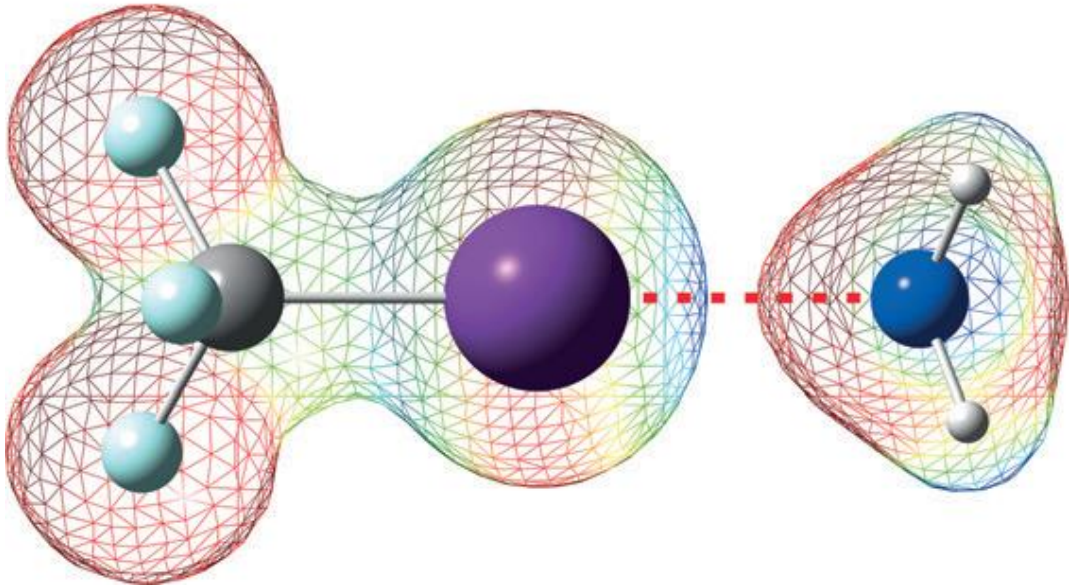
Halogen Bond
Applications in Organic Synthesis



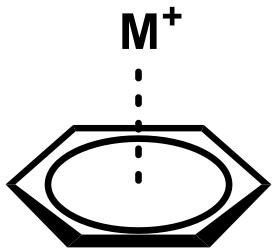
Literature Seminar
2018/7/14
M1 Katsuya Maruyama

Contents

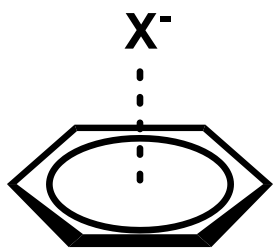
1. Introduction

Non-covalent Interactions

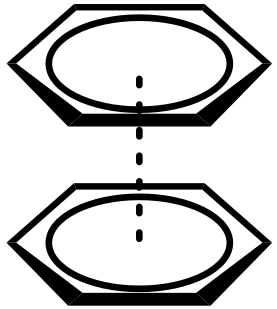
ion-ion
ion-dipole
dipole-dipole
Van der Waals



cation-π

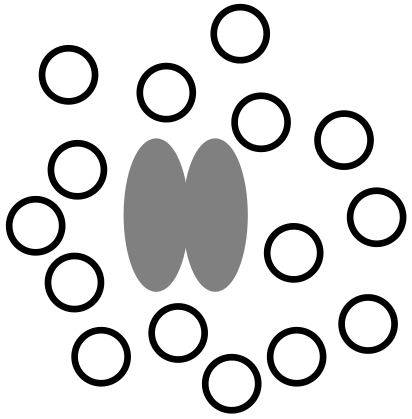


anion-π



π-π

Non-covalent Interactions



hydrophobic

R—X----Y

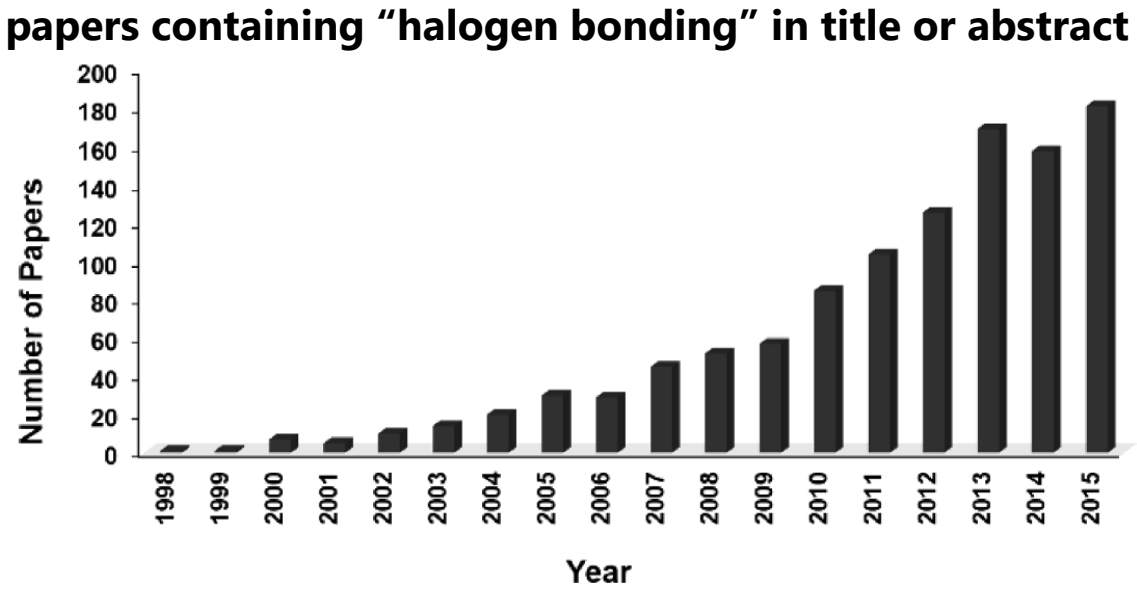
halogen bond

R—H----Y

hydrogen bond

History of Halogen bond

1814	I_2-NH_3, I_2-amylose complex formation
1819	$I_2+I^- \rightarrow I_3^-$
1883	quinoline-CHI_3 adduct
18XX	Br_2 or Cl_2-amine adduct
195X	X-ray crystallographic study
1983	analysis in solution
199X	F_2-NH_3, F_2-OH_2 adduct
2007	concept of σ-hole was introduced
2013	halogen bond definition by IUPAC



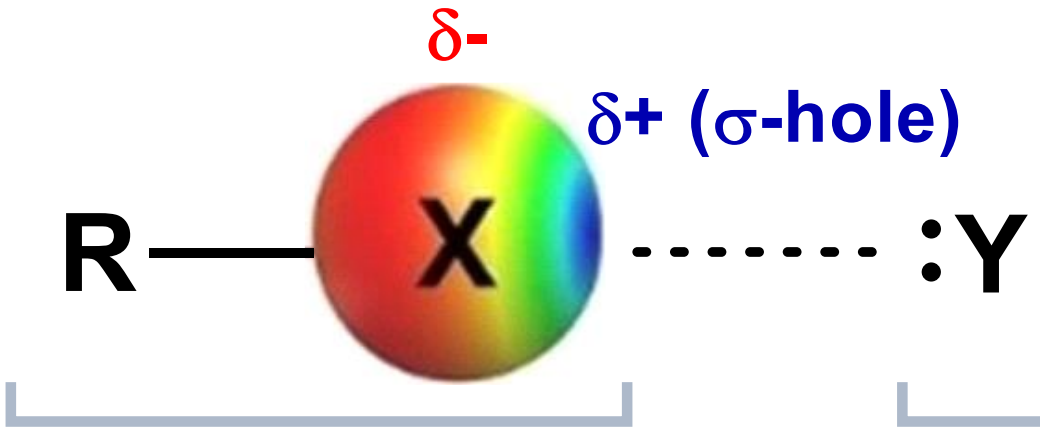
Applications of halogen bond

- Crystal engineering
- Supramolecule
- Biological systems
- Medicinal chemistry (protein-ligand interaction)
- Organic synthesis

Metrangolo, P.; Resnati, G. *et al. Chem. Rev.* **2016**, *116*, 2478–2601.

2. Property of Halogen Bond

Halogen Bond (XB)



XB donor (Lewis acid)

R = C, halogen, N, ...

X = I, Br, Cl, F, (At)

XB acceptor (Lewis base)

Y = N, O, S, Se, ...

I^-, Br^-, Cl^-, F^-, ...

Features

- Directionality
- Strength tunability
- Hydrophobicity
- Donor atom size

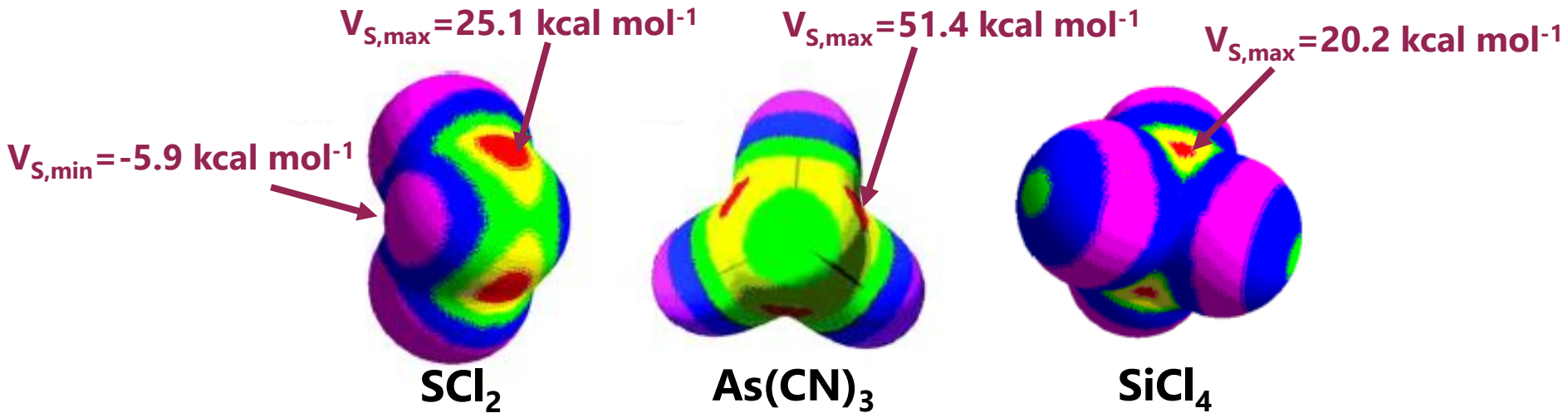
Definition of halogen bond (IUPAC, 2013)

"A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity."

Metrangolo, P.; Resnati, G. *et al. Chem. Rev.* **2016**, *116*, 2478–2601.

σ-hole

Electrostatic potential



σ-hole mediated interactions

group 14: tetrel bond
15: pnicogen bond
16: chalcogen bond
17: halogen bond

Donor atom

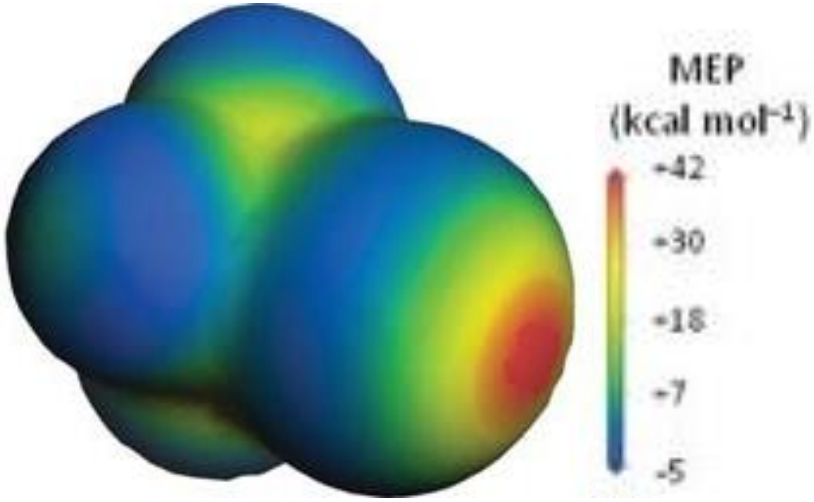
More polarizable
Less electronegative

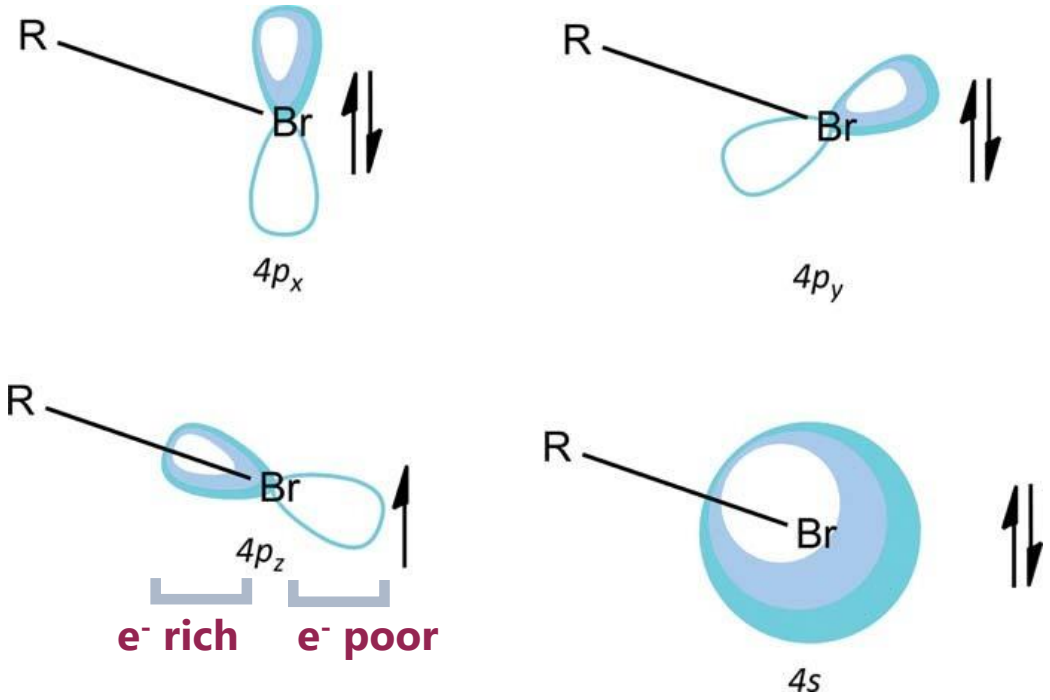
More positive σ-hole

Metrangolo, P.; Resnati, G. *et al. Chem. Rev.* **2016**, *116*, 2478–2601.

Origin of σ-Hole

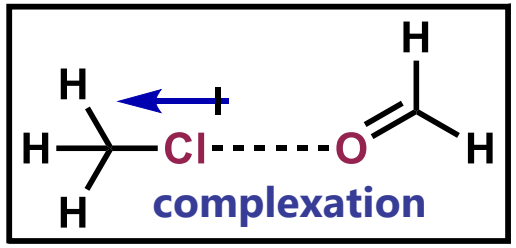
$CF_3\underline{Br}$: $4s^2 4p_x^2 4p_y^2 4p_z^1$





Origins of σ-hole

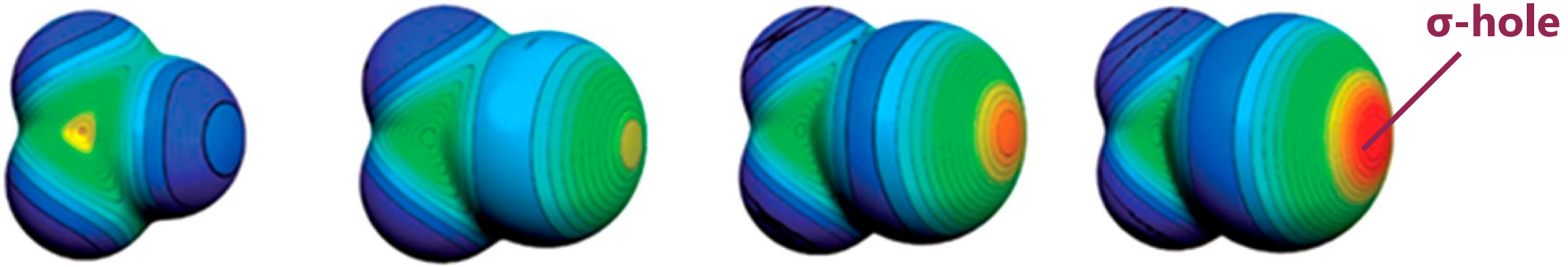
1. **$4p_z$** : half filled, localized between C and Br to form C-Br σ bond.
2. Appear along with polarization by XB acceptor.



