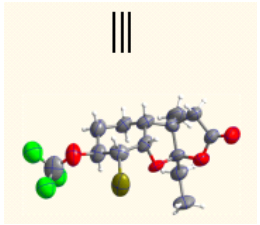
3s 82%, (36%)
r.r. = 5.8:1

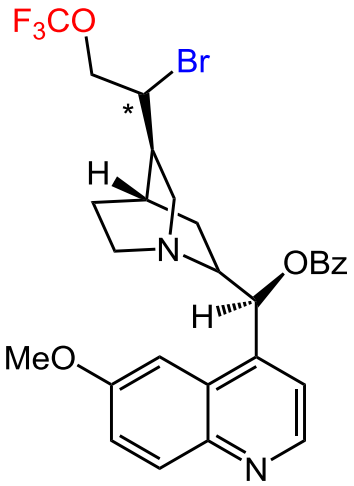
Substrate Scope-Complex Small Molecules



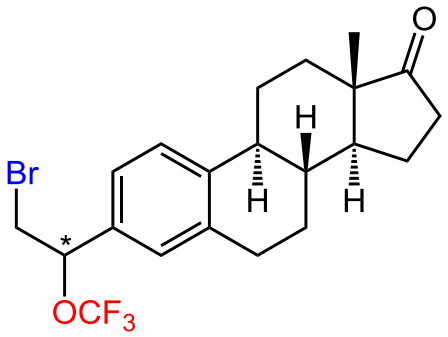


3t 72% yield
r.r. = 4.6:1
d.r. > 20:1



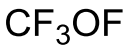


3u 42% yield
r.r. = 3.9:1
d.r. = 1.8:1

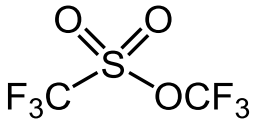


3v 70% yield
d.r. = 3.2:1

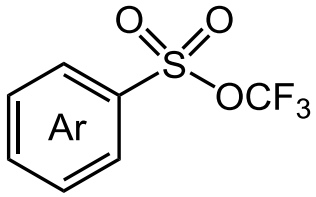
Introduction



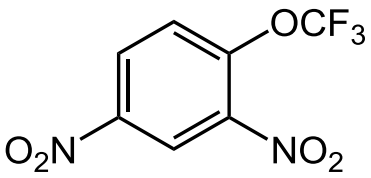
FMT (**1948**)
Gas, toxic



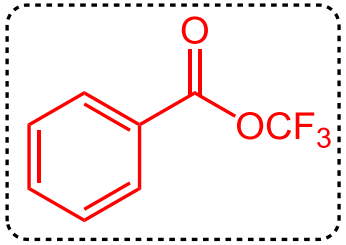
TFMT (**1965**)
Volatile liquid, expensive



