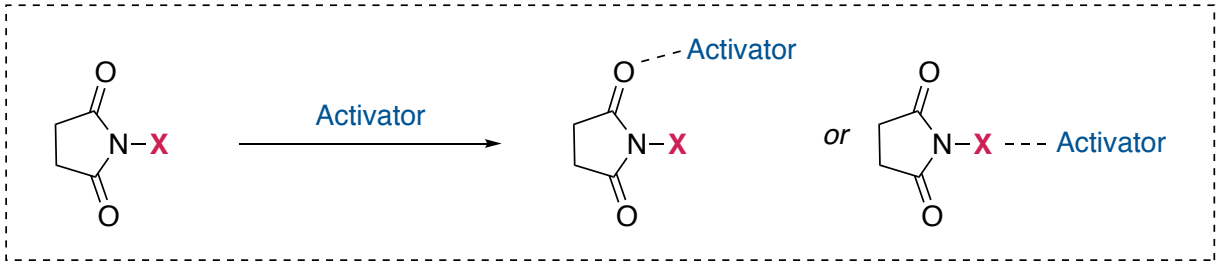
M2 Seminar
2021.10.02

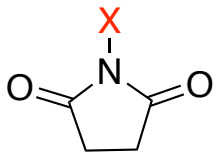
Activation Methods of Electrophilic Halogenating Agents



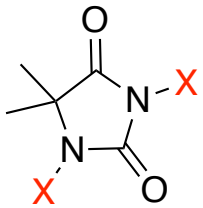
Sachiko KUMAGAI

1. Typical Activation Models of Electrophilic Halogenating Agents

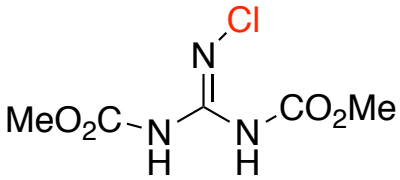
a. Typical electrophilic halogenationg reagents



NXS



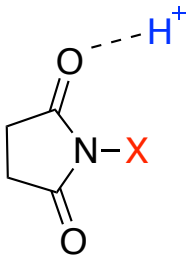
DXDMH



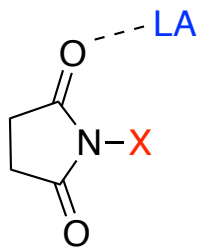
Palau' chlor

b. Typical activation models of NXS (X = Cl, Br, I)

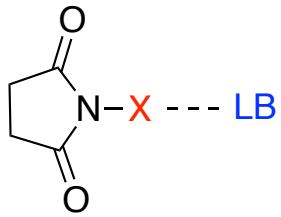
Type I. Bronsted acid



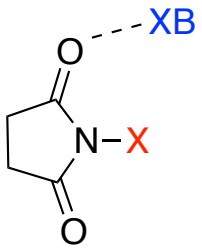
Type II. Lewis acid



Type III. Lewis base



Type IV. Halogen bond



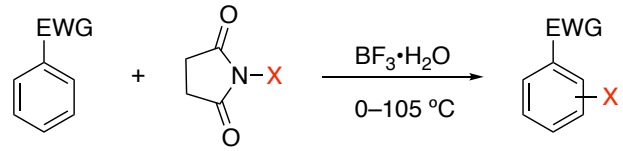
others…complex type

[3] Baran, P. S.* *et al. J. Am. Chem. Soc.* **2014**, 6908.

2. Type I : Bronsted Acid

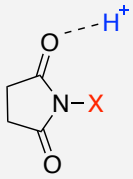
N-Halosuccinimide/BF_3-H_2O, Efficient Electrophilic Halogenating Systems for Aromatics

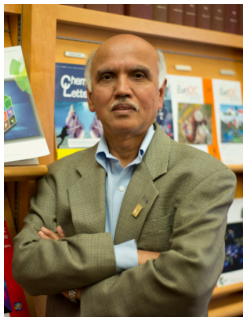
G. K. Surya Prakash* *et al. J. Am. Chem. Soc.* **2004**, 15770



EWG = NO_2, halogen X = Cl, Br, I up to 96% yield, 27 examples

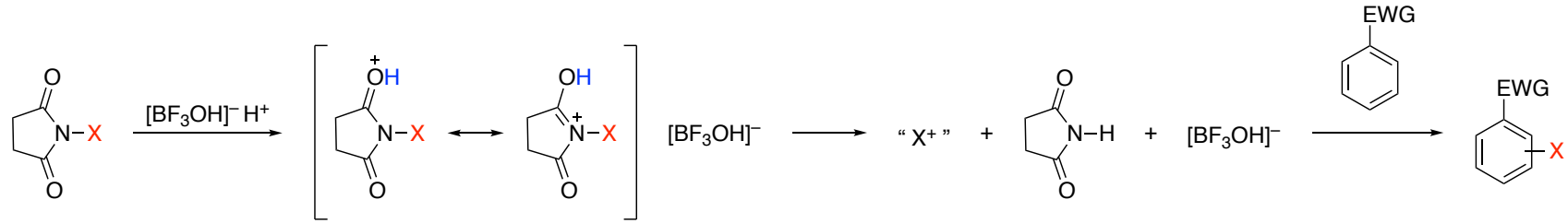
Type I. Bronsted acid



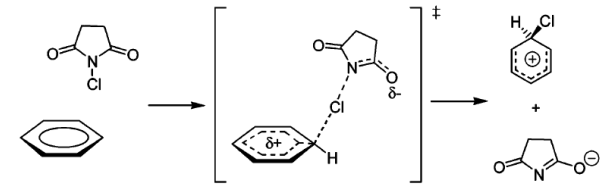


G. K. Surya Prakash (1953–)

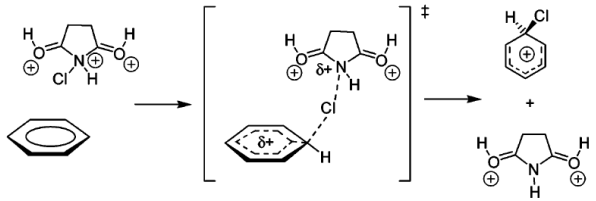
Reaction mechanism

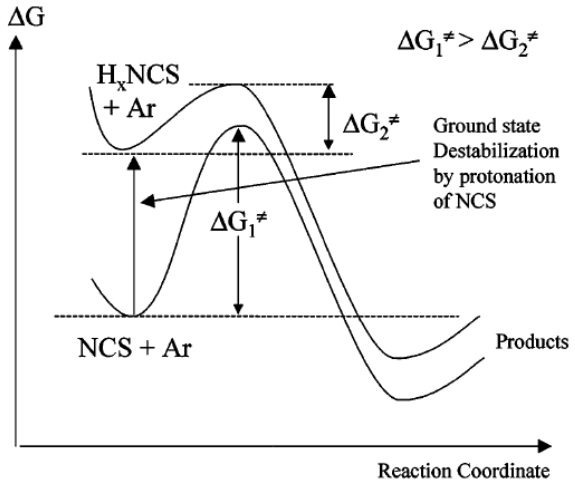


(a) Uncatalyzed Reaction



(b) Acid catalyzed reaction; nte the charge-charge repulsionrelief in the transition state and in the products



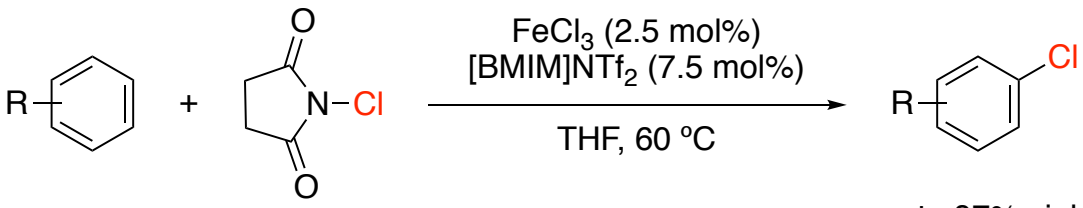


3. Type II : Lewis Acid

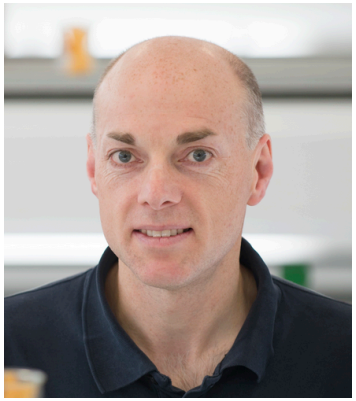
Iron(III)-Catalyzed Chlorination of Activated Arenes