Clark, T. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2013**, *3*, 13–20.

XB Strength

Electrostatic potential of CF_3X



CF_4 CF_3Cl CF_3Br CF_3I

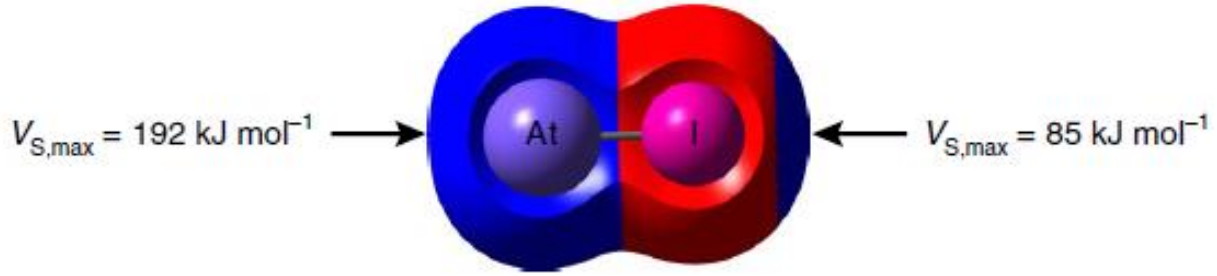
XB strength

electronegative

I > Br > Cl > F

polarizable

Astatine as XB donor



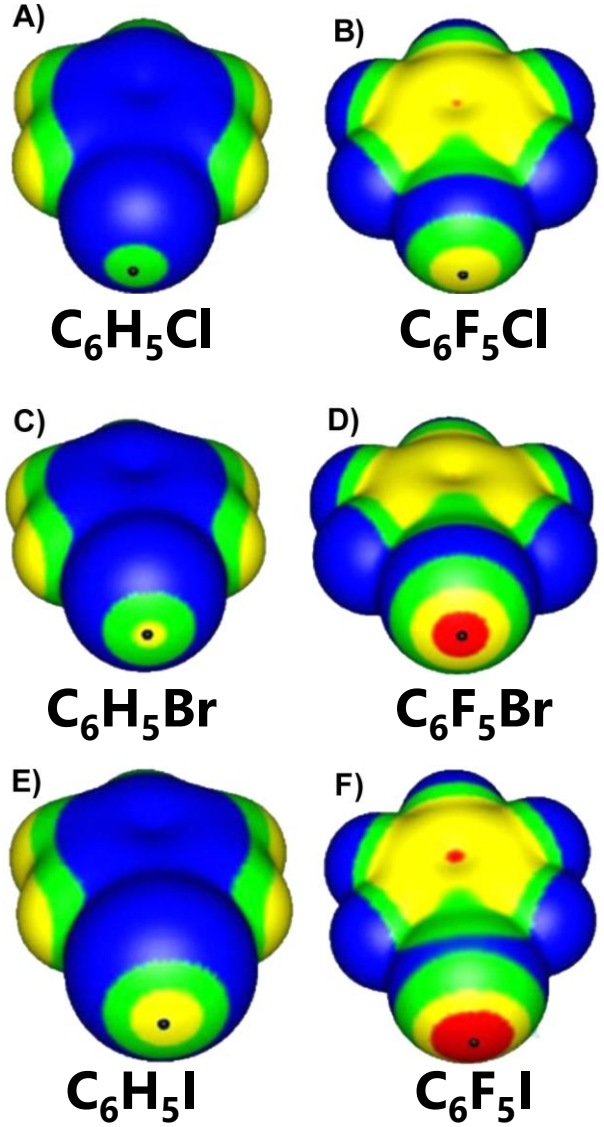
- Astatine can be extremely good XB donor.

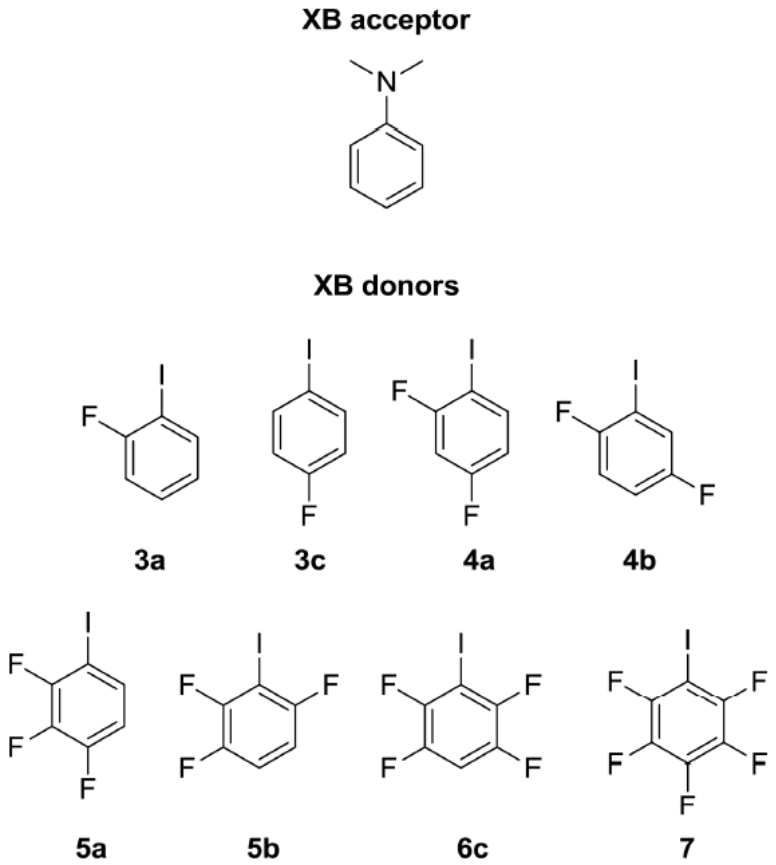
Metrangolo, P.; Resnati, G. *et al. Chem. Rev.* **2016**, *116*, 2478–2601.

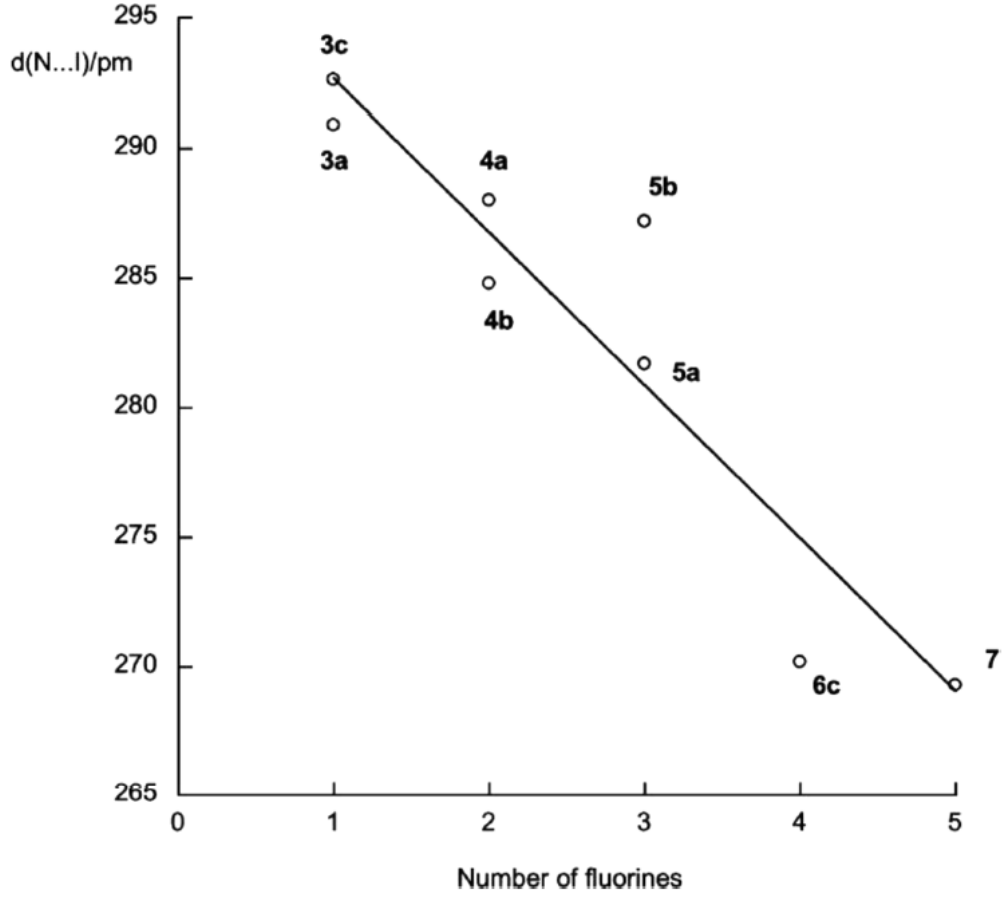
Montavon, G.; Galland, N. *Nat. Chem.* **2018**, *10*, 1–7.

XB strength

Introduction of electron-withdrawing group



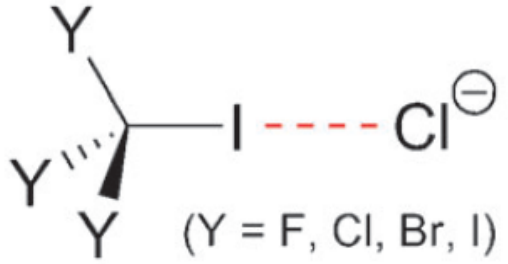




- Introduction of EWG -> strong XB

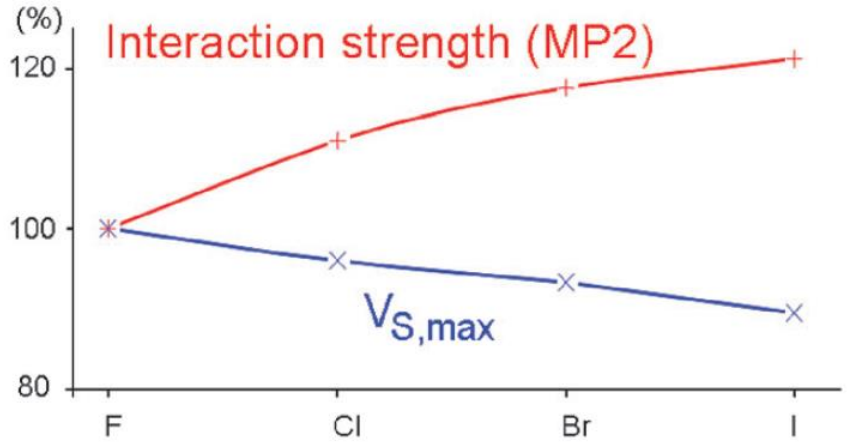
Metrangolo, P.; Resnati, G. *et al. Chem. Rev.* **2016**, *116*, 2478–2601.

Unexpected Trend of XB Strength

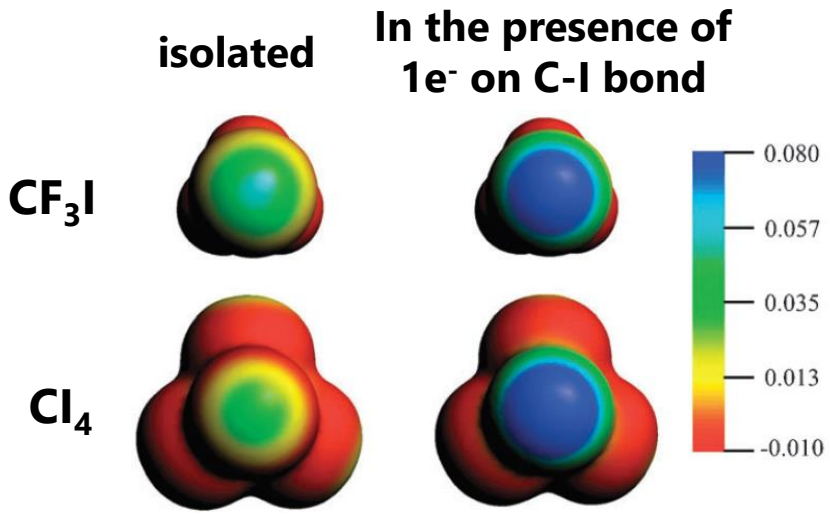


Comparison of $CY_3I\cdots Cl^-$ (Y=F, Cl, Br, I) complex

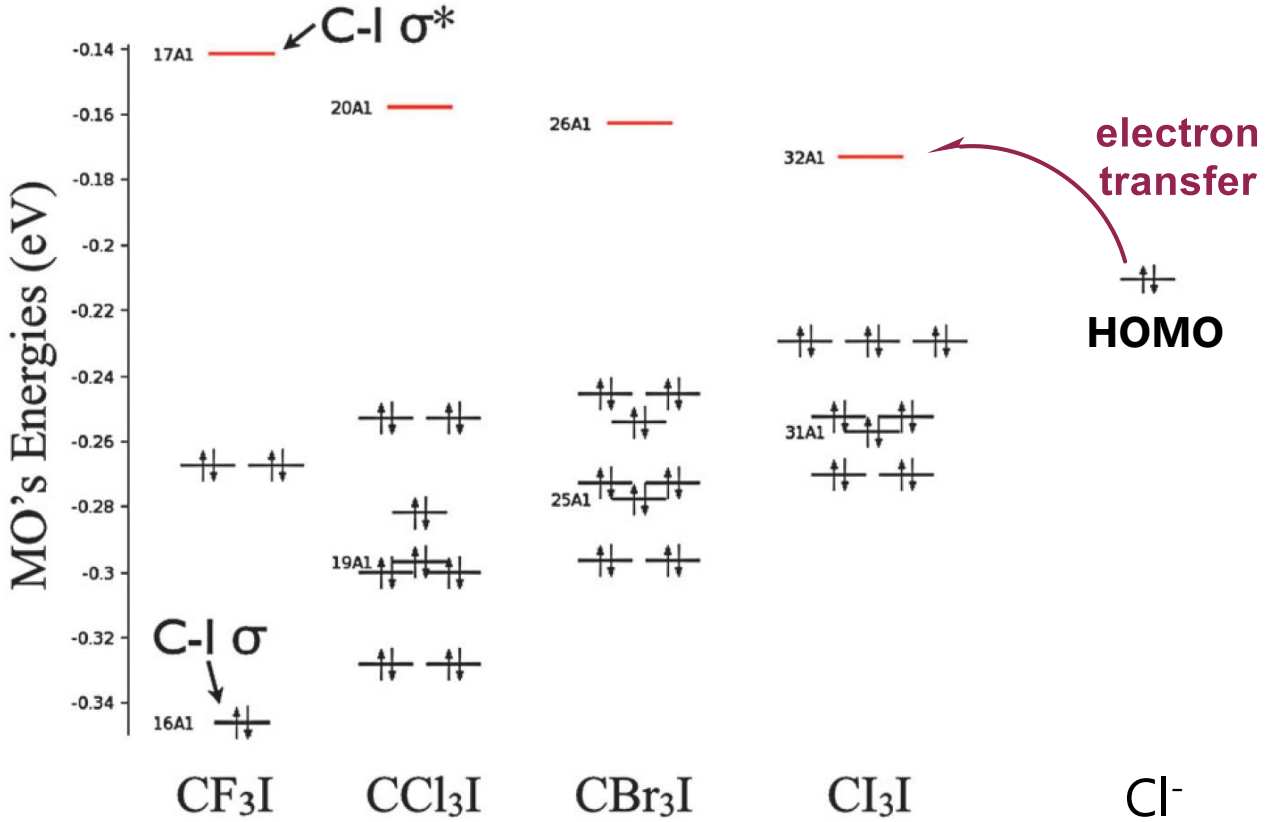
Electrostatic potential and interaction energy



Electrostatic potential



Molecular orbital



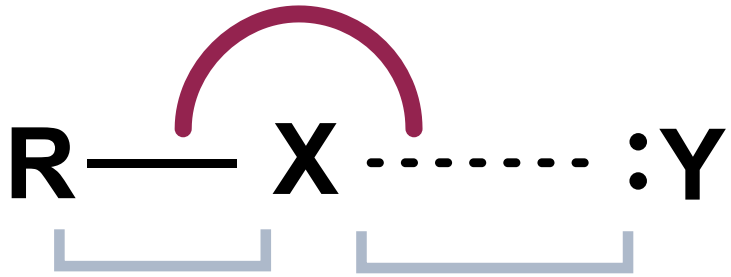
- Charge-transfer (orbital-orbital interaction) is also important.