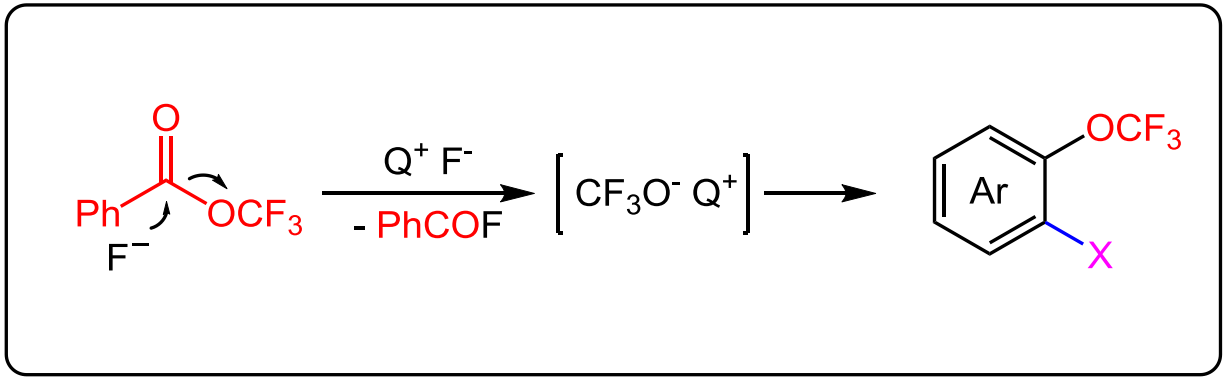
TFMS (**2009**)
Mini-scale



DNTFB (**2010**)
Low reactivity



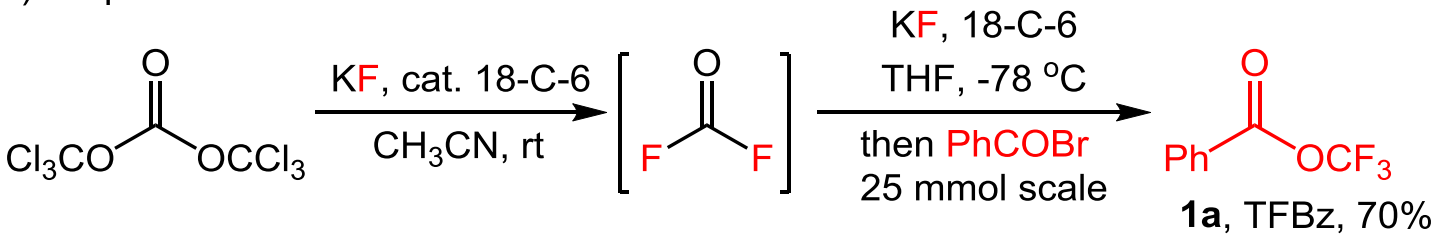
TFB_Z (**2018**)
This work



Hu, J. *et al. J. Am. Chem. Soc.* **2018**, *140*, 6801.

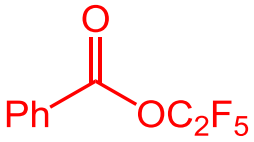
Preparation of TFBz

a) Preparation of TFBz

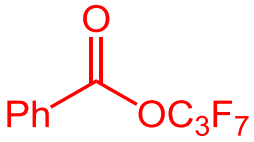


1a, TFBz, 70%

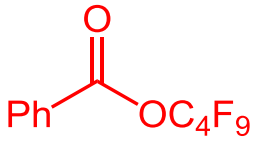
b) Other perfluoroalkyl benzoates prepared
(TBAT was used instead of KF/18-C-6)



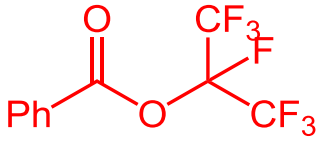
1b, 52%
from CF_3COF



1c, 57%
from C_2F_5COF

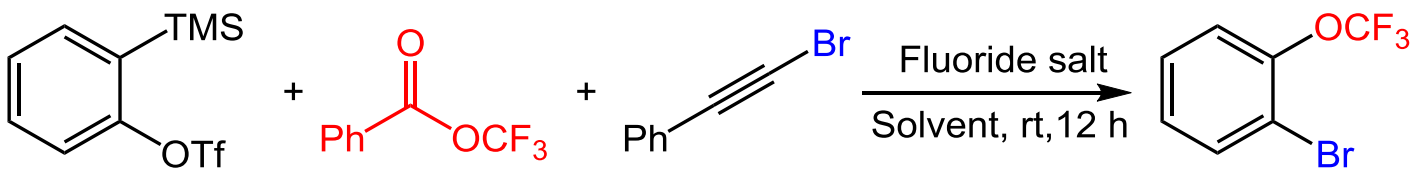


1d, 54%
from C_3F_7COF



1e, 81%
from $(CF_3)_2CO$

Reaction Optimization

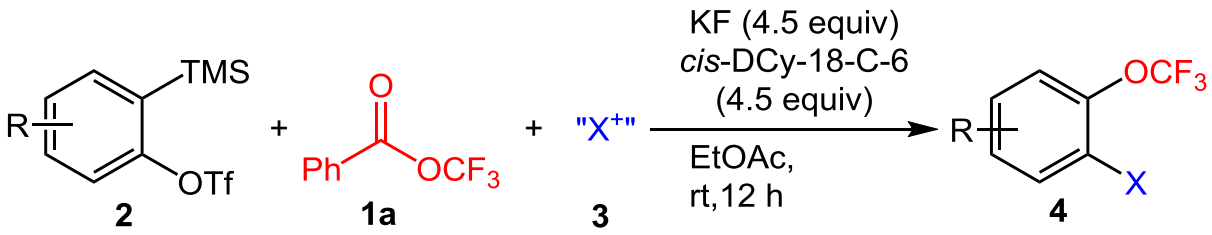


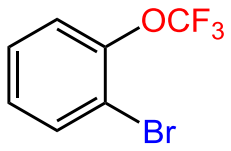
2a **1a** **3a** **4a**

Entry[a]	Fluoride salt	Solvent	Conv. (**2a**, %)[b]	Yield (**4a**, %)[b]
1	TASF	THF	100	0
2	TBAF	THF	19	0
3	KF/18-C-6	THF	100	49
4	KF/18-C-6	DME	100	51
5	KF/18-C-6	Diglyme	100	64
6	KF/18-C-6	EtOAc	100	67
7	KF/*cis*-Dcy-18-C-6	EtOAc	100	76
8[c]	KF/*cis*-Dcy-18-C-6	EtOAc	100	81