Sutherland, A.* *et al. J. Org. Chem.* **2017**, 7529

Sutherland, A.* *et al. Org. Lett.* **2015**, 4782

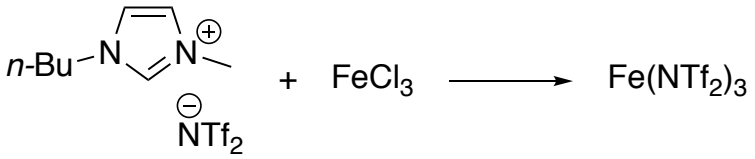


up to 97% yield
26 examples

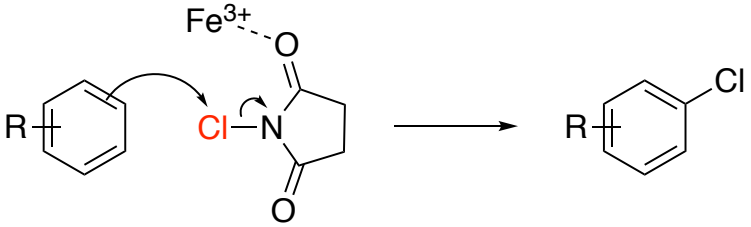


Sutherland, A

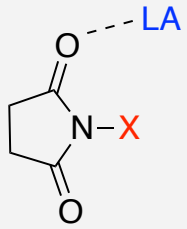
Reaction Mechanism



[BMIM]NTf$_2$



Type II. Lewis acid



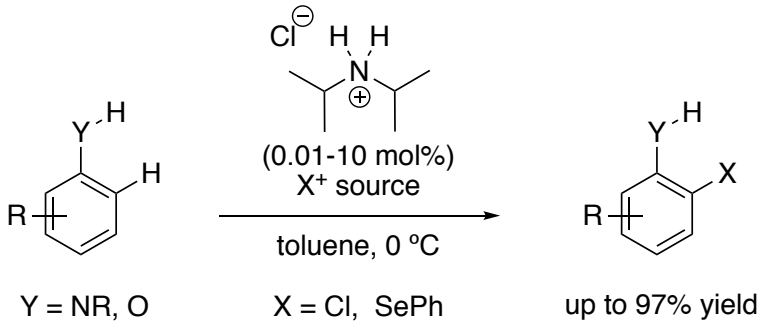
4-1. Type III : Lewis Base

A. Previous lewis base catalysts in halogenation

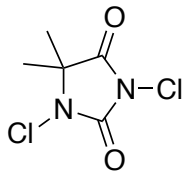
a. *N*-centered

1) Highly *ortho*-Selective Chlorination of Anilines Using a Secondary Ammonium Salt Organocatalyst
Yeung, Y.-Y.* *et al. Angew. Chem. Int. Ed.* **2016**, 16101

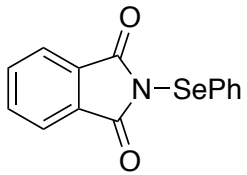
2) Ammonium Salt-Catalyzed Highly Practical *Ortho*-Selective Monohalogenation and Phenylselenation of Phenols: Scope and Applications
Yeung, Y.-Y.* *et al. ACS Catal.* **2018**, 4033



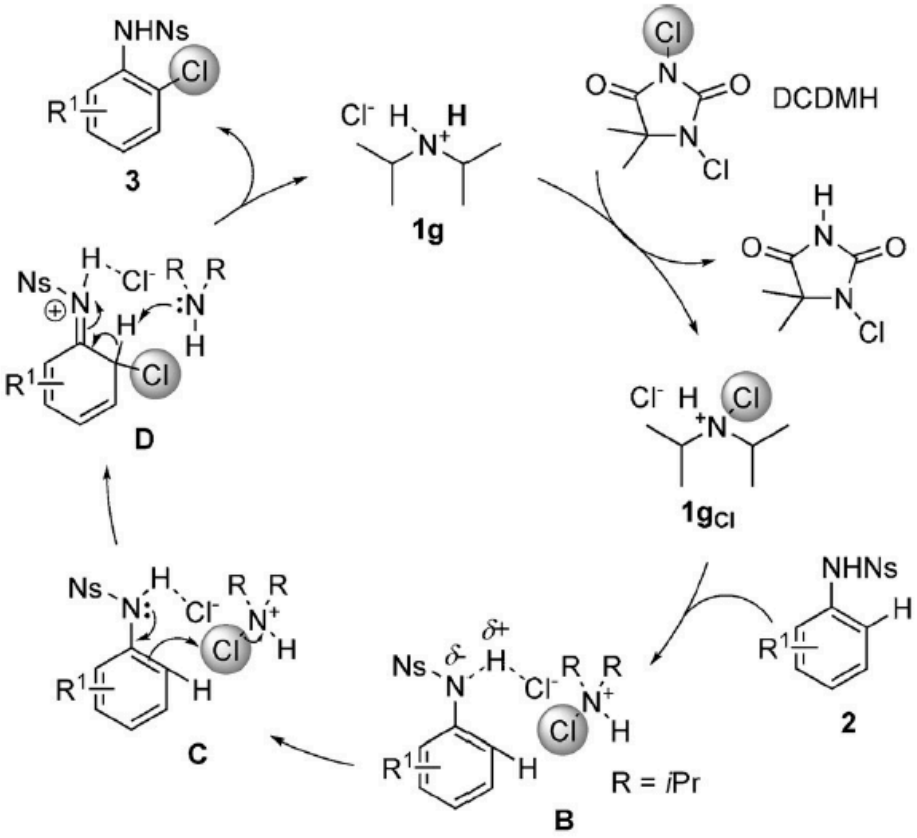
X+ source



DCDMH



N-(phenylseleno)phthalimide



Reaction mechanism

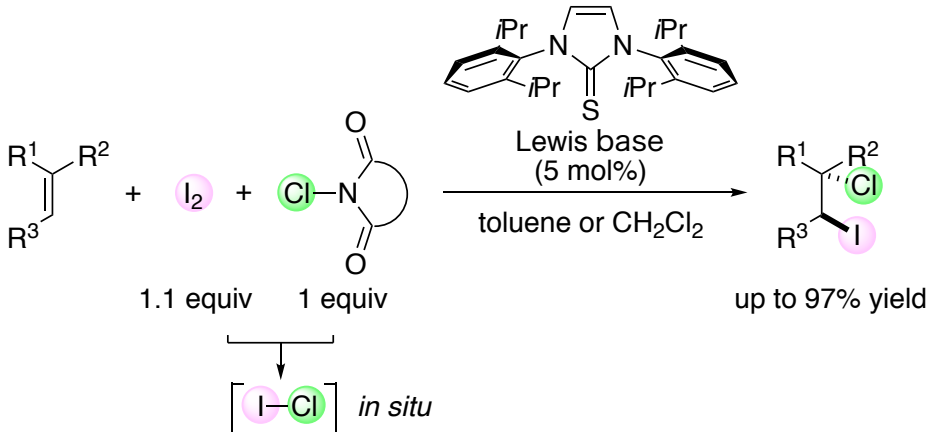
4-2. Type III : Lewis Base

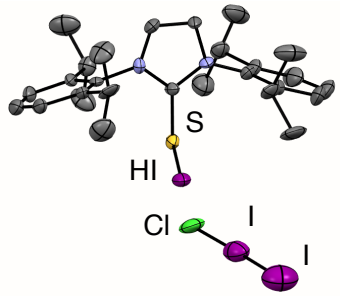
A. Previous lewis base catalysts in halogenation

b. *S*-centered

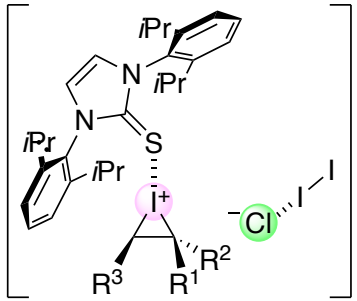
Thiourea–I_2 as Lewis Base–Lewis Acid Cooperative Catalysts for Iodochlorination of Alkene with In Situ-Generated I–Cl