Huber, S. M.; Infante, I. *et al. Chem. Commun.* **2012**, *48*, 7708–7710.

Geometry

directionality

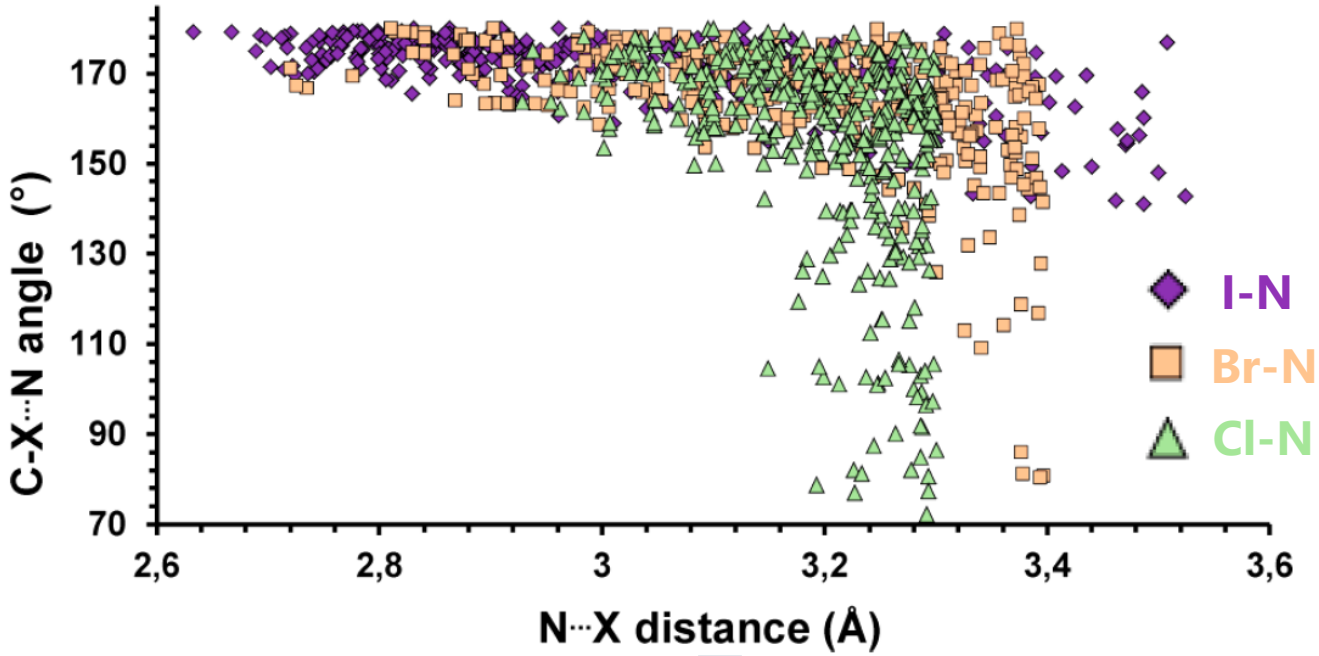
θ ~ 180°



Slight elongation

80-90% of the sum of Van der Waals radii

CSD crystal structure containing X···N halogen bond



mean C-X···N angle (θ)

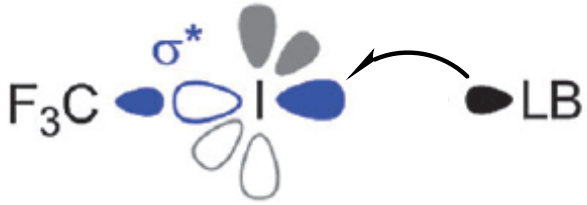
X =	**I**	**171.4°**
	Br	**164.1°**
	Cl	**154.6°**

Metrangolo, P.; Resnati, G. *et al. Chem. Rev.* **2016**, *116*, 2478–2601.

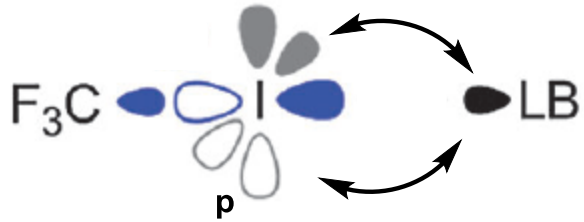
Directionality

Possible factors for directionality

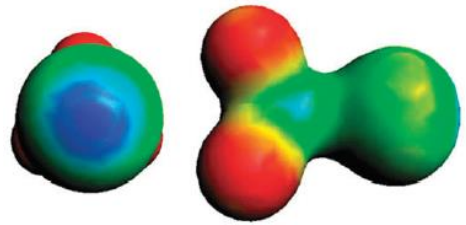
1. Charge transfer



2. Lone pair repulsion

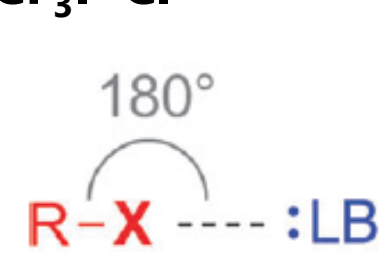


3. σ-hole (electrostatic interaction)



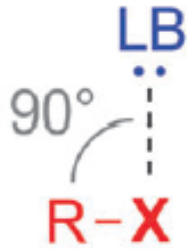
DFT calculation (NEDA: Natural Energy Decomposition Analysis)

$CF_3I\cdots Cl^-$



linear

vs.

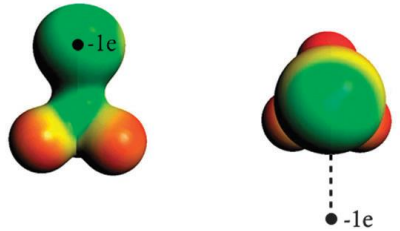


perpendicular

Directionality

Contribution of
- 1, 2 is large.
- 3 is small.

$1e^-$ on perpendicular side

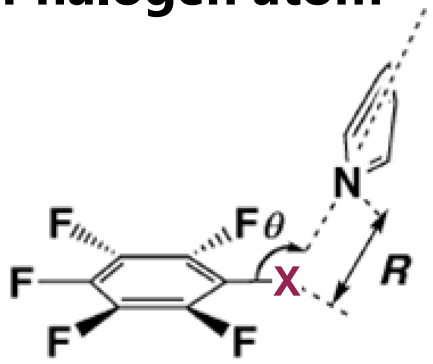


not disfavored

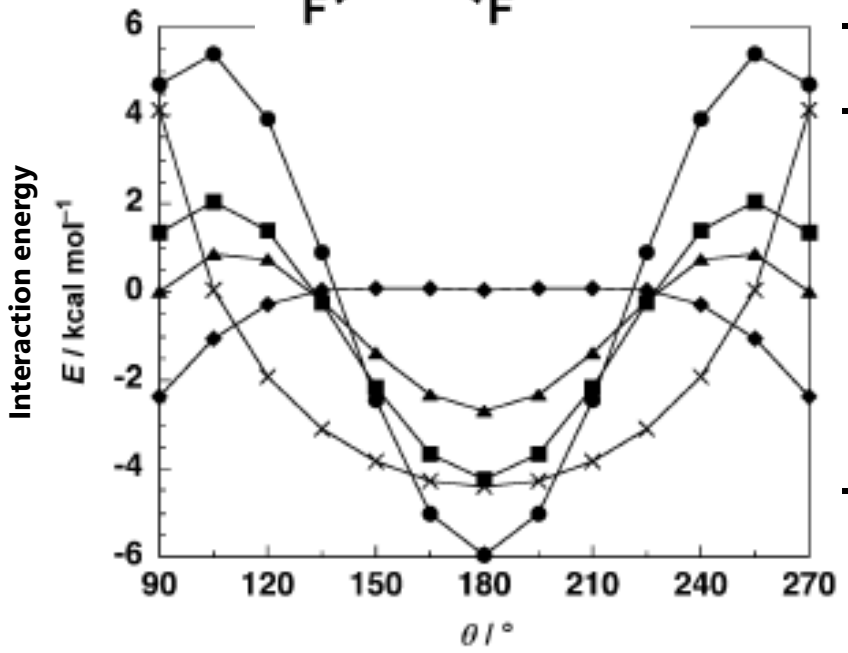
Huber, S. M.; Infante, I. *et al.* *Phys. Chem. Chem. Phys.* **2013**, *15*, 10350–10357.

Directionality

Effect of halogen atom



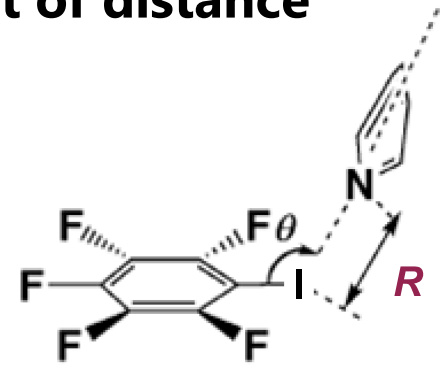
C_6F_5X-pyridine



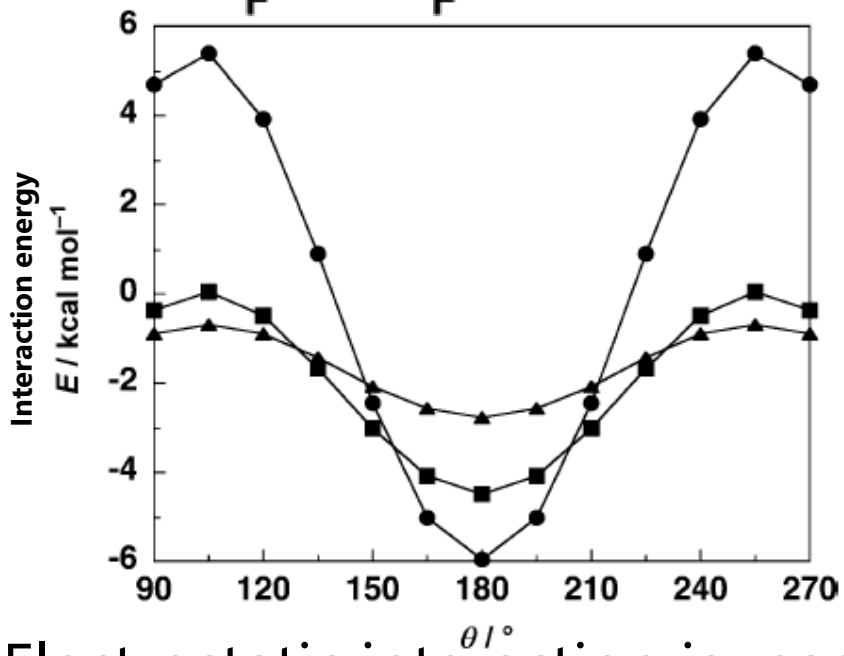
X	R (Å)
● I	3.0
■ Br	
▲ Cl	
◆ F	
× H	2.2

R: interaction maximum

Effect of distance



C_6F_5I-pyridine



R (Å)
● 3.0
■ 3.5
▲ 4.0

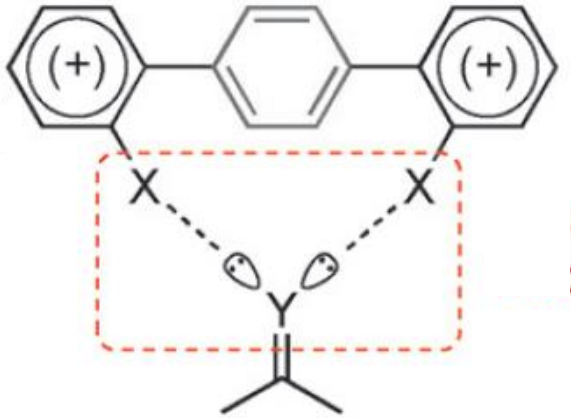
- Electrostatic interaction is responsible for directionality.

Tsuzuki, S. *et al. Chem. - A Eur. J.* **2012**, *18*, 951–960.

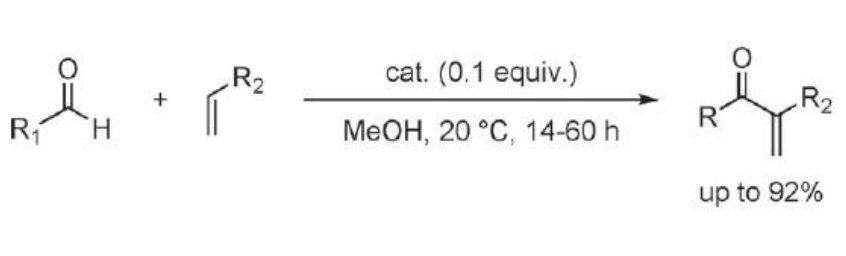
3. Application to Organic Synthesis

XB in Organic Synthesis

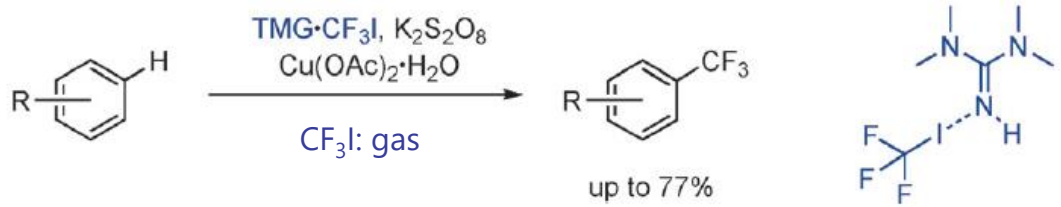
Activation of substrate (catalyst, activator)



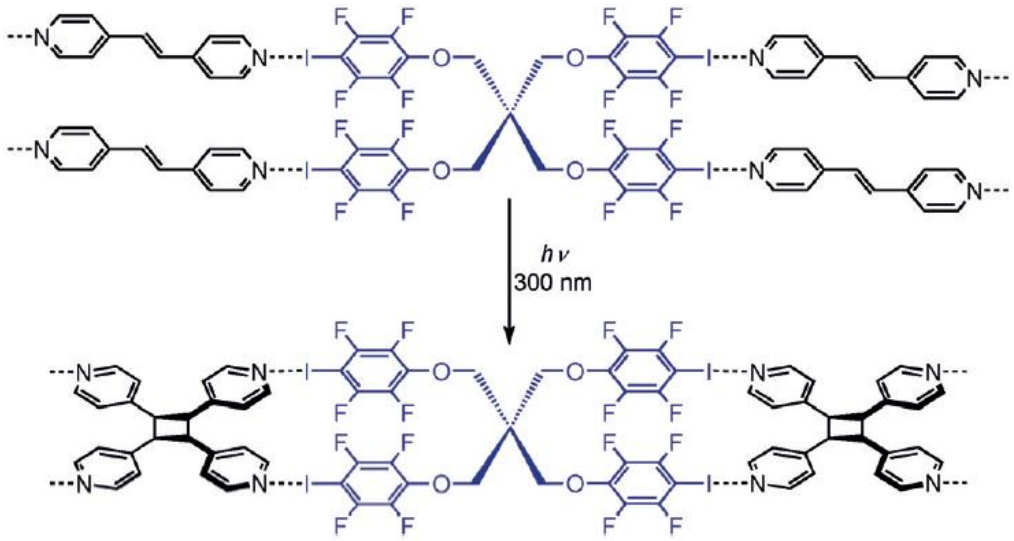
Facilitating handling of reagents or catalysts



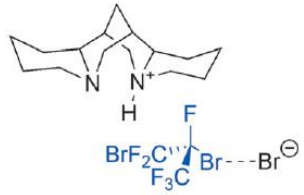
Recovered by precipitation

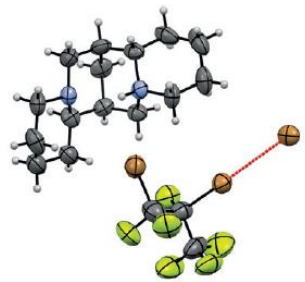


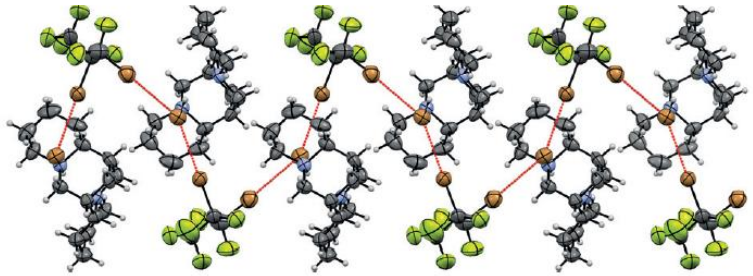
Alignment of substrate



Optical resolution



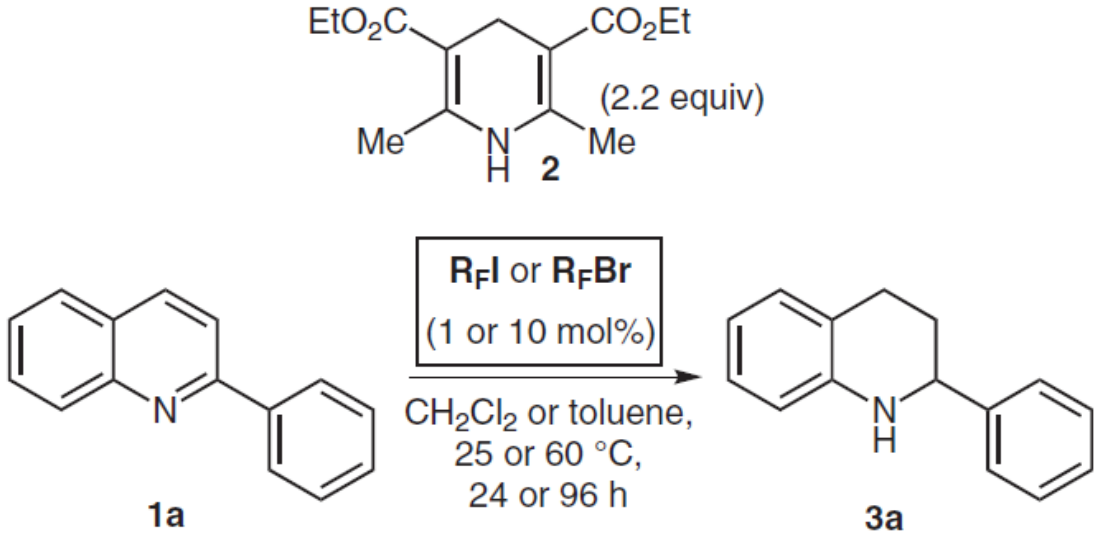


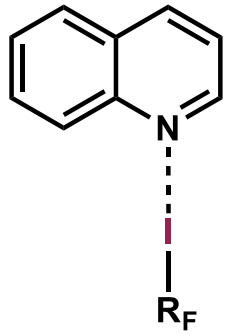


Bulfield, D.; Huber, S. M. *Chem. - A Eur. J.* **2016**, *22*, 14434–14450.