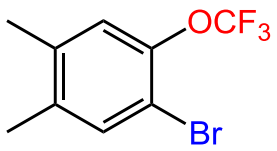
[a]Conditions: **2a** (0.05 mmol), **1a** (0.125 mmol), **3a** (0.2 mmol), fluoride salt (0.2 mmol), solvent (2.0 mL), rt, 12 h. [b]Yields and conversions were determined by ^{19}F NMR with $PhCF_3$ as internal standard. In all cases, the conversion of **1a** was 100%. [c]Optimized conditions: **2a** (0.05 mmol), **1a** (0.15 mmol), **3a** (0.2 mmol), KF (0.225 mmol), *cis*-DCy-18-C-6 (0.225 mmol), EtOAc (1.0 mL), rt, 12 h.

Substrate Scope

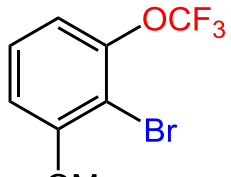




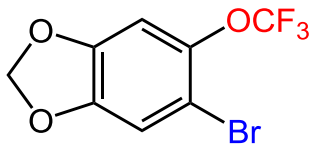
4a 77%



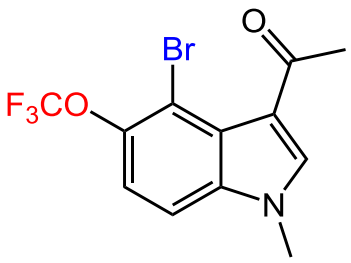
4b 84%



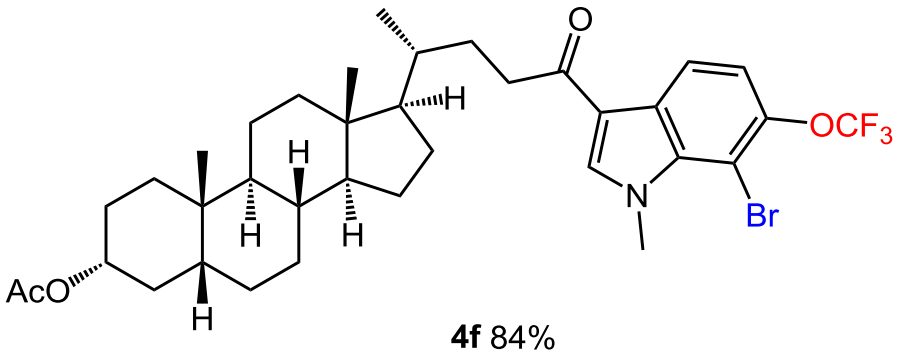
4c 77%



4d 87%

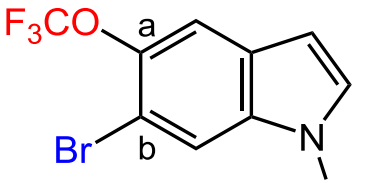


4e 80%

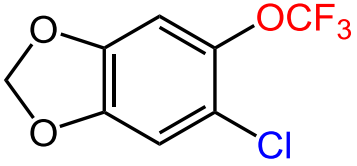


4f 84%

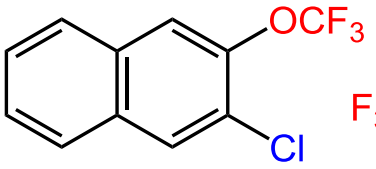
Substrate Scope



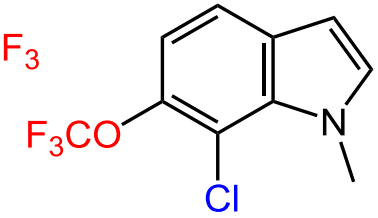
4g 75%
ab/ba = 1.9:1



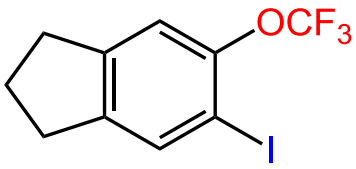
4h 55%



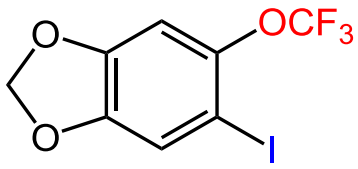
4i 48%



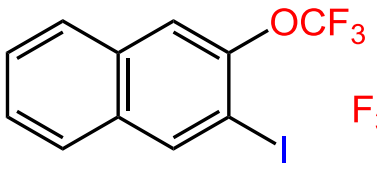
4j 70%