Horibe, T.; Tsuji, Y.; Ishihara, K. *ACS Catal.* **2018**, 6362





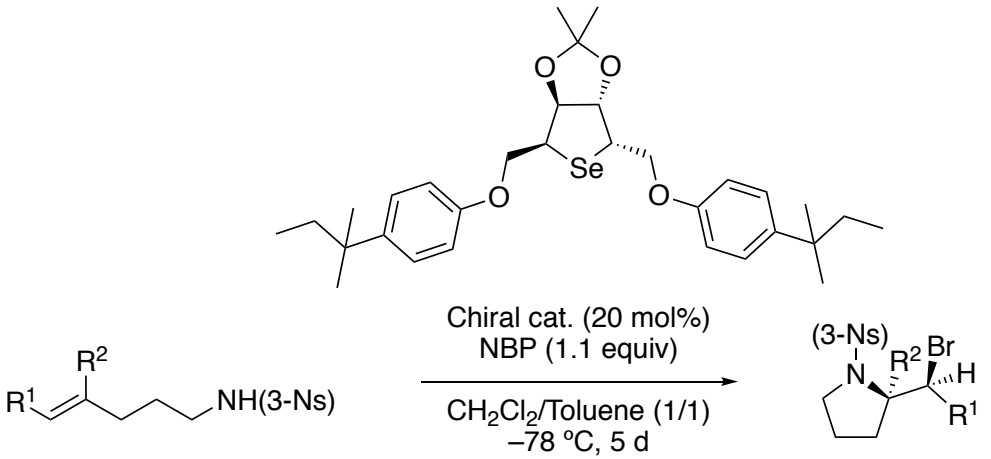
active species



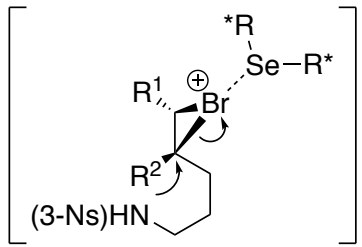
c. *Se*-centered

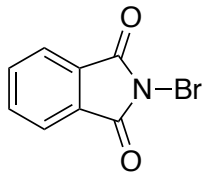
C_2-Symmetric Cyclic Selenium-Catalyzed Enantioselective Bromoaminocyclization

Yeung, Y.-Y.* *et al. J. Am. Chem. Soc.* **2013**, 1232



up to 93% yield, 91% ee





NBP

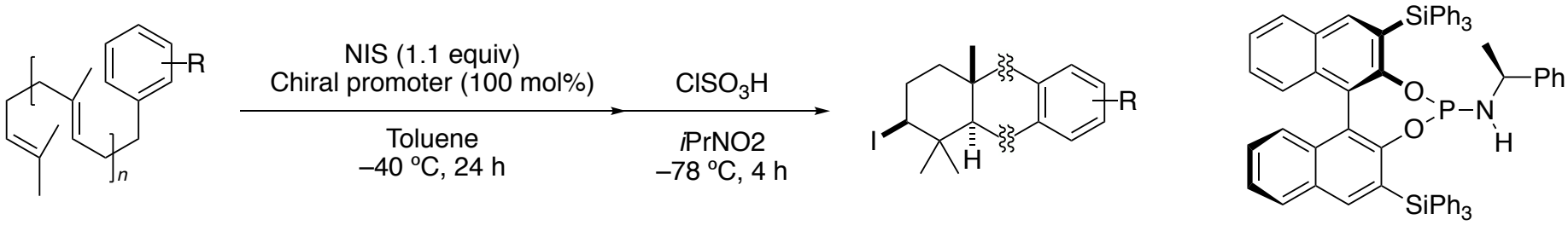
4-3. Type III : Lewis Base

A. Previous lewis base catalysts in halogenation

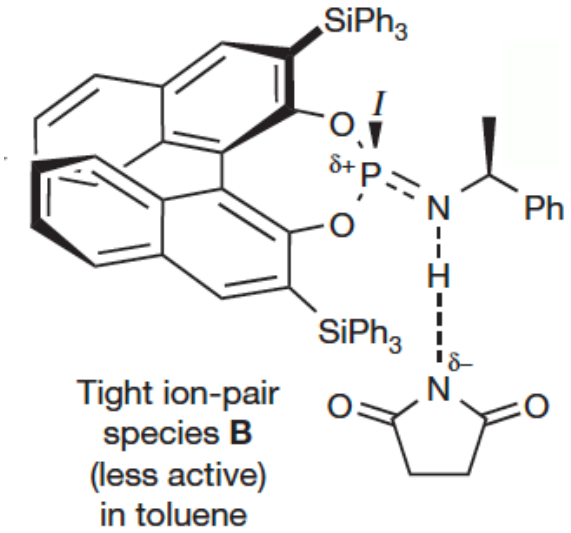
d. *P*-centered

Enantioselective halocyclization of polyprenoids induced by nucleophilic phosphoramidites

Sakakura, A.; Ukai, A.; Ishihara, K. *Nature*, **2007**, 900

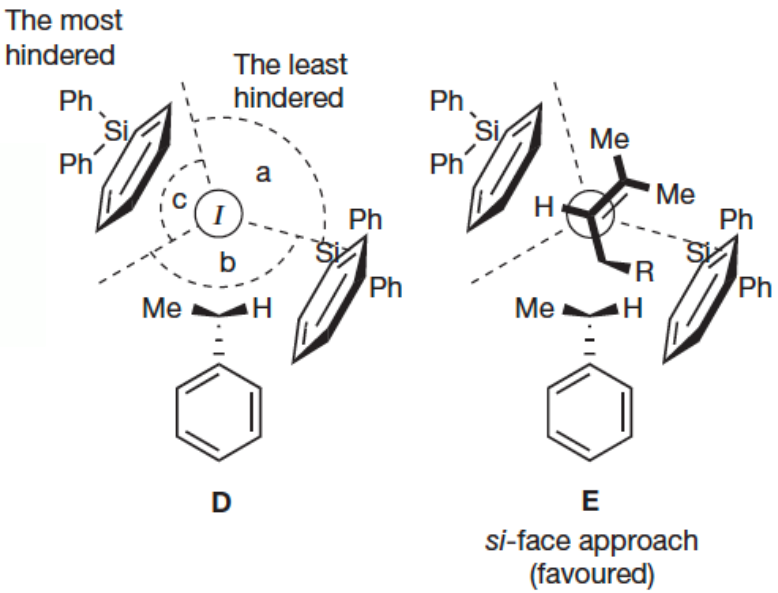


up to 64% yield, 99% ee



Tight ion-pair species **B** (less active) in toluene

ion-pair species

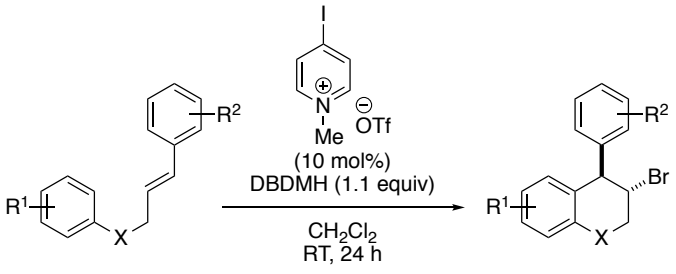


Newman projection of ion-pair species

5. Type IV : Halogen Bond

Halogen Bond Catalyzed Bromocarbocyclization

Yeung, Y.-Y.* *et al. Angew. Chem. Int. Ed.* **2018**, 3483

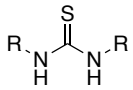


X = NTs, O

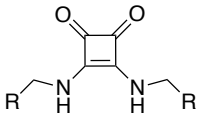
up to 99% yield
d.r. >99:1

Yeung, Y.-Y.*
(1980–)