Early Report of XB Mediated Catalysis

Reduction of quinoline by Hantzsch ester





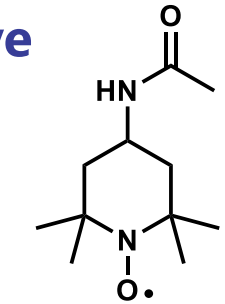
Activation by XB

NMR experiment (in CD_2Cl_2)

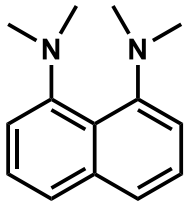
^{13}C: 0.01-0.06 ppm lower field shift (quinoline)

^{19}F: ~0.06-0.1 ppm lower field shift ($CF_3(CF_2)_7I$)

Additive



4-acetamido-TEMPO



1,8-bis(dimethylamino) naphthalene

Reaction inhibition

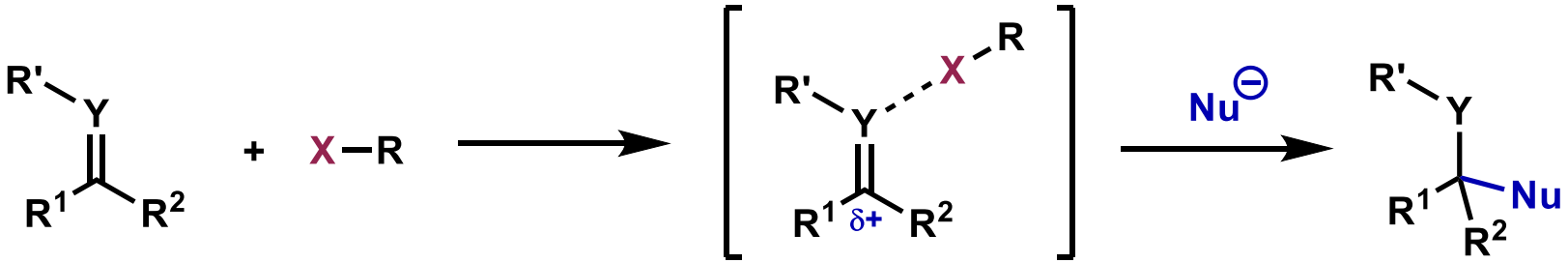
Entry	R_FX	Amount (mol%) of R_FX	Solvent	Temp (°C)	Yield of **3a** (%)[a]
1	–	–	CH_2Cl_2	25	–
2	–	–	toluene	60	–
3	$BrCF_2CBrFCF_3$	10	CH_2Cl_2	25	–
4	$BrCF_2CBrFCF_3$	10	toluene	60	39 (67)[b]
5	$CF_3CF_2CFICF_3$	10	CH_2Cl_2	25	72[b]
6	$CF_3(CF_2)_5I$	10	CH_2Cl_2	25	35[b]
7	$CF_3(CF_2)_5I$	10	toluene	60	63[b]
8	$CF_3(CF_2)_5Br$	10	CH_2Cl_2	25	20[b]
9	$CF_3(CF_2)_5Br$	10	toluene	60	12[b]
10	$CF_3(CF_2)_6I$	10	CH_2Cl_2	25	90
11	$CF_3(CF_2)_7I$	10	CH_2Cl_2	25	98
12	$CF_3(CF_2)_7I$	1	CH_2Cl_2	25	69[b]
13	$CF_3(CF_2)_7Br$	10	CH_2Cl_2	25	38[b]
14	$CF_3(CF_2)_9I$	10	CH_2Cl_2	25	88

Bolm, C. *et al. Synlett* **2008**, No. 6, 900–902.

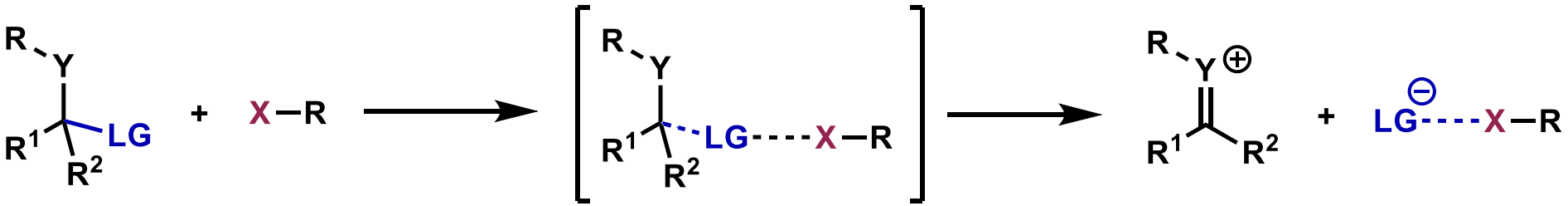
Activation Types of XB Catalyst

X–R : XB donor (catalyst)

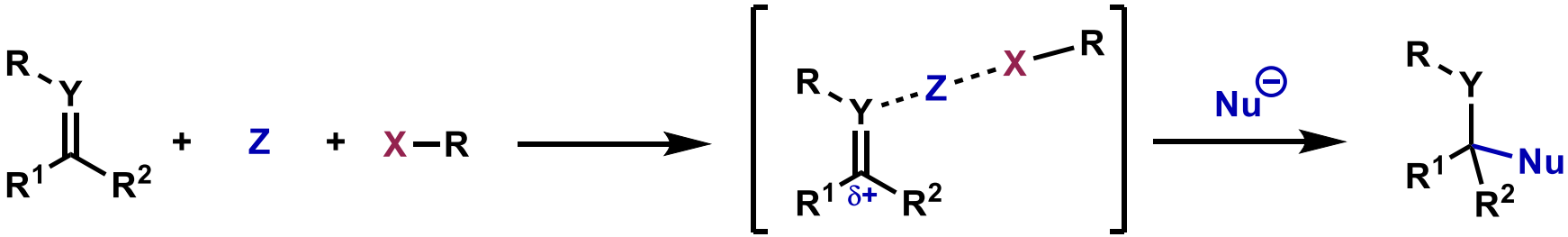
(1) Direct activation of reactant



(2) Anion abstraction from reactant

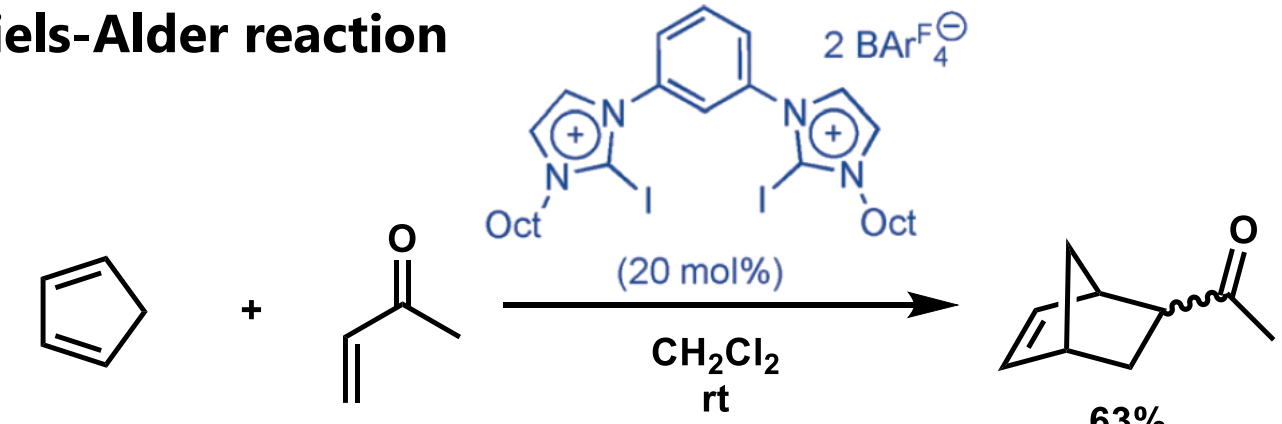


(3) Activation of another activator



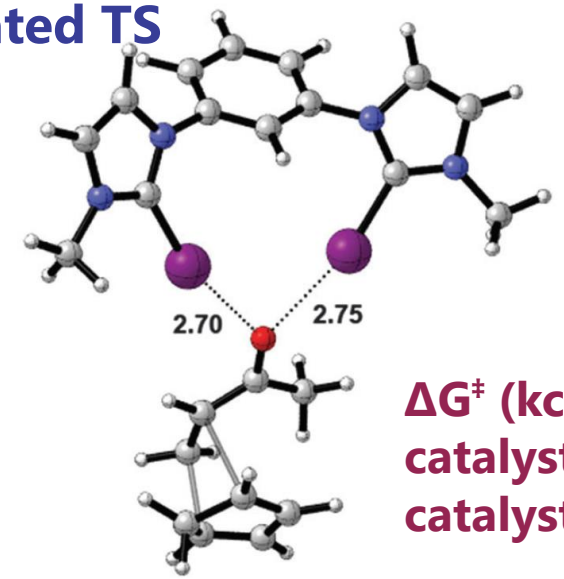
(1) Direct Activation of Reactant

Diels-Alder reaction



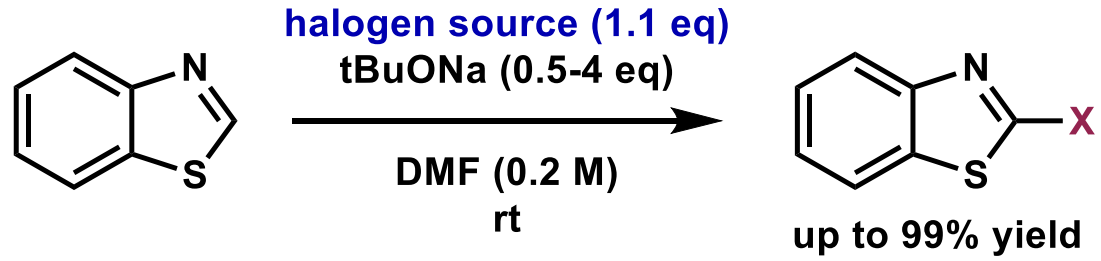
Huber, S. M. *et al. Chem. Commun.* **2014**, *50*, 6281–6284.

Calculated TS



$\Delta G^{\ddagger}$ (kcal mol^{-1})
catalyst (-) 29.5
catalyst (+) 26.5

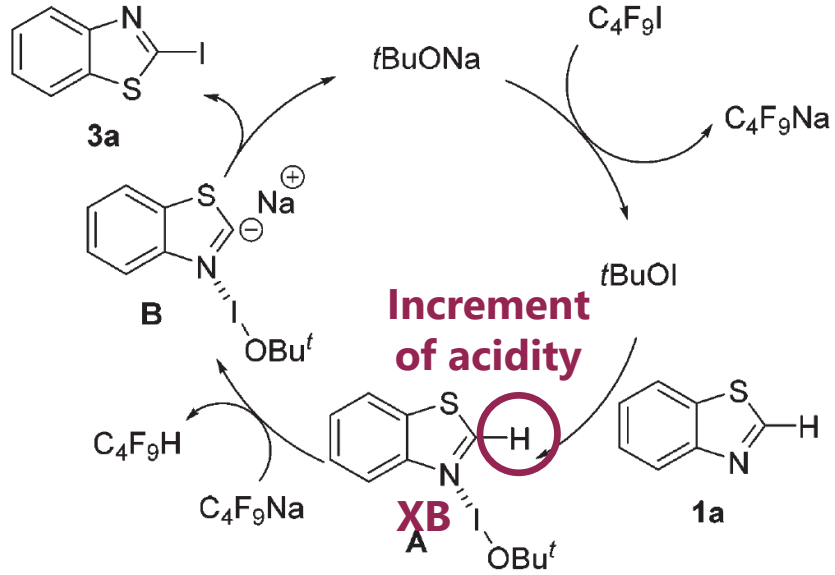
C–H halogenation of heteroarenes



halogen source = C_4F_9I, CBr_4, CCl_4

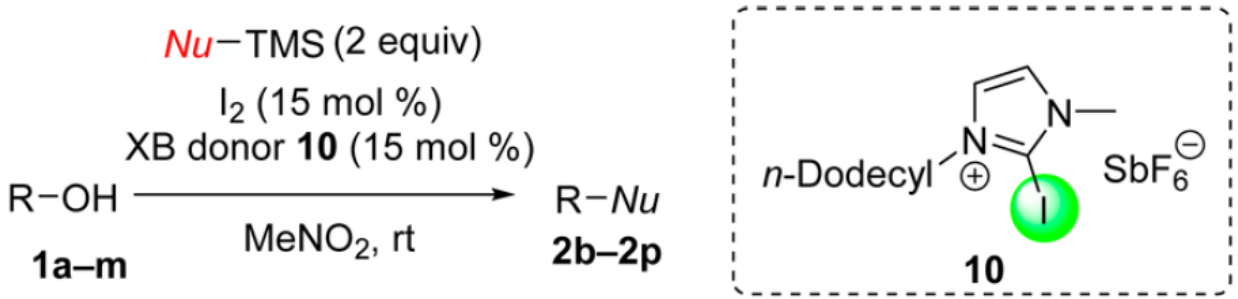
Liang, F.; Ren, B. *et al. Org. Biomol. Chem.* **2018**, *16*, 886–890.