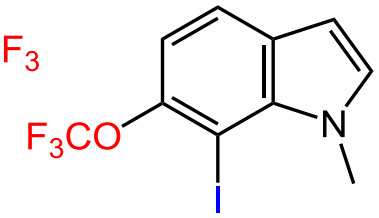
4k 69%



4l 74%

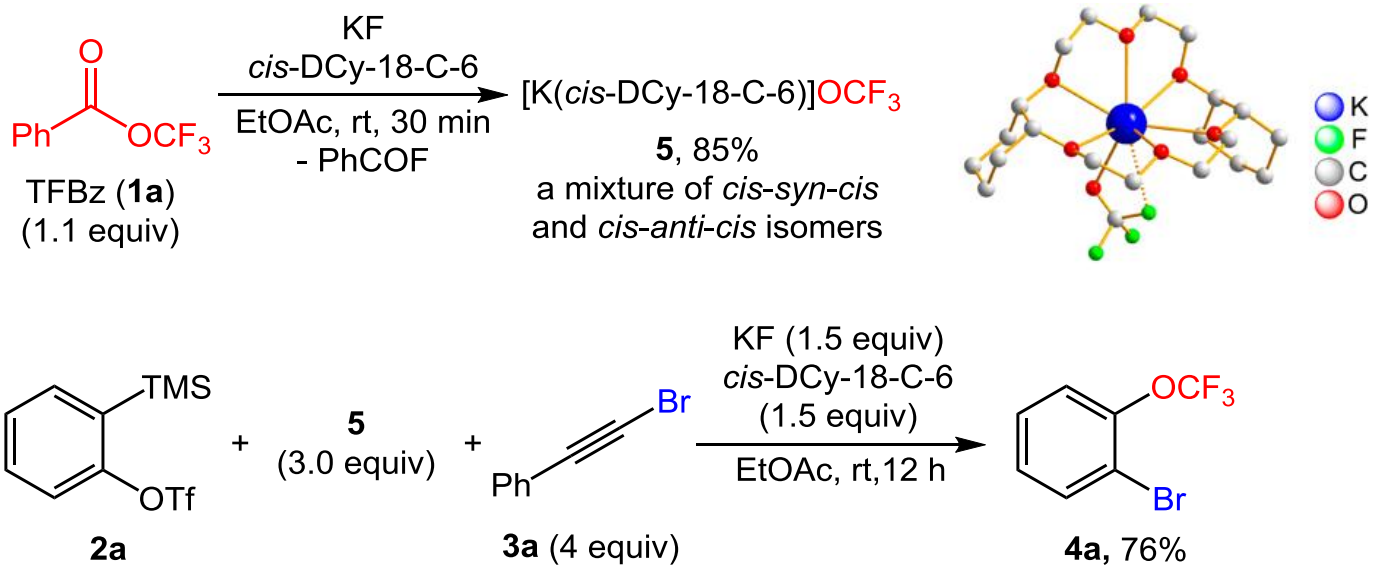


4m 70%

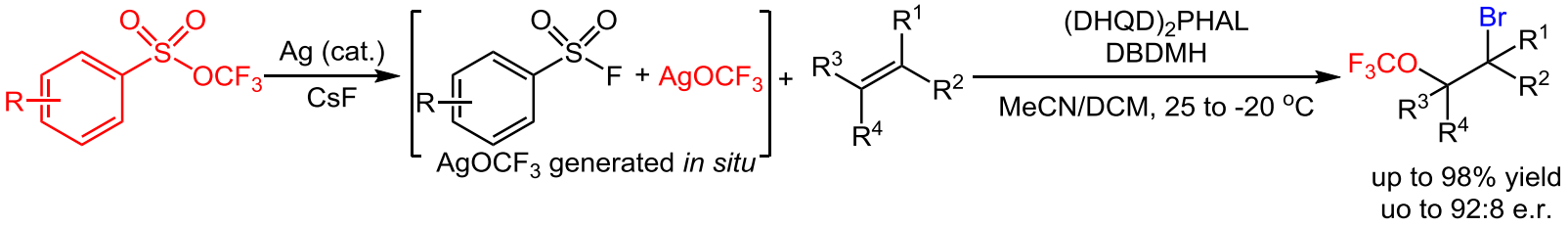


4n 78%

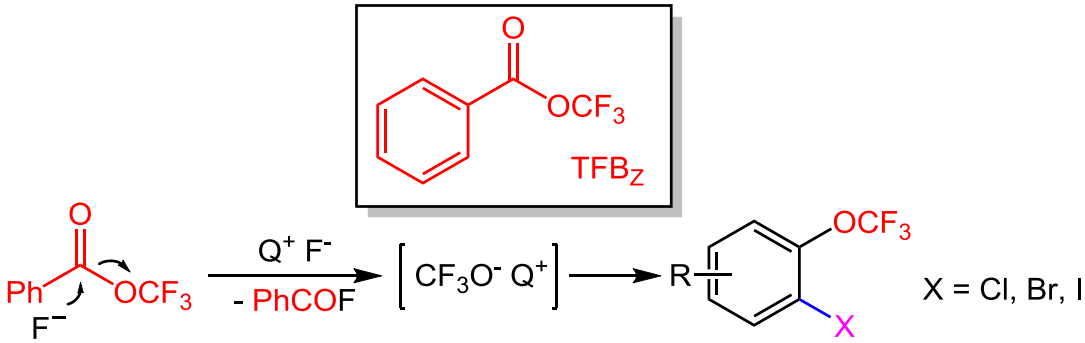
Mechanistic Investigations



Summary



Tang, P. *et al. Nat. Chem*. **2017**, *9*, 546.



Hu, J. *et al. J. Am. Chem. Soc.* **2018**, *140*, 6801.

The First Paragraph

The development of new methods for the introduction of fluorine into small molecules has recently received significant attention due to the growing importance of fluorinated organic compounds in pharmaceuticals, agrochemicals and materials. In particular, the trifluoromethoxy group (OCF_3) is of great interest in new drug and agrochemical design because of its electron-withdrawing effects and high lipophilicity.

The First Paragraph

However, due to the reversible decomposition of trifluoromethoxide anion to afford fluoride and fluorophosgene, as well as β-fluoride elimination from transition-metal-trifluoromethoxide complexes, methods for the introduction of this functional group remain a significant challenge. Furthermore, to the best of our knowledge, no catalytic enantioselective trifluoromethoxylation reaction has been reported to date.