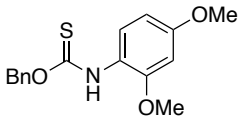
Entry	Catalyst	Yield (%)
9	**2a**	trace
10	**2b**	20
11	**2c**	10
12	$Ph_3P{=}S$	trace
13	iPr_2NEt	trace
14	DMAP	trace
15	CF_3CO_2H	18
16	**3** (BINAP phosphoric acid)	12
17	TMSOTf	13



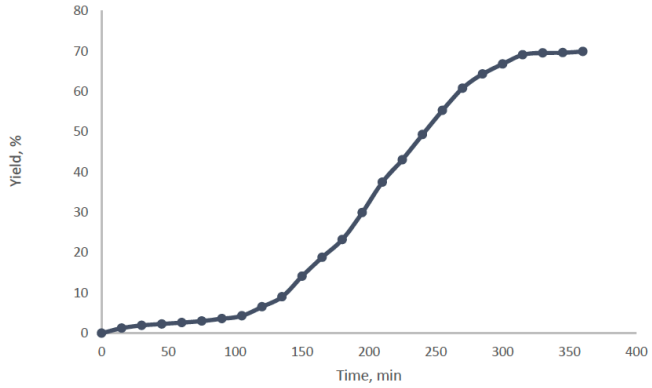
2a



2b

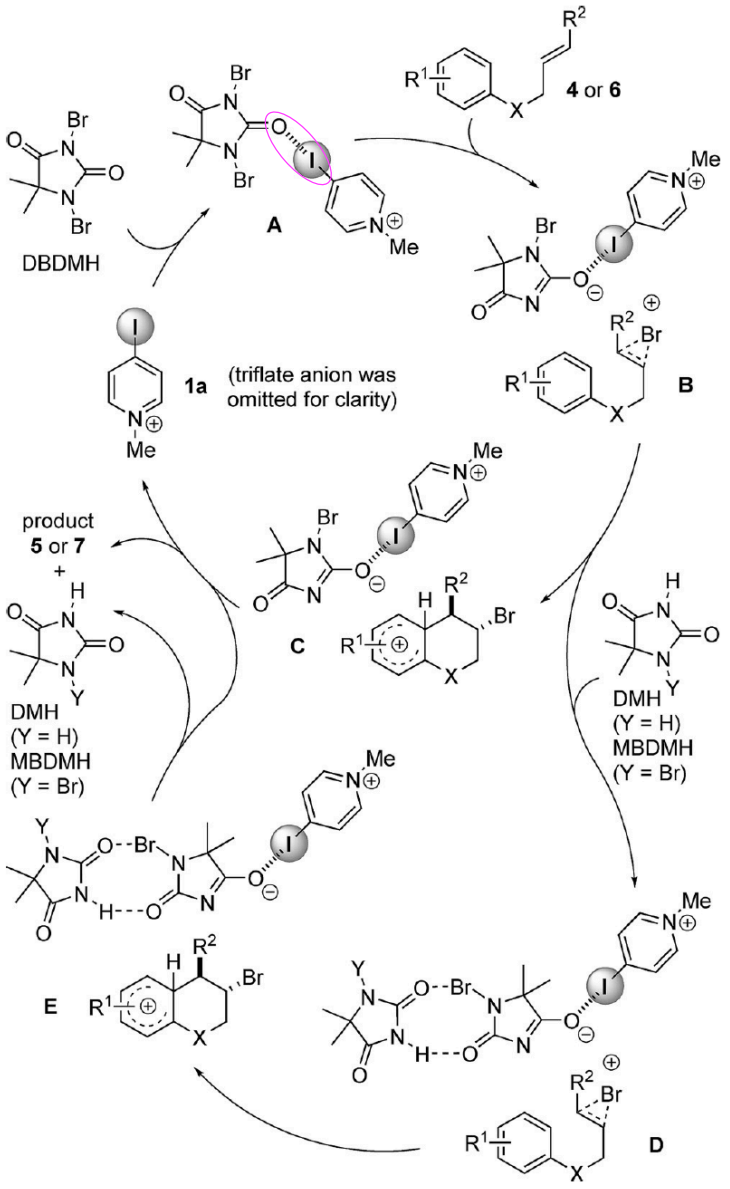


2c



Time-Dependent NMR Study

Reaction mechanism



6. Features of Each Type

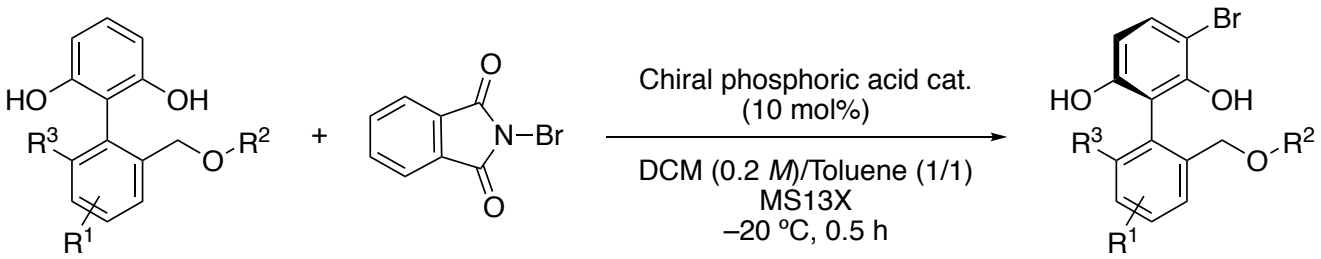
	Feature	Function
Type I Bronsted Acid	• Indirect activation →require FGs to interact with X^+ reagents • Established synthetic method (especially chiral phosphoric acid)	• As an activator
Type II Lewis Acid	• Indirect activation →require FGs to interact with X^+ reagents • Wide range of design (metal counter-anion etc.)	• As an activator
Type III Lewis Base	• Direct interaction of X^+ moiety • Easy to change hetero atoms (optimization of catalyst) • Lots of literature	• As both an activator and a stabilizer
Type IV Halogen Bond	• Indirect or direct activation of X^+ reagents • Directional interaction • A little literatue	• As both an activator and a stabilizer

7-1. Desymmetrization/Kinetic Resolution Sequence

Type I : Bronsted Acid

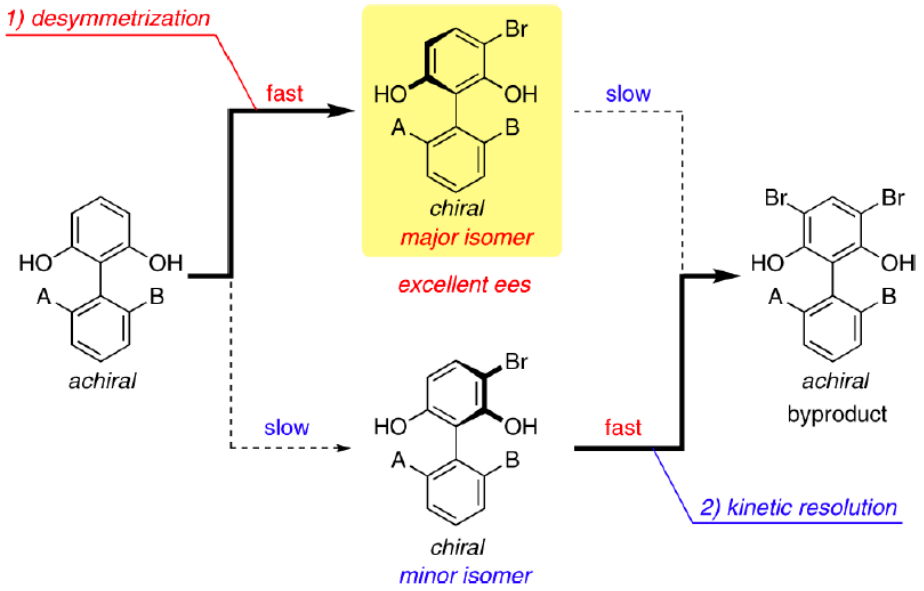
Enantioselective Synthesis of Multisubstituted Biaryl Skeleton by Chiral Phosphoric Acid Catalyzed Desymmetrization/Kinetic Resolution Sequence