Mechanism



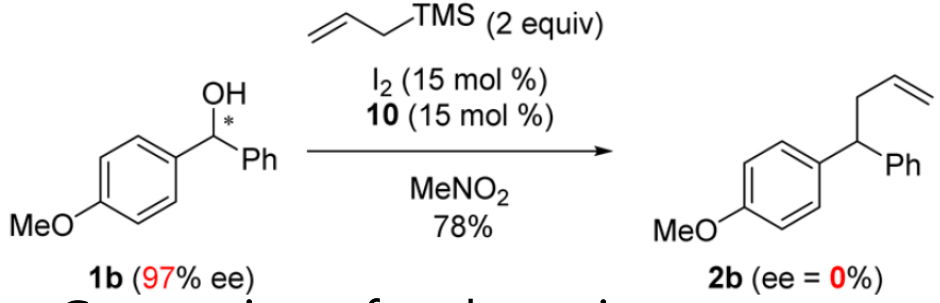
(3) Activation of Another Activator

Dehydroxylative coupling of alcohol through Si-X bond activation



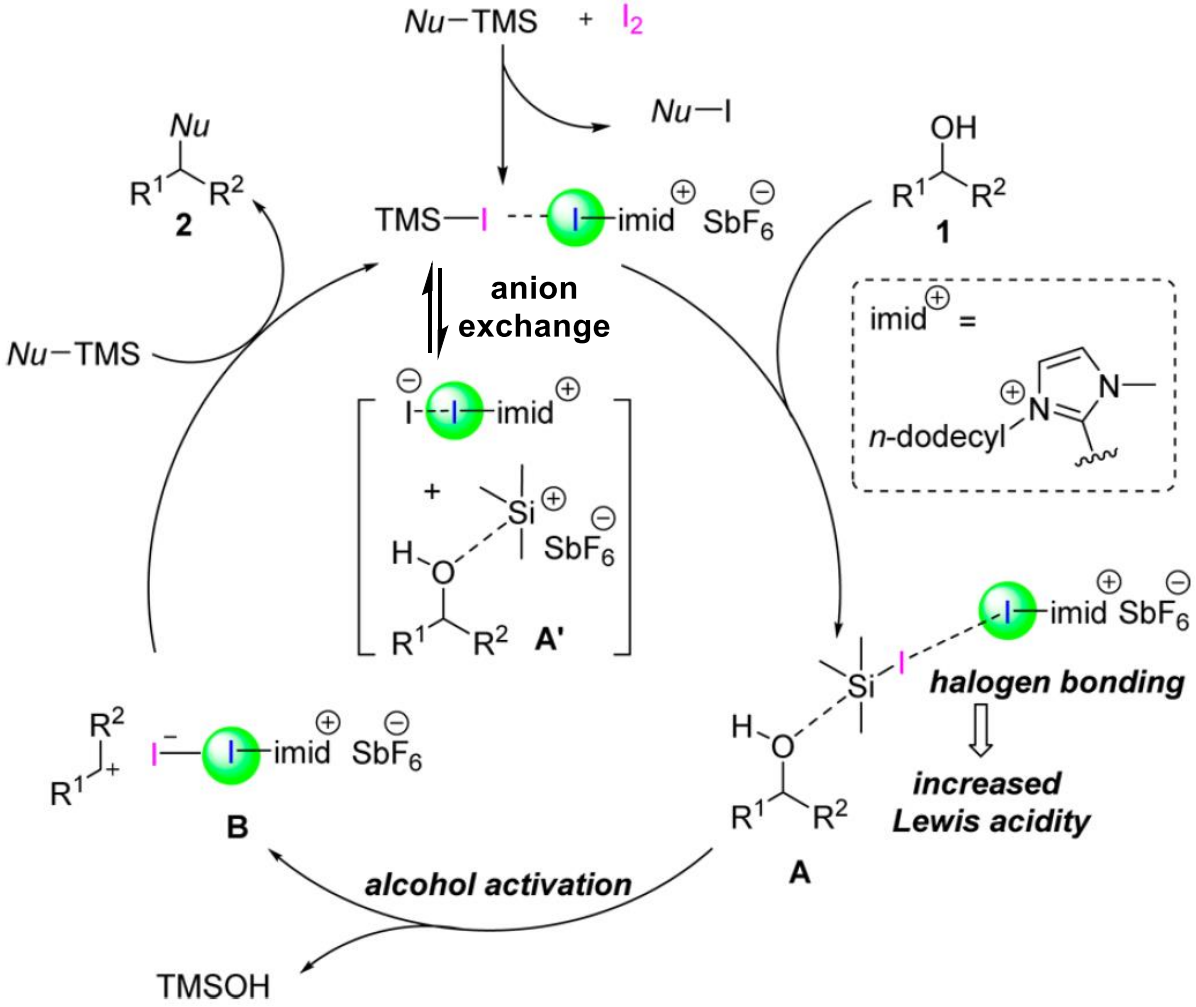
Verification of mechanism

- Anion exchange isn't likely.



- Generation of carbocation

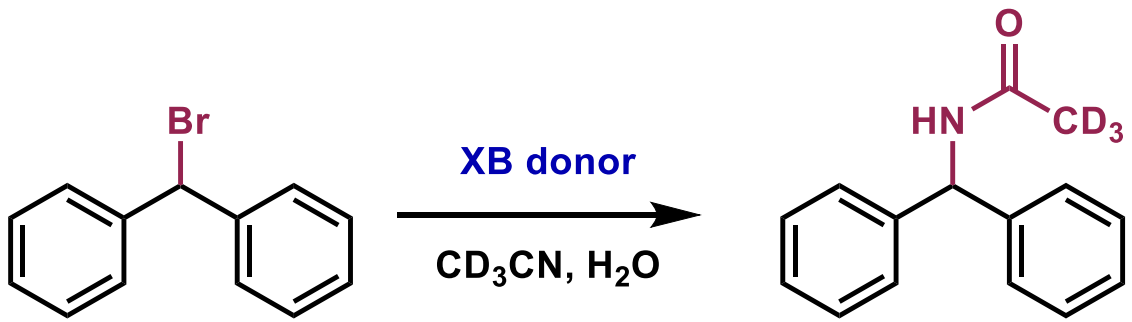
Plausible mechanism

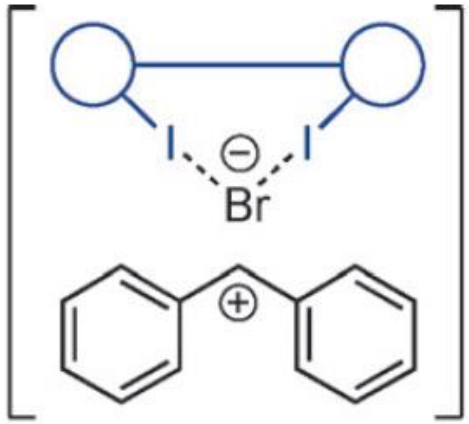


Takemoto, Y. *et al. Org. Lett.* **2015**, *17*, 3000–3003.

(2) Anion Abstraction from Reactant

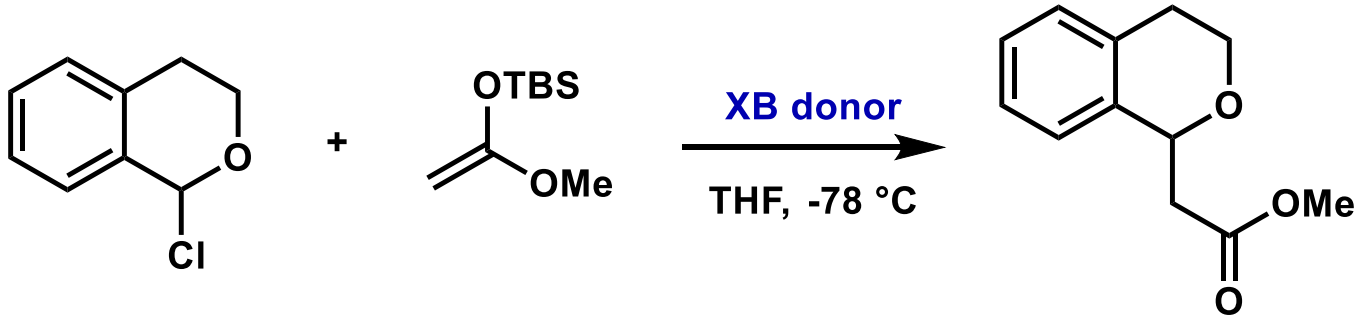
Ritter-type Solvolysis

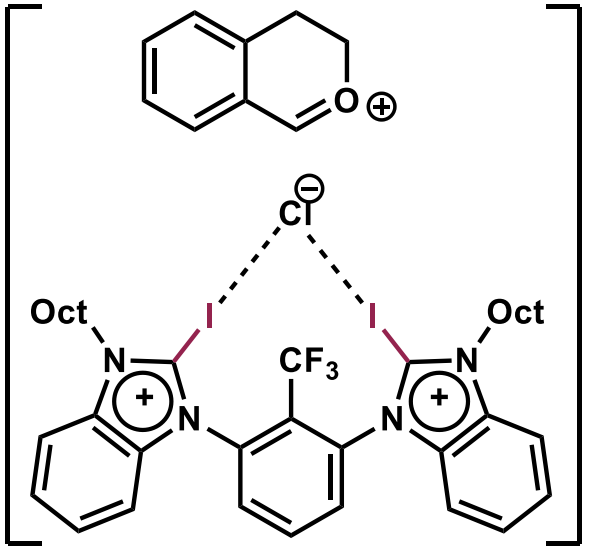




Huber, S. M. *et al. Angew. Chemie - Int. Ed.* **2011**, *50*, 7187–7191.

Addition to oxocarbenium ion

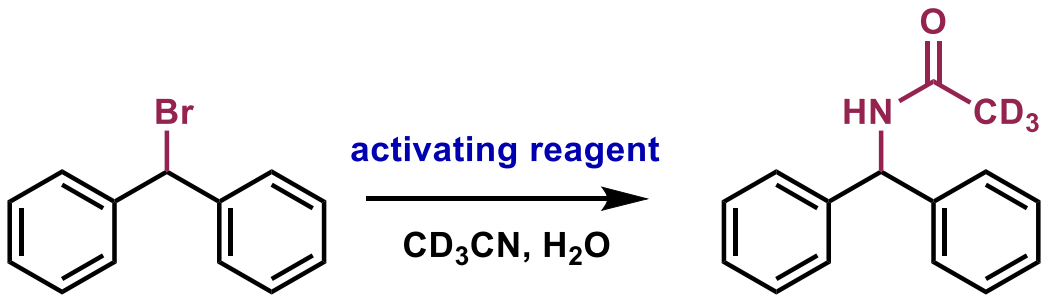




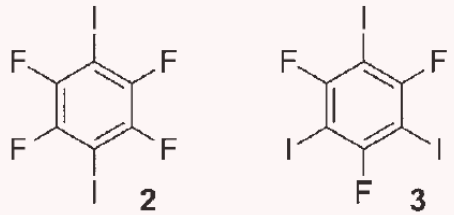
Huber, S. M. *et al. Angew. Chemie - Int. Ed.* **2013**, *52*, 7028–7032.

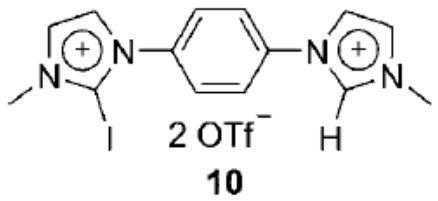
(2) Anion Abstraction from Reactant

Ritter-type Solvolysis

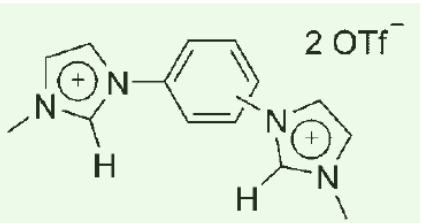


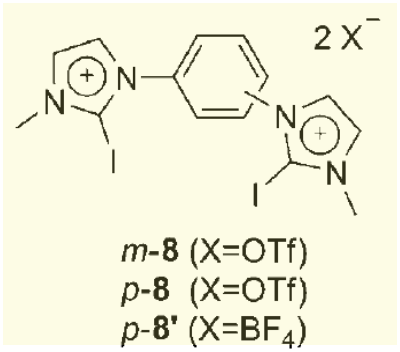
Monodentate XB donors

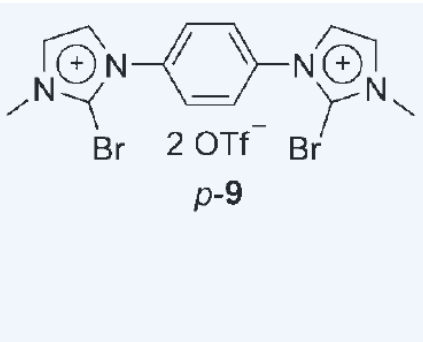




Bidentate XB donors (imidazolium type)







Entry	Activating reagent	(Equiv.)[a]	Additive[b]	Yield [%][c]
1	–	–	–	≤5
2	–	–	py	≤5
3	HOTf	0.05	–	12
4	HOTf	0.05	py	7
5	HOTf	1.0	–	25
6	NBu_4OTf	2.0	–	≤5
7	**2**	1.0	–	≤5
8	**3**	1.0	–	≤5
9	*p*-**7**	1.0	–	7
10	*p*-**7**	1.0	py	≤5
11	*p*-**8**	1.0	–	85 [88][d]
12	*p*-**8**	1.0	py	85
13	*m*-**7**	1.0	–	12
14	*m*-**7**	1.0	py	7
15	*m*-**8**	0.2	–	28
16	*m*-**8**	1.0	–	80 [71][d]
17	*m*-**8**	1.0	py	75
18	*p*-**8'**	1.0	–	97
19	*p*-**9**	1.0	–	54
20	**10**	2.0	–	49

Huber, S. M. *et al. Angew. Chemie - Int. Ed.* **2011**, *50*, 7187–7191.

(2) Anion Abstraction from Reactant

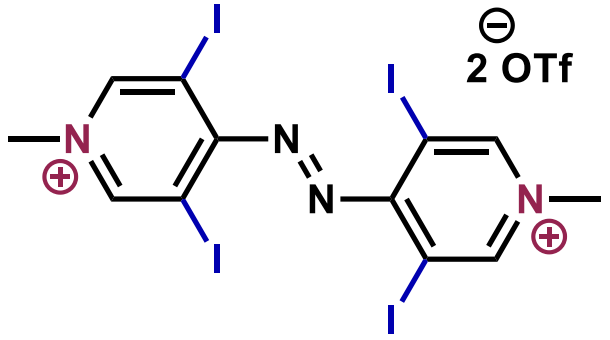
Cationic vs polyfluoro XB donor

Problems of cationic XB donor

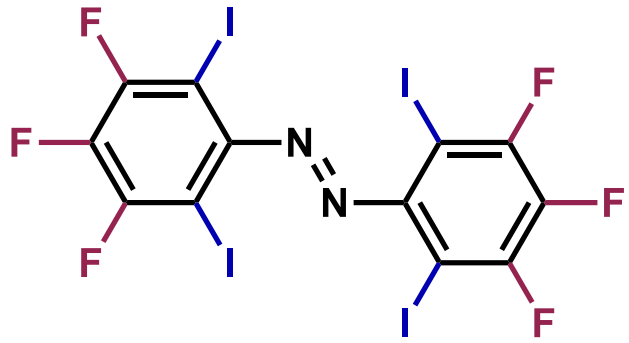
- Solubility
- Synthetic accessibility
- Presence of counteranion
- Stability

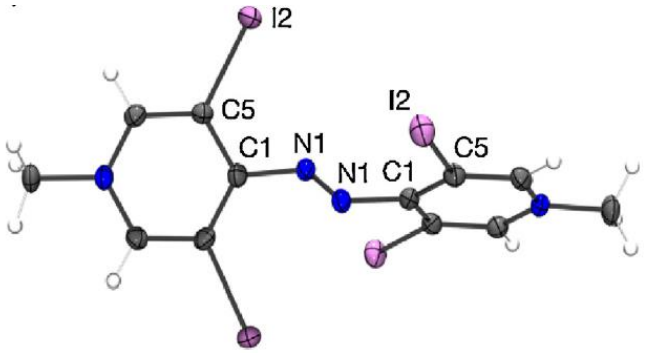
Structure comparison

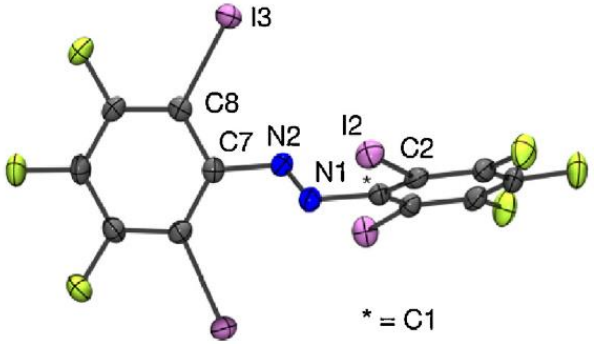
Iodopyridinium XB donor



Polyfluoro XB donor



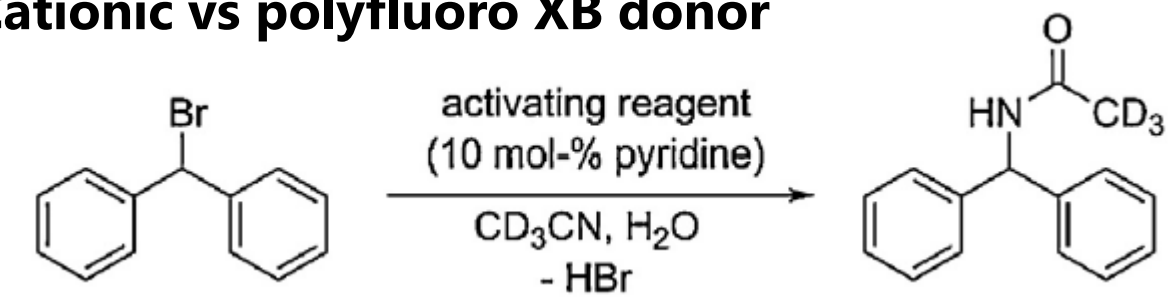


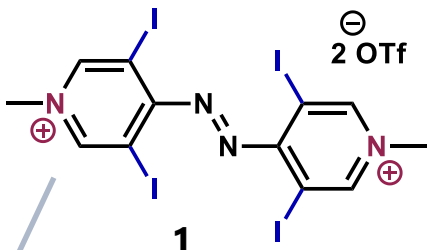


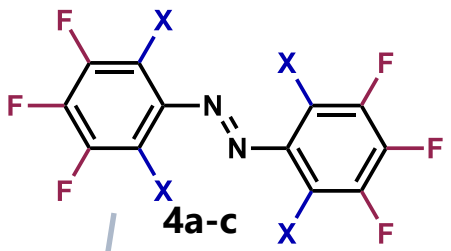
Huber, S. M. *et al. J. Fluor. Chem.* **2013**, *150*, 14–20.