The Last Paragraph

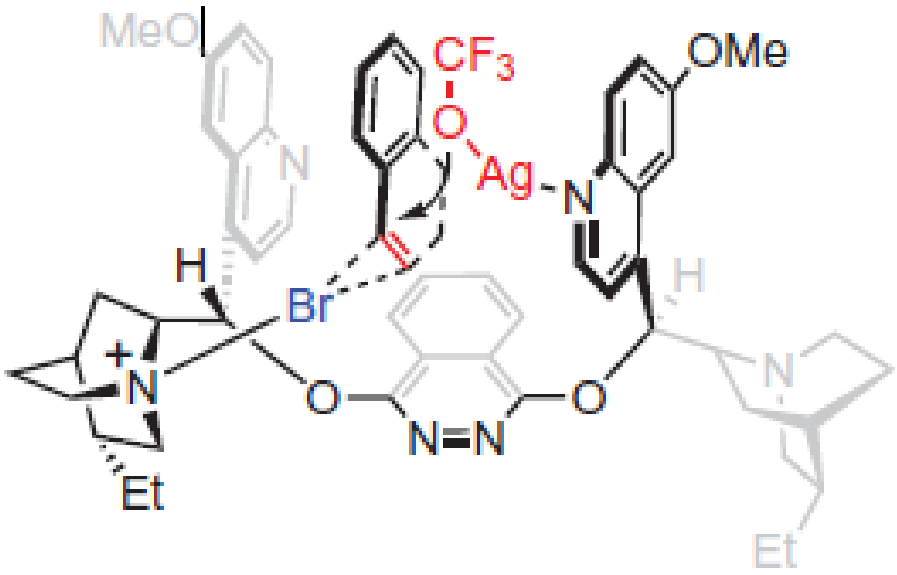
We have developed an asymmetric silver-catalysed intermolecular bromotrifluoromethoxylation of alkenes with TFMS as a new trifluoromethoxylation reagent. This new method offers direct access to a variety of trifluoromethoxylated compounds from olefin substrates including natural products and their derivatives. Compared to other trifluoromethoxylation reagents, TFMS is easily prepared and thermally stable with good reactivity.

The Last Paragraph

Additionally, the reaction tolerates a wide range of functional groups and is amenable to gram-scale synthesis. With its operational simplicity and mild conditions, this method could enable wide applications in pharmaceutical and agrochemical research and development for the synthesis of trifluoromethoxylated compounds.

Acknowledgement

Thanks for your kind attention!


MeO
N
CF3
O
Ag
N
OMe
H
Br
+
N
O
N=N
O
H
N
Et
Et