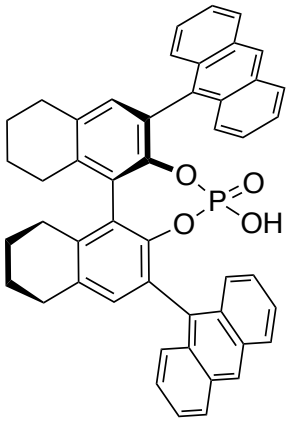
Akiyama, T. *et al. J. Am. Chem. Soc.* **2013**, 3964



Akiyama, T.
(1958-)

Sequential Asymmetric Bromination Reaction



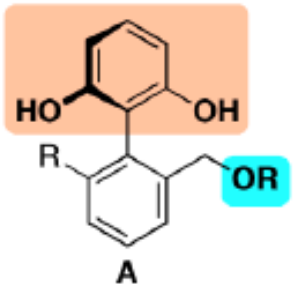


Chiral phosphoric acid catalyst

7-2. Desymmetrization/Kinetic Resolution Sequence

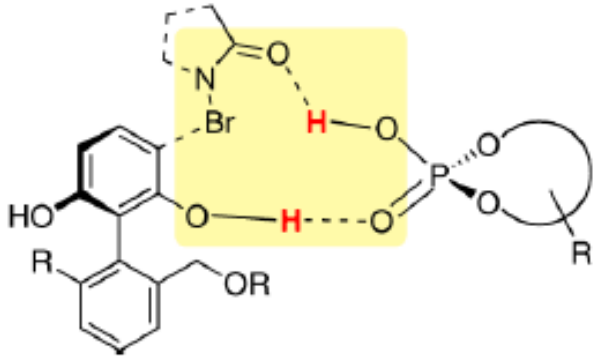
K.ISHIHARA GROUP green catalysis

Substrate Design

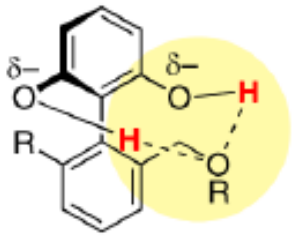


A

i) hydrogen bond network among substrate, catalyst, and brominating reagent

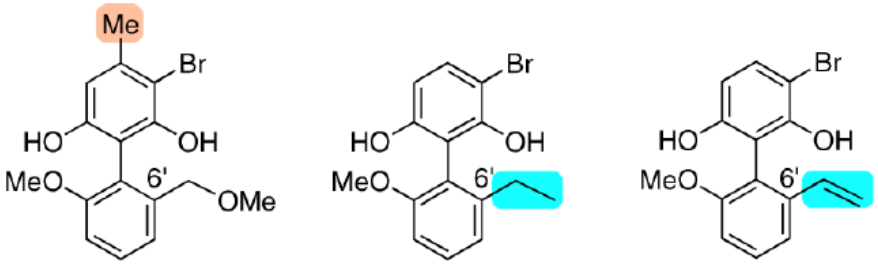


ii) intramolecular hydrogen bond for high reactivity and structural rigidity



Control Experiments

a) Examination of the substituent effect on selectivity



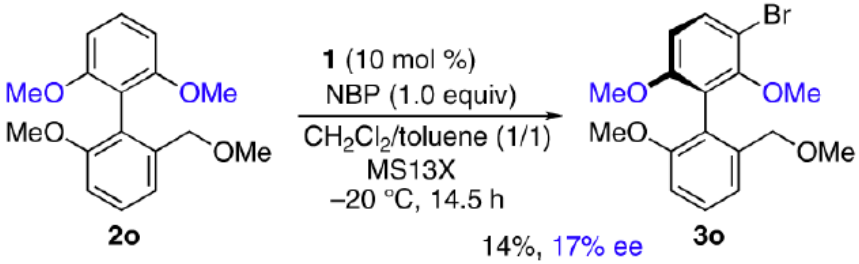
3l 80%, 44% ee

3m 86%, 0% ee

3n 84%, 2% ee

Reaction conditions: **1** (10 mol %), NBP (1.0 equiv), CH_2Cl_2/toluene (v/v=1/1), MS13X, –20 °C, 0.5 h

b) masking the hydroxy group



2o

3o 14%, 17% ee

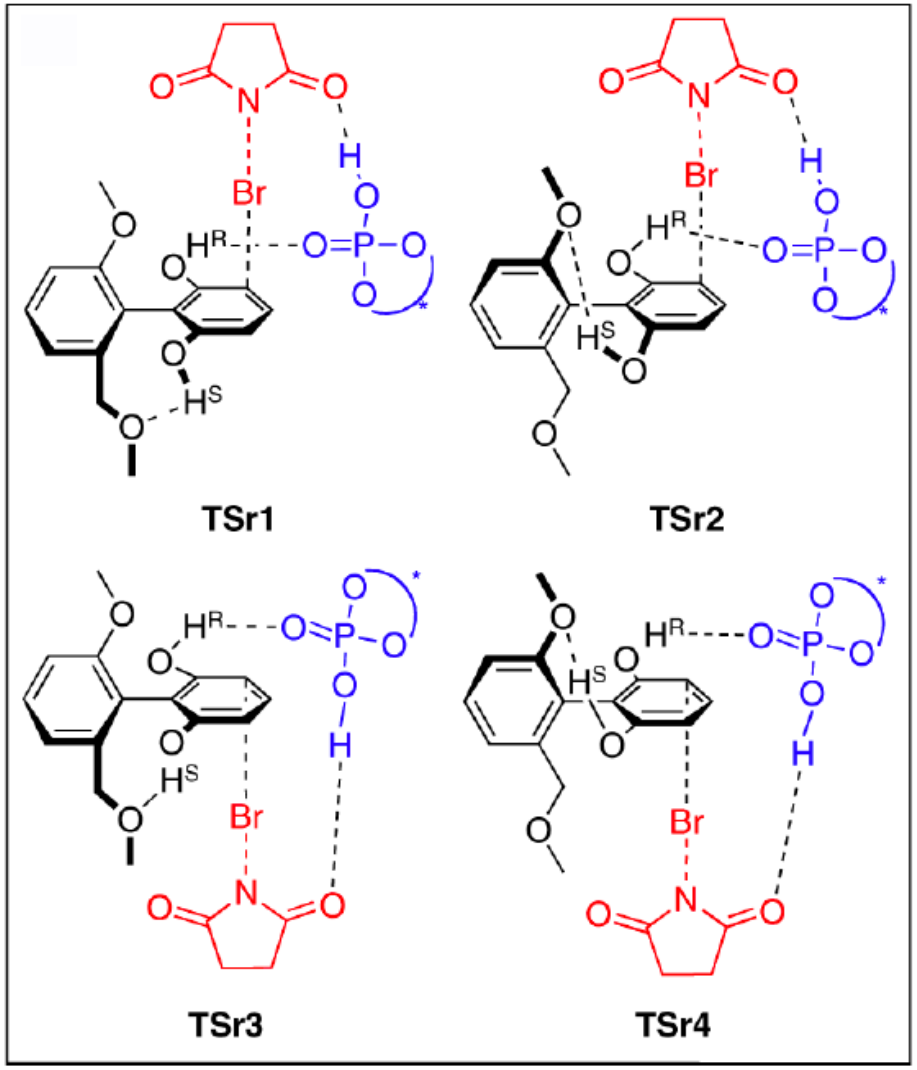
a) C6'-alkoxy group played a crucial role in the enantioselectivity