(2) Anion Abstraction from Reactant

Cationic vs polyfluoro XB donor

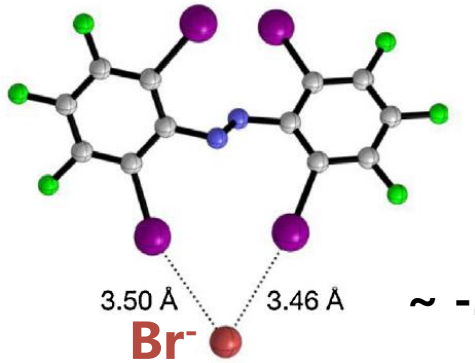






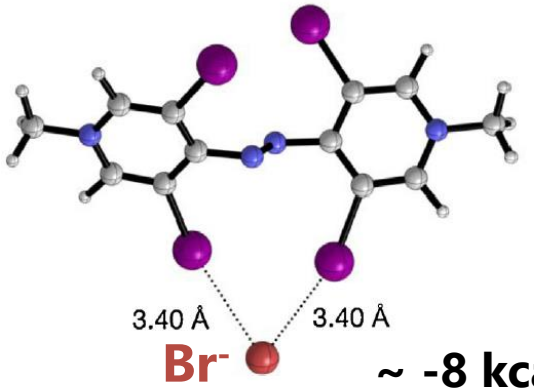
Complex structure (DFT calculation)

Polyfluoro XB donor



~ -3 kcal mol^{-1}

Iodopyridinium XB donor



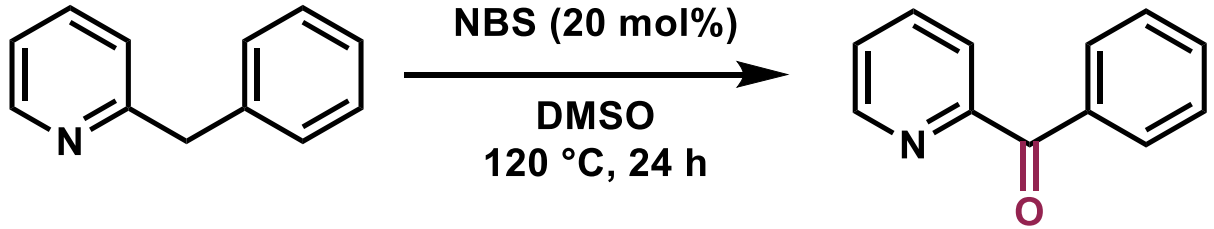
~ -8 kcal mol^{-1}

- Cation backbone is effective in spite of the presence of counteranion.

Huber, S. M. *et al. J. Fluor. Chem.* **2013**, *150*, 14–20.

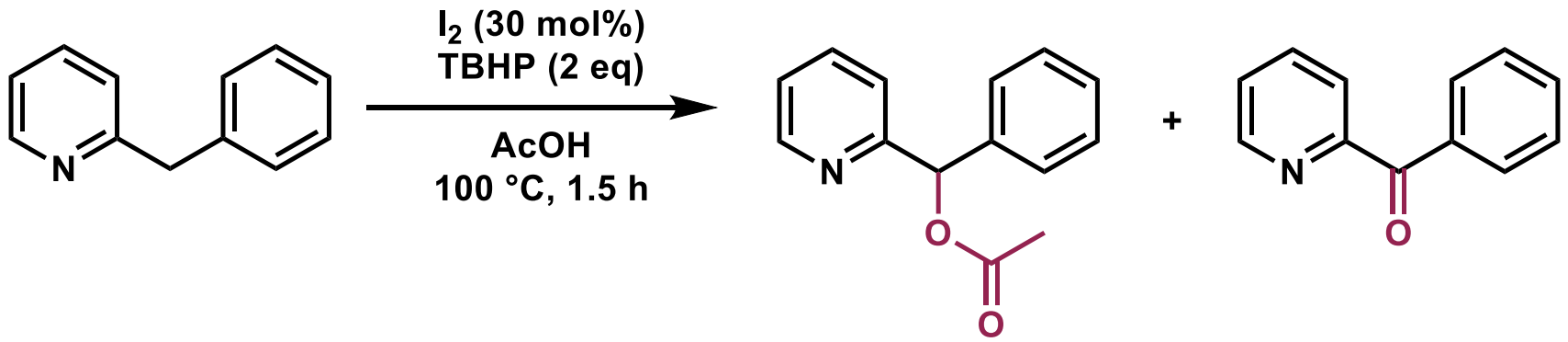
Oxidation of Heterobenzyl position to C(sp^2)=O or C(sp^3)-O

Oxidation to C(sp^2)=O



96%

Oxidation to C(sp^3)-O



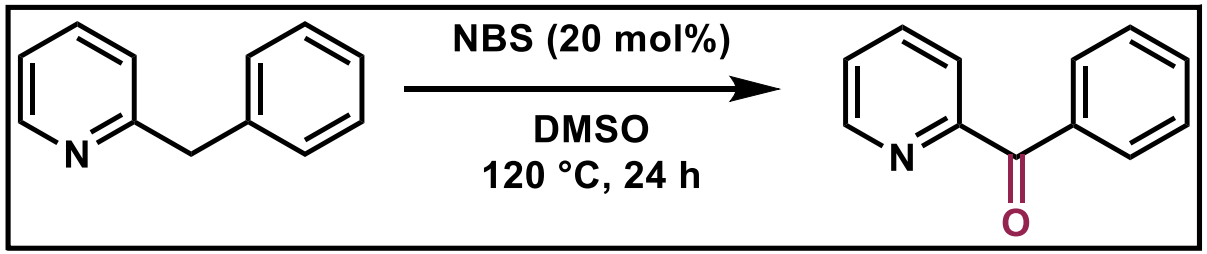
85% 10%

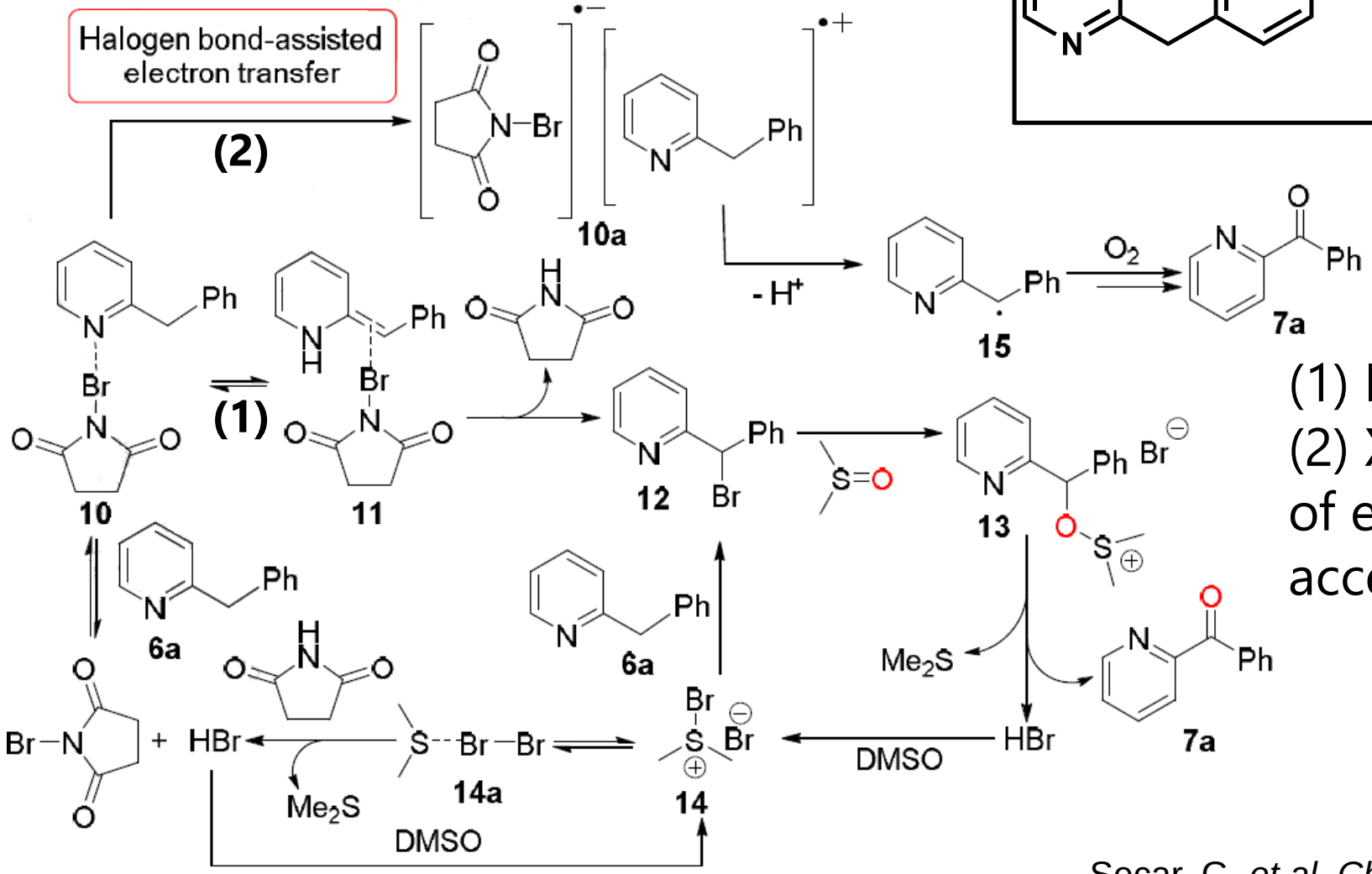
Secar, G. *et al. Chem. Eur. J.* 10.1002/chem.201801717

Oxidation of Heterobenzyl position to C(sp^2)=O or C(sp^3)-O

Oxidation to C(sp^2)=O

Plausible mechanism





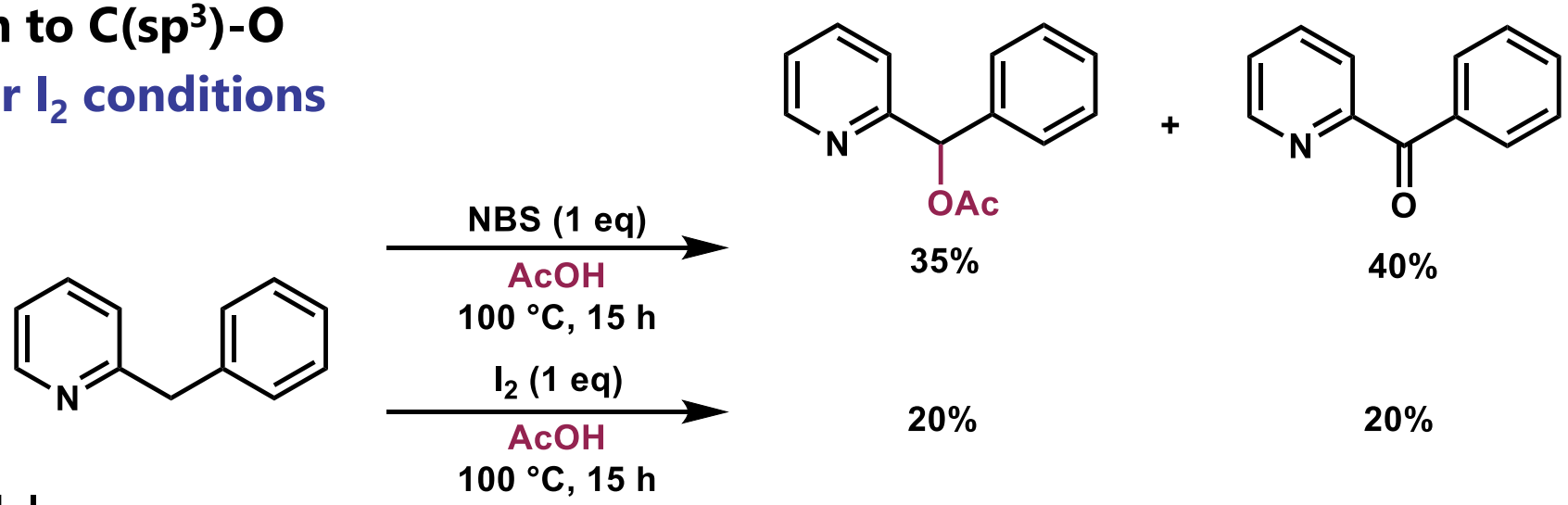
(1) Imine-enamine tautomerization
(2) XB lowers the activation energy of electron transfer from XB acceptor to donor.

Secar, G. *et al. Chem. Eur. J.* 10.1002/chem.201801717

Oxidation of Heterobenzyl position to C(sp^2)=O or C(sp^3)-O

Oxidation to C(sp^3)-O

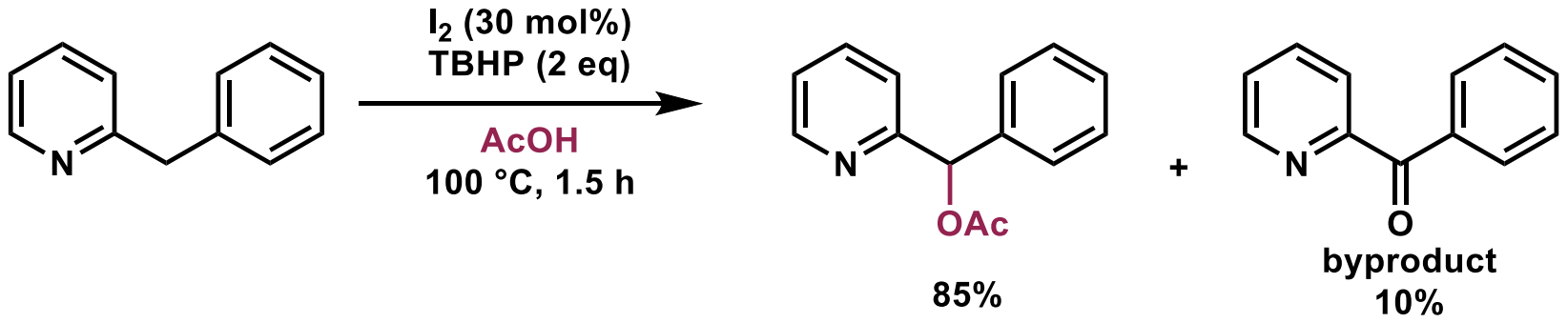
NBS or I_2 conditions



Problem

Background electron transfer to form benzyl radical, then ketone.