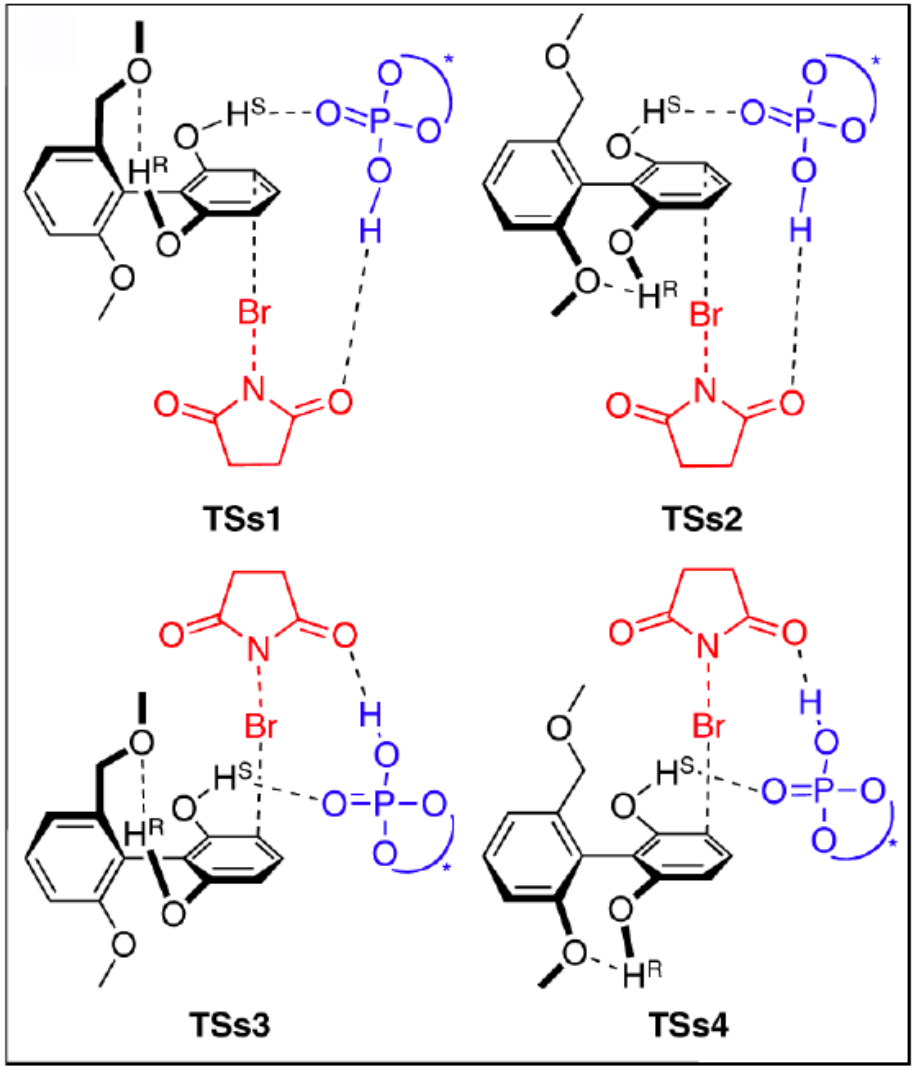
b) Important role of OH in both reactivity and enantioselectivity

7-3. Desymmetrization/Kinetic Resolution Sequence

K.ISHIHARA GROUP
green catalysis

Transition State Model by Gaussian





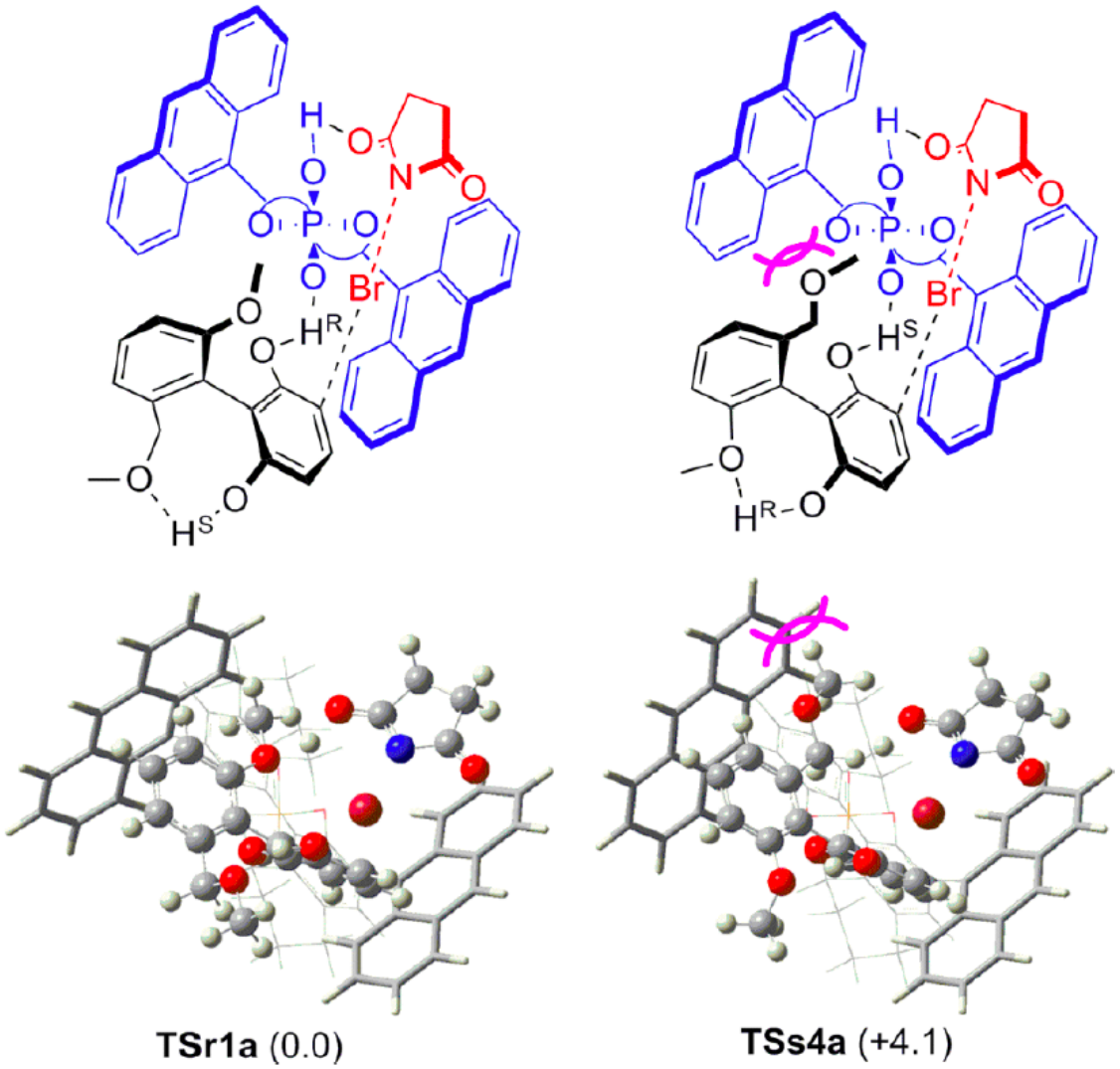
***R*-product**

***S*-product**

7-4. Desymmetrization/Kinetic Resolution Sequence

K.ISHIHARA GROUP green catalysis

Lowest Transition State Model



Major factor affecting

the relative energies

→ the steric interaction

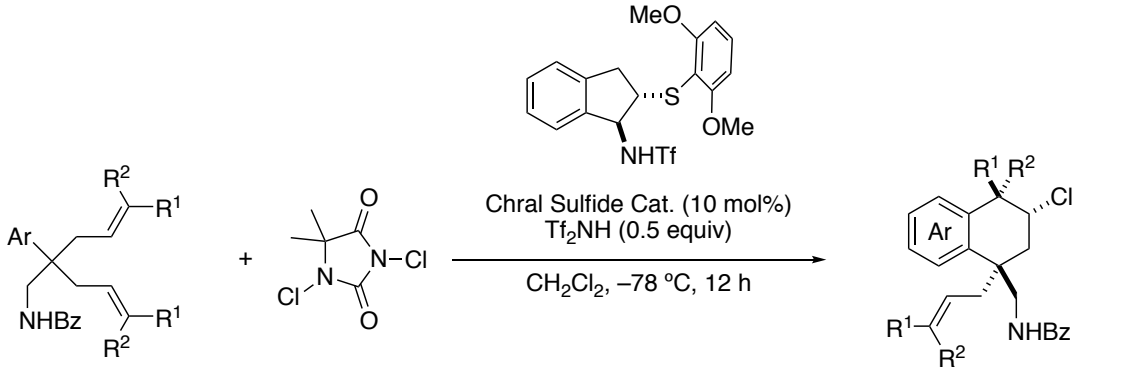
(OMe vs. CH_2-OMe)

8-1. Chiral Sulfide-Catalyzed Enantioselective Chlorination

Type III : Lewis Base

Chiral Sulfide Catalysis for Desymmetrizing Enantioselective Chlorination

Zhao, X.* *et al. Angew. Chem. Int. Ed.* **2019**, 1315



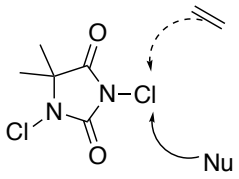
R^1 = Ar, Alkyl, Halogen
R^2 = H, Me, Et

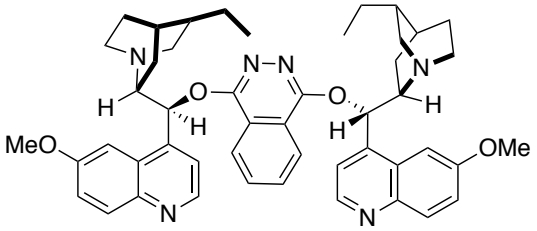
(1 equiv)

up to >99% yield, 99% ee
d.r. >20:1
32 examples

Challenging Tasks

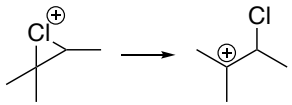
1



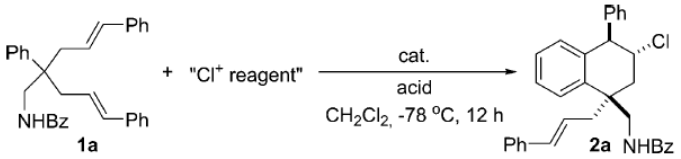


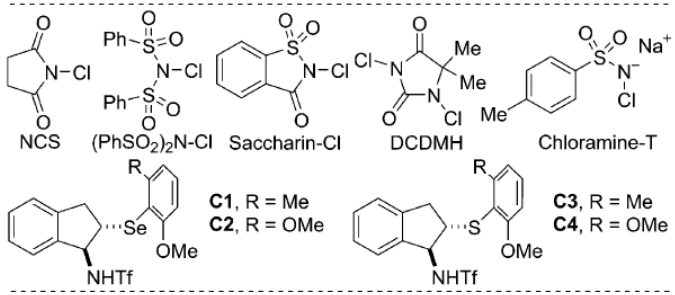
cf. $(DHQD)_2PHAL$ (10 mol%)
w/o Tf_2NH
82% yield, 80% ee ↓

2



Optimization





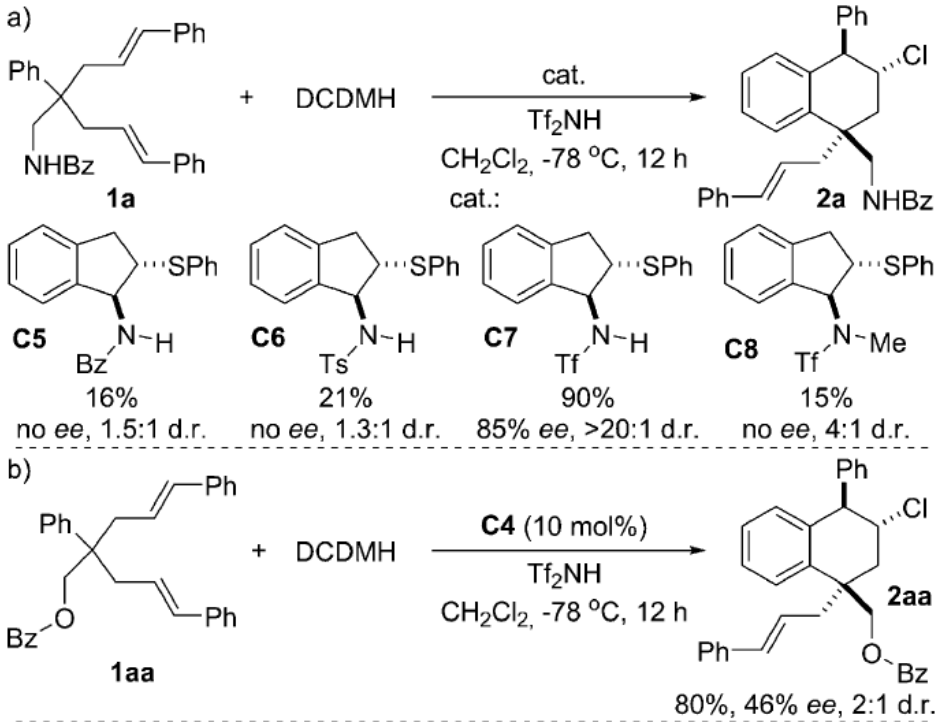
Entry	Cat.	Cl^+ reagent	Acid	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	**C1**	NCS	–	< 5	–	–
2	**C1**	NCS	TFA	< 5	–	–
3	**C2**	NCS	TFA	< 5	–	–
4	**C3**	NCS	TFA	39	53	8:1
5	**C4**	NCS	TFA	45	57	7:1
6	**C4**	$(PhSO_2)_2N$-Cl	TFA	63	21	2:1
7	**C4**	Saccharin-Cl	TFA	35	21	2:1
8	**C4**	DCDMH	TFA	40	73	10:1
9	**C4**	Chloramine-T	TFA	< 5	–	–
10	**C4**	DCDMH	TMSOTf	35	−60	2:1
11	**C4**	DCDMH	$BF_3{\cdot}OEt_2$	32	−25	3:1
12	**C4**	DCDMH	Tf_2NH	31	66	8:1
13[e]	**C4**	DCDMH (1 eq.)	Tf_2NH	68	74	7:1
14[e,f]	**C4**	DCDMH (1 eq.)	Tf_2NH (0.5 eq.)	91	93	31:1
15[e,f]	–	DCDMH (1 eq.)	Tf_2NH (0.5 eq.)	0	–	–

[a] Reaction conditions: **1a** (0.05 mmol), Cl^+ reagent (1.5 equiv), acid (2.0 equiv), catalyst (10 mol%), CH_2Cl_2 (2.0 mL), −78 °C, 12 h. [b] Yield determined by NMR spectroscopy using benzyl benzoate as the internal standard. [c] Determined by chiral HPLC analysis. [d] Determined by NMR spectroscopy. [e] DCDMH (1.0 equiv). [f] Tf_2NH (0.5 equiv).

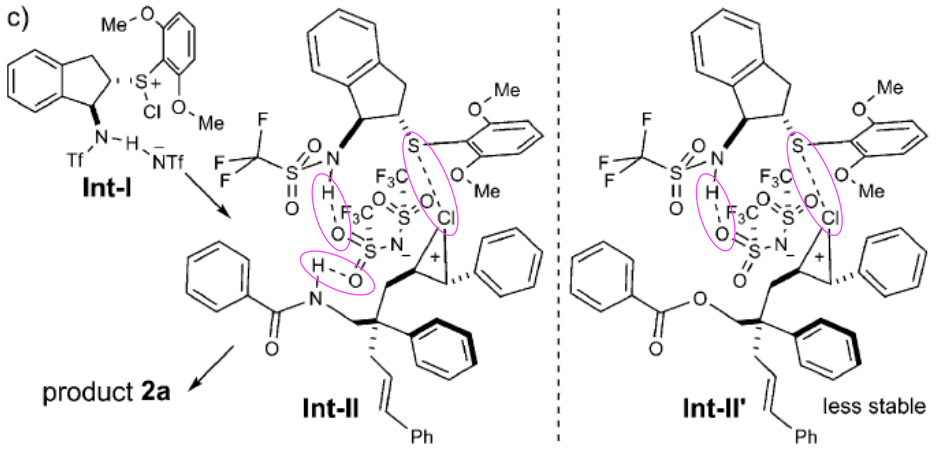
8-2. Chiral Sulfide-Catalyzed Enantioselective Chlorination