I_2+TBHP conditions



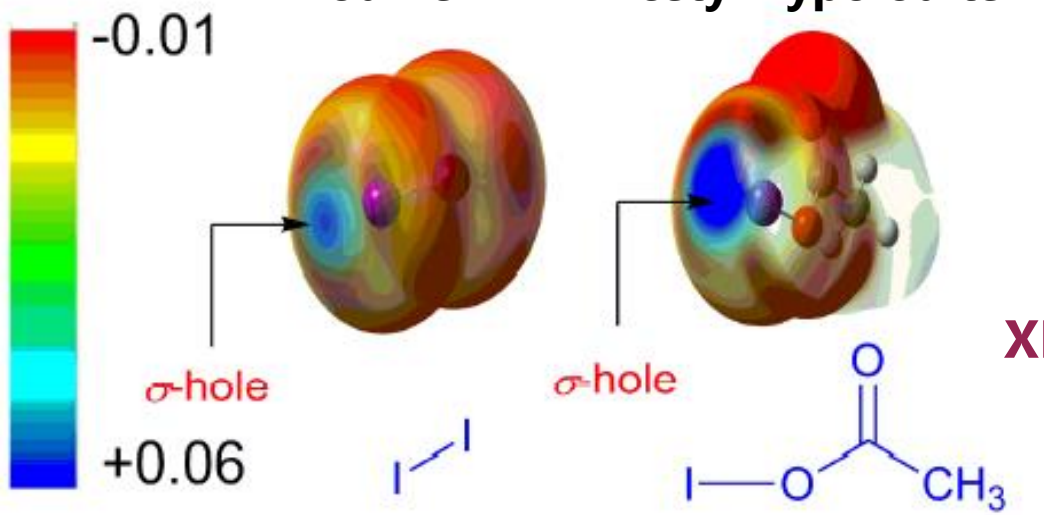
Secar, G. *et al. Chem. Eur. J.* 10.1002/chem.201801717

Oxidation of Heterobenzyl position to C(sp^2)=O or C(sp^3)-O

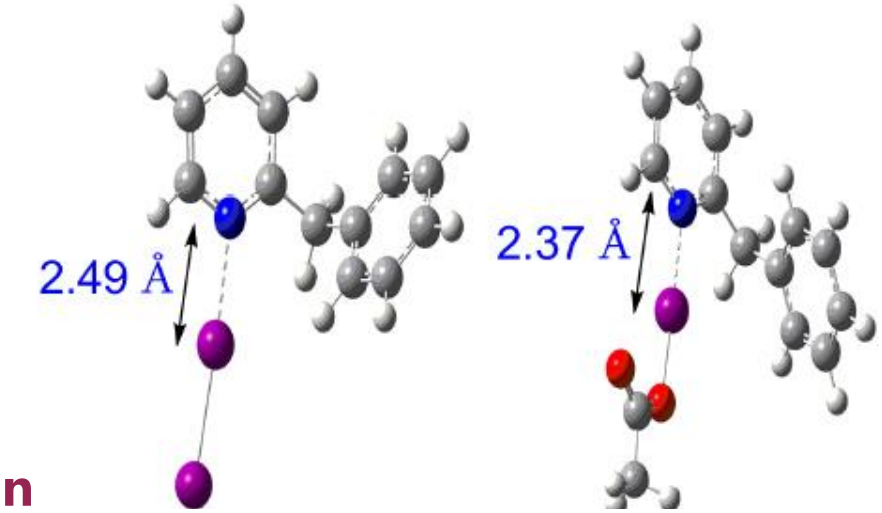
Oxidation to C(sp^3)-O

Active species

Iodine **Acetyl hypoiodite**



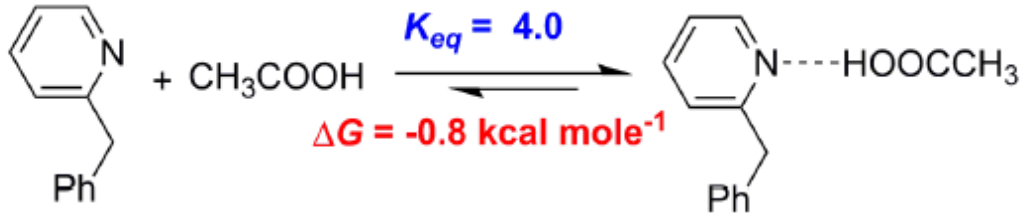
XB formation

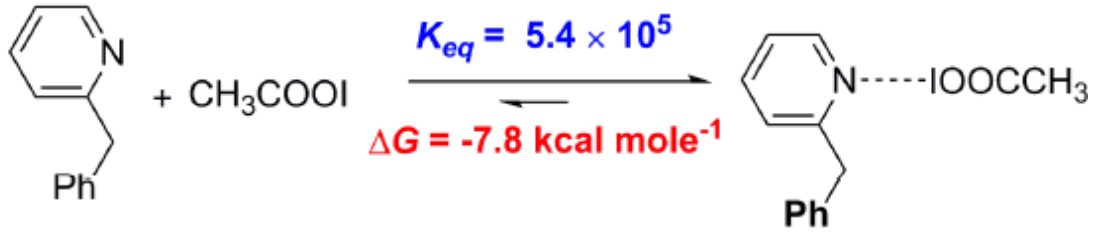


ΔE = -25.6 kcal mol^{-1} ΔE = -33.0 kcal mol^{-1}

Imine-enamine tautomerization

- Activation by hydrogen bond is less likely.

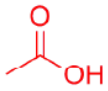
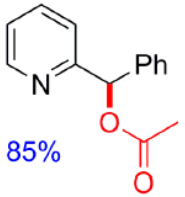
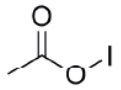
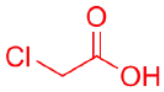
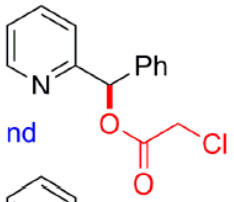
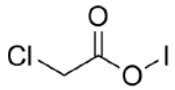
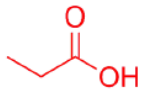
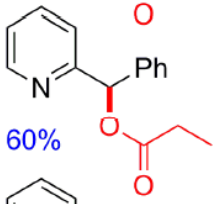
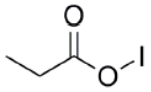
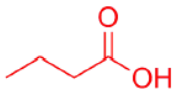
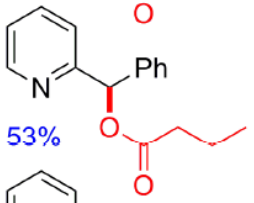
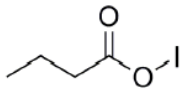
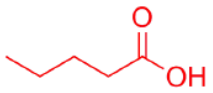
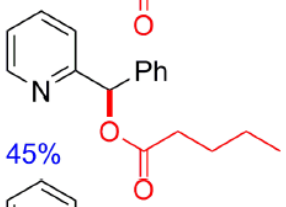
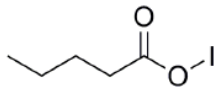
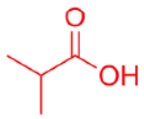
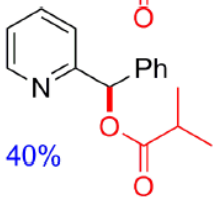
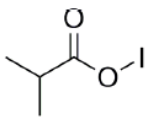




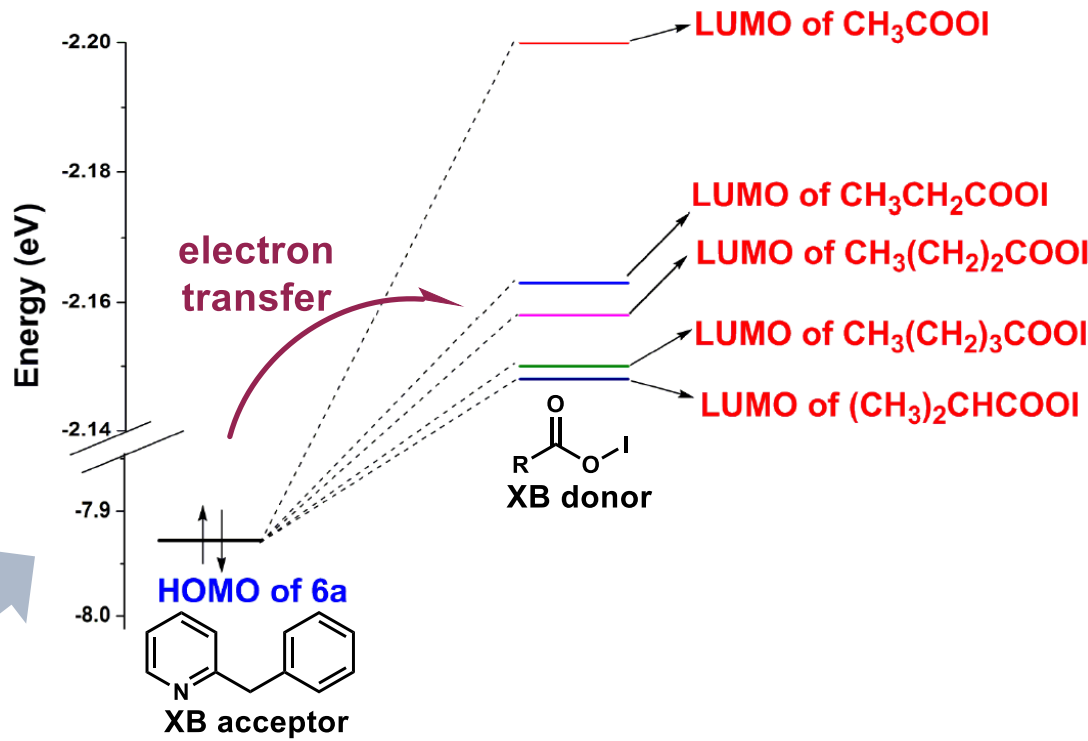
Secar, G. *et al. Chem. Eur. J.* 10.1002/chem.201801717

Oxidation of Heterobenzyl position to C(sp^2)=O or C(sp^3)-O

Oxidation to C(sp^3)-O

entry	acid	*pKa*	yield of acyloxylated product	yield of ketone **7a** (%)	acyl hypoiodites (RCOOI)	interaction energy (ΔE) of RCOOI.**6a** (kcal mol^{-1})
1		4.76	 85%	10		- 40.3
2		2.85	 nd	nd		-
3		4.86	 60%	25		- 42.5
4		4.83	 53%	35		- 45.0
5		4.84	 45%	50		- 47.1
6		4.88	 40%	50		- 45.9

Strong acid:
Cannot form XB complex with acid,
I_2 remains in its free form.
(acyl hypoiodite isn't generated)

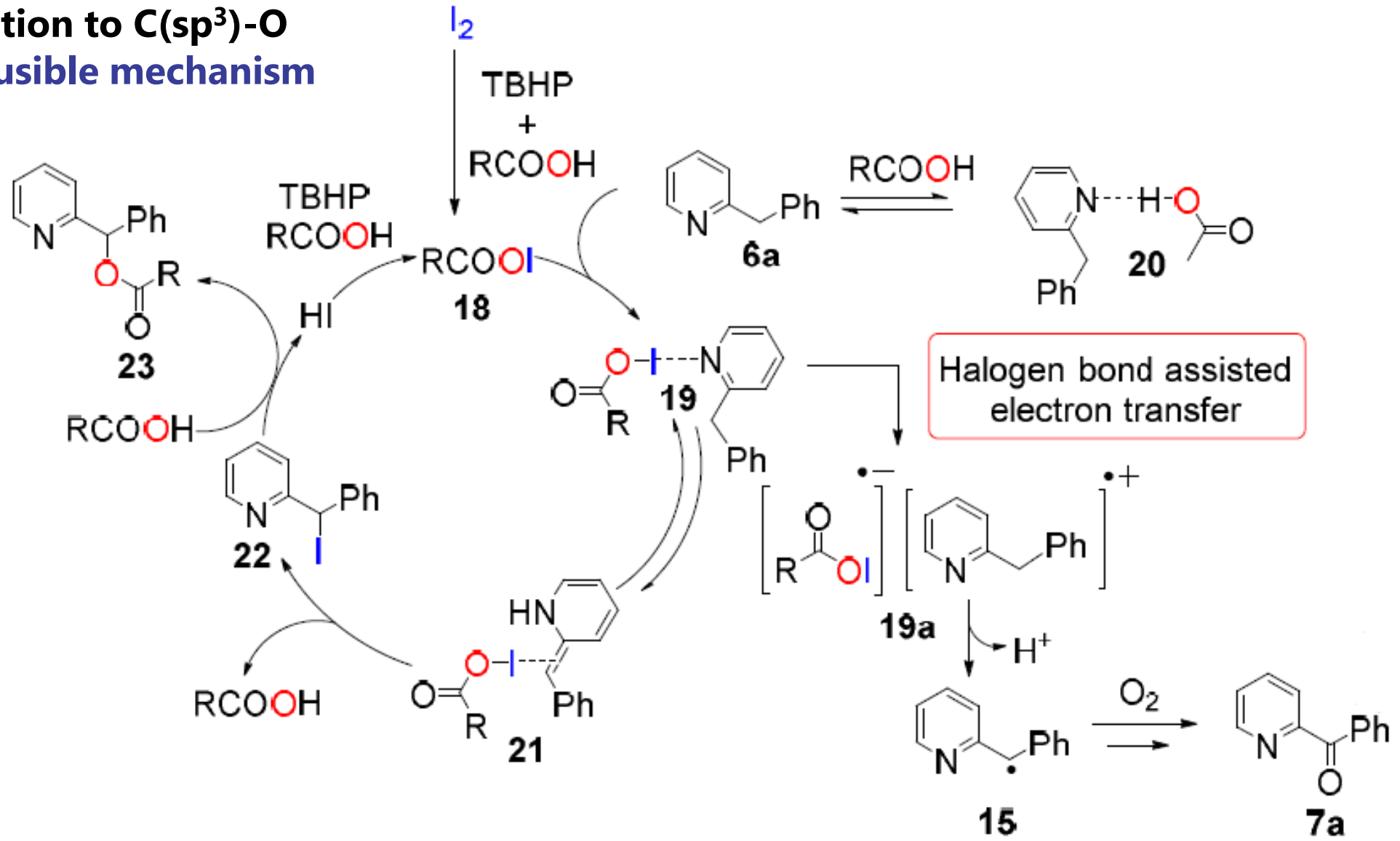


Secar, G. *et al. Chem. Eur. J.* 10.1002/chem.201801717

Oxidation of Heterobenzyl position to C(sp^2)=O or C(sp^3)-O

Oxidation to C(sp^3)-O

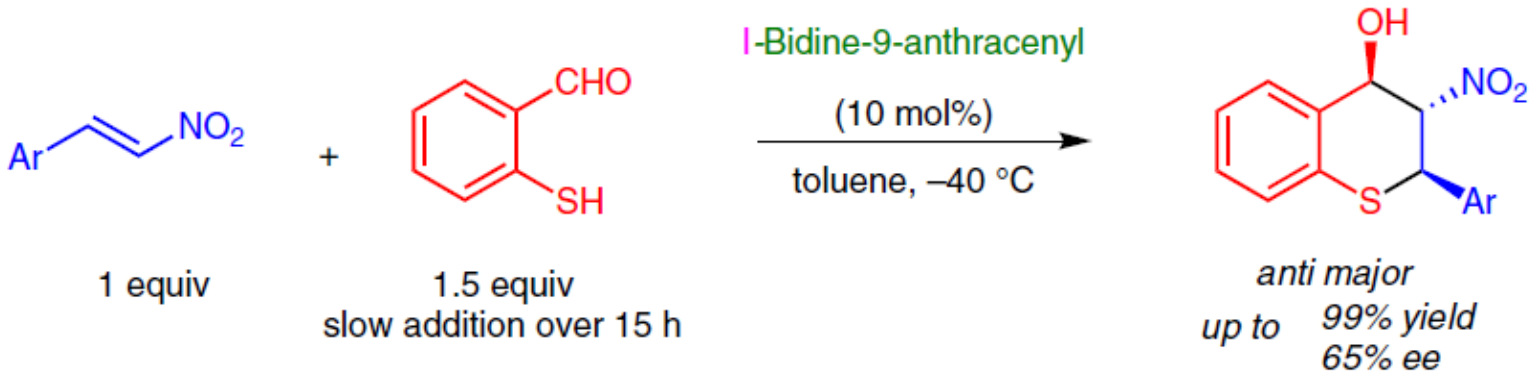
Plausible mechanism



Secar, G. *et al. Chem. Eur. J.* 10.1002/chem.201801717

Enantioselective Reaction Involved by XB

Michael/Henry reaction

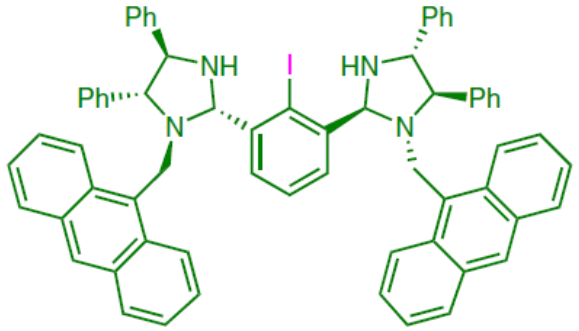


1 equiv

1.5 equiv
slow addition over 15 h

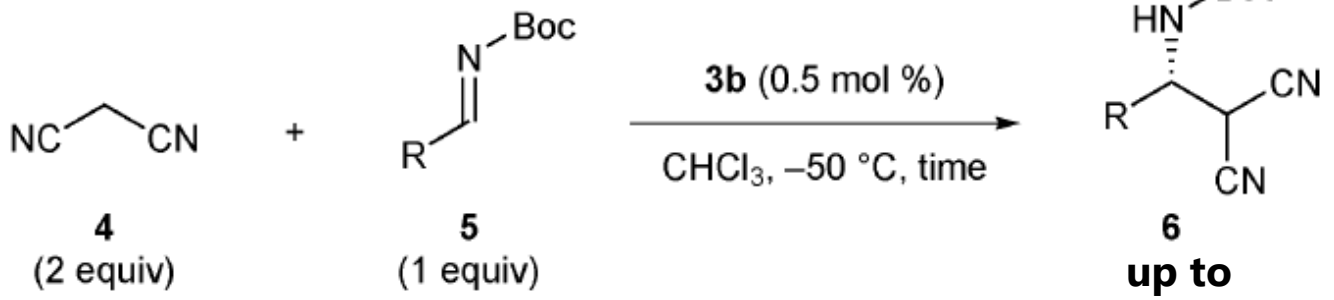
anti major
up to 99% yield
65% ee

XB donor



Arai, T. *et al. Synlett* **2017**, *28*, 122–127.