K.ISHIHARA GROUP
green catalysis

Control Experiments



Proposed Reaction Mechanism



1a (-NHBz) **1aa** (-OBz)

c) Acid-derived anion bridge through hydrogen-bond

⇩

– accelating the attack of the phenyl group

– stereoselectivity

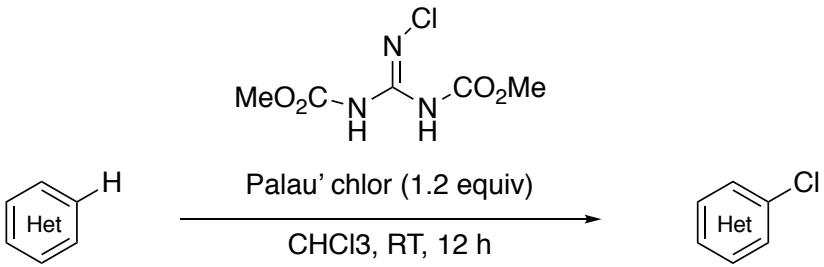
a) Tf : Strong hydrogen-bond donor

b) NHBz : Hydrogen-bond interaction is essential

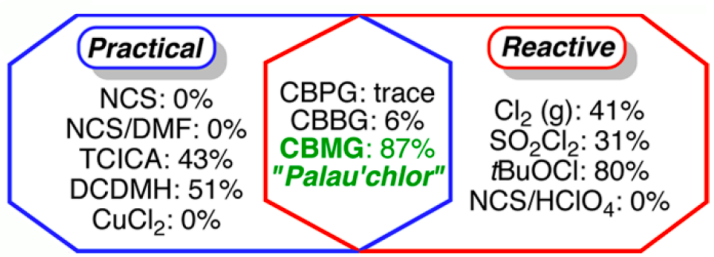
9-1. Background : Chlorination of (hetero)arenes

1. Palau'chlor: A Practical and Reactive Chlorinating Reagent

Baran, P. S.* *et al. J. Am. Chem. Soc.* **2014**, 6908



up to 99% yield
28 examples



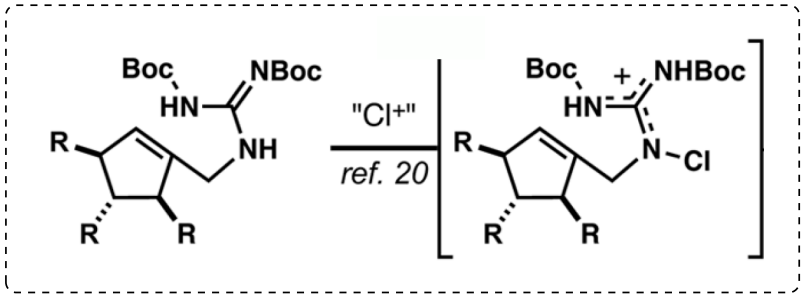
– Elegant selectivity and reactivity

– Air stable

– Safe chlorinating reagent

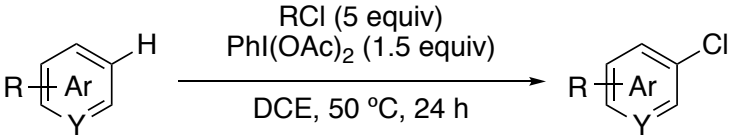
– Good thermal stability

inspired…



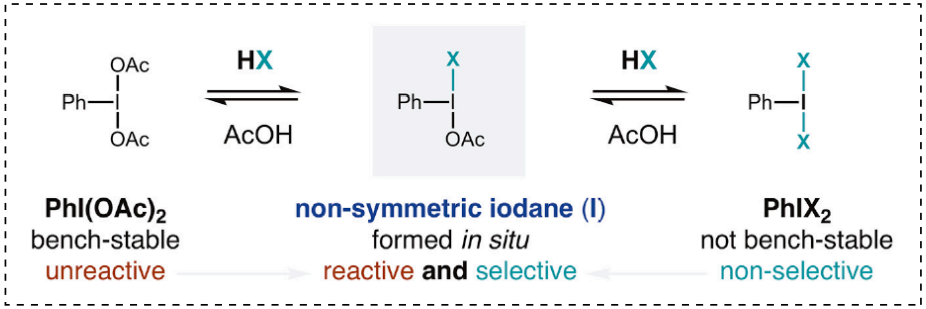
2. Site-Selective C–H Functionalization of (Hetero)Arenes via Transient, Non-symmetric Iodanes

Nagib, D. A. *et al. Chem* **2019**, 417



up to 99% yield
34 examples

Y=CH, RCl=HCl
Y=N, RCl=HCl, Bu_4NCl, EtO_2CCl, C_6F_5COCl, AcCl



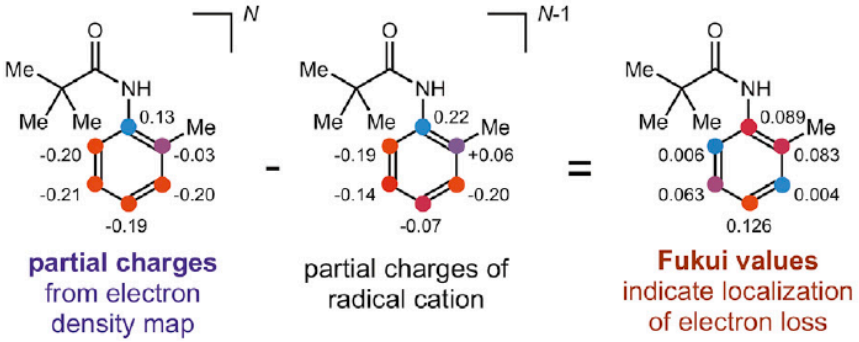
– Site-selectivity

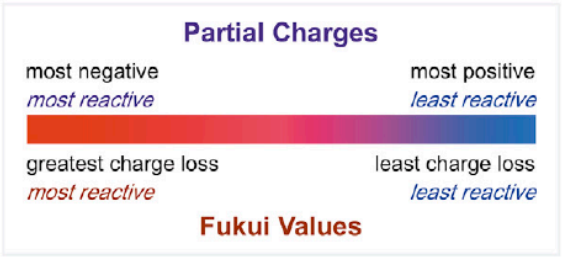
– More reactive system

9-2. Background : Chlorination of (hetero)arenes

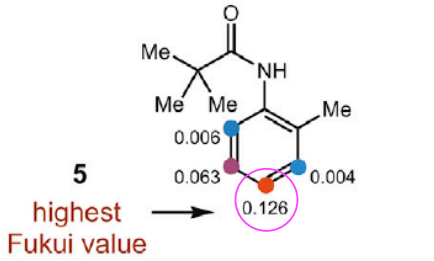
K.ISHIHARA GROUP green catalysis

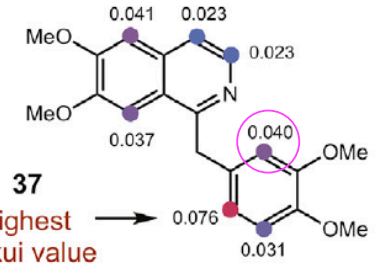
Computationally Experiments

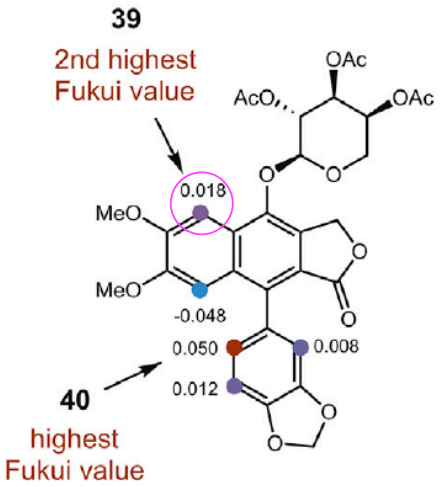




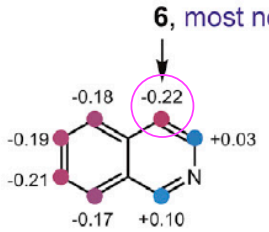
arenes: Fukui values predict selectivity