Mannich reaction

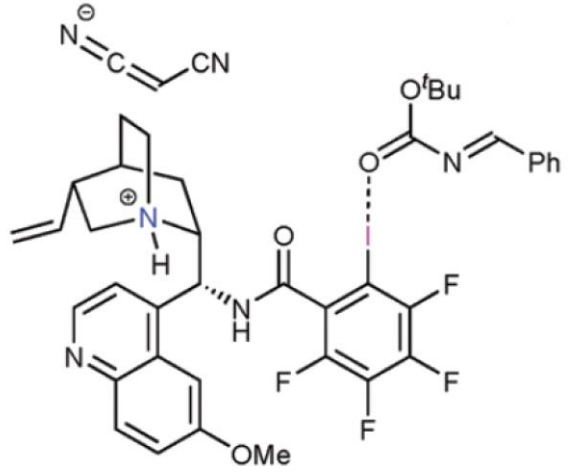


4
(2 equiv)

5
(1 equiv)

6
up to
99% yield
98% ee

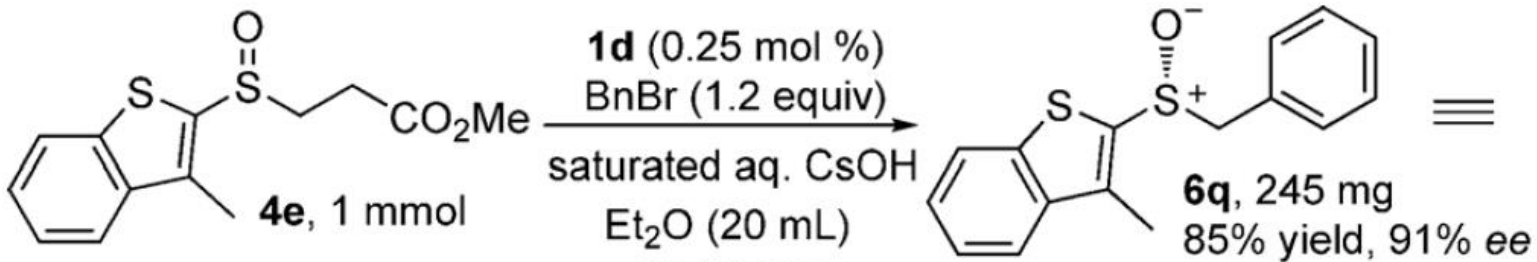
XB donor



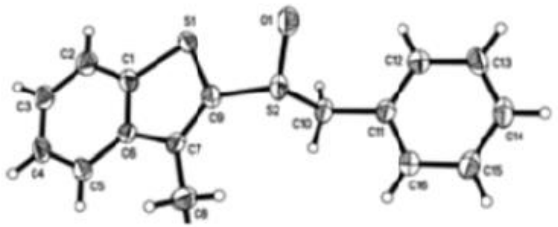
Arai, T. *et al. Chem. Commun.* **2018**, *54*, 3847–3850.

Enantioselective Reaction Involved by XB

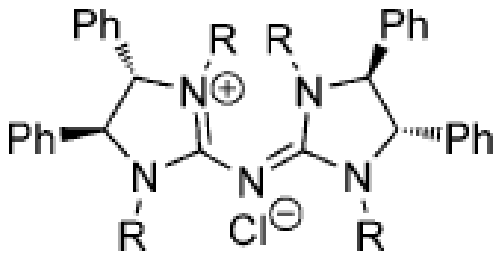
Alkylation of sulfenate anion

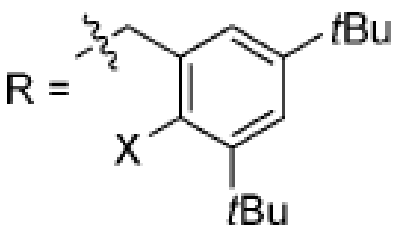


up to
99% yield
99% ee



Crystal structure of (*R*)-**6q**





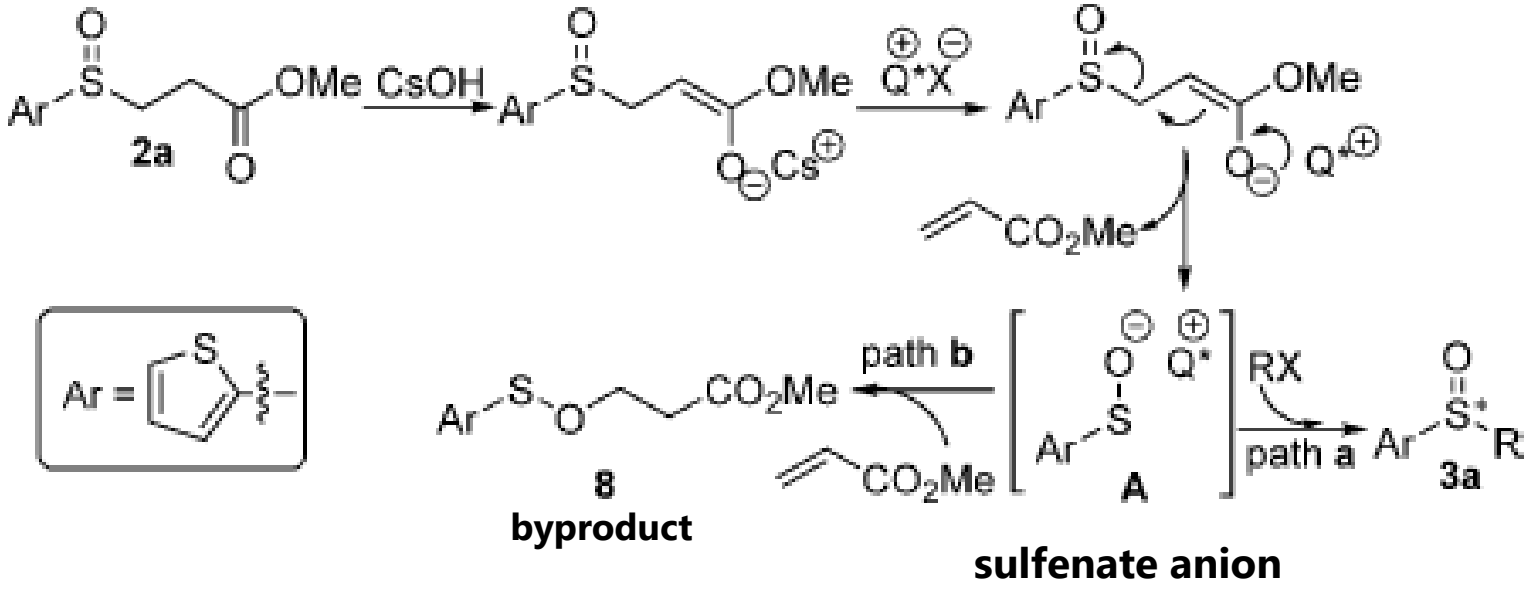
1a X=H
1b X=Cl
1c X=Br
1d X=I

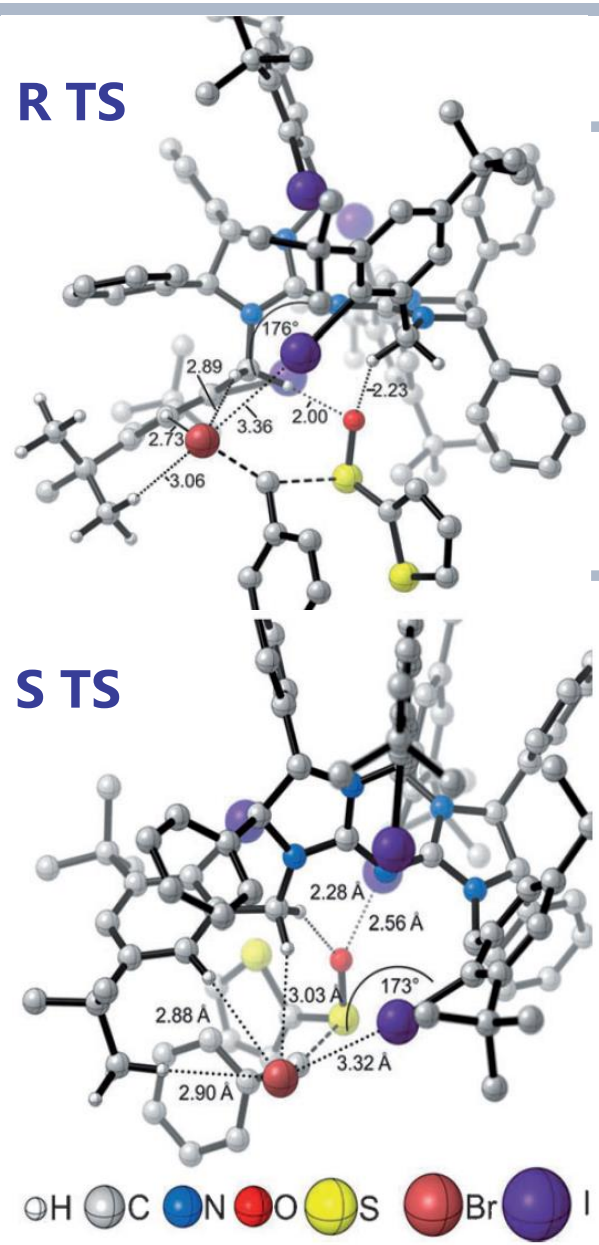
Chiral phase-transfer catalyst

Kee, C. W.; Tan, C. H. *et al. Angew. Chemie - Int. Ed.* **2014**, *53*, 11849–11853.

Enantioselective Reaction Involved by XB

Plausible mechanism





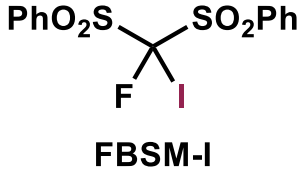
1.2 kcal mol^{-1} more stable

R : S = 95.5 : 4.5

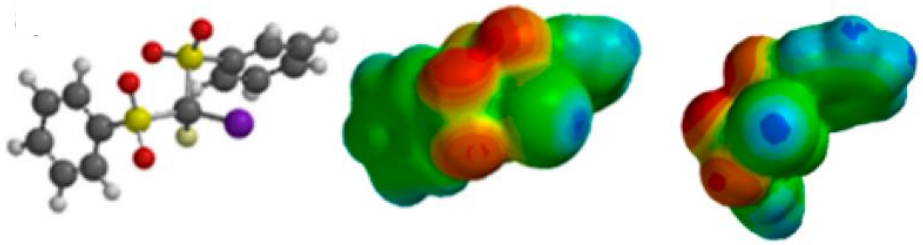
Kee, C. W.; Tan, C. H. *et al. Angew. Chemie - Int. Ed.* **2014**, *53*, 11849–11853.

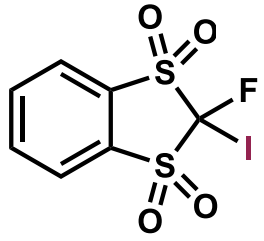
sp^3 XB Donor

Fluorobissulfonylmethyl Iodide

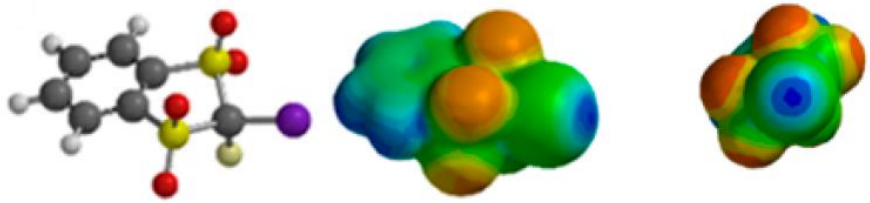


FBSM-I

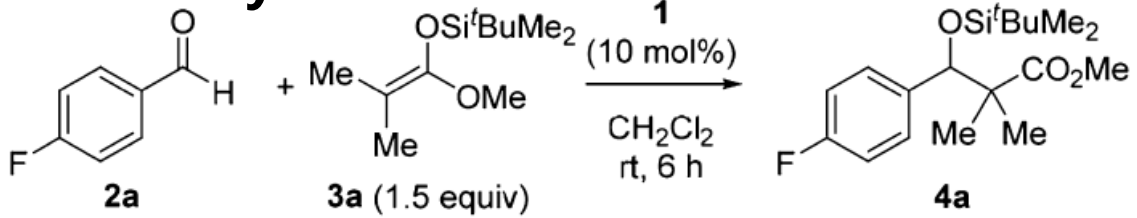




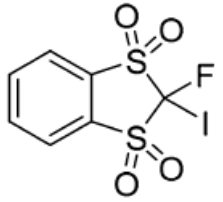
FBDT-I



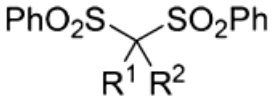
Mukaiyama aldol reaction



1a, 84%



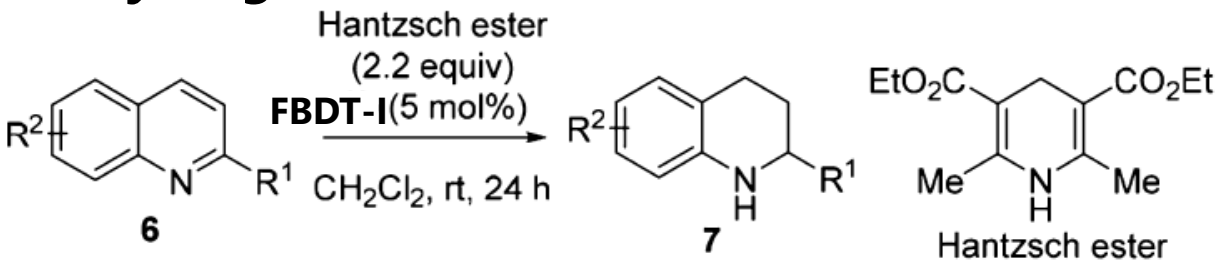
1b, 88%



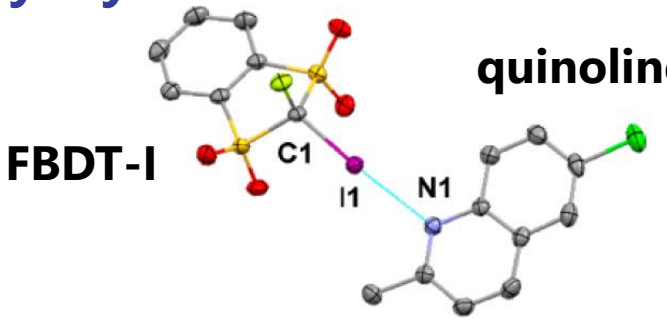
R^1 = F, R^2 = F: **1c**, < 5%
R^1 = F, R^2 = Cl: **1d**, < 5%
R^1 = F, R^2 = Br: **1e**, < 5%
R^1 = F, R^2 = H: **1f** (FBSM), < 5%
R^1 = Me, R^2 = I: **1g**, 18%

R = SO_2Ph: **1h**, <5%
R = F: **1i**, 23%[b]
R = nC_7F_{15}: **1j**, <5%

Hydrogen transfer



X-ray crystal structure



Shibata, N. *et al. ACS Catal.* **2018**, *8*, 6601−6605.

Summary

- Application of XB in synthesis and organocatalysis is in early stage and many example are before the stage of practical application.

- XB may overcome hydrogen bond in some situations if appropriate reaction design is done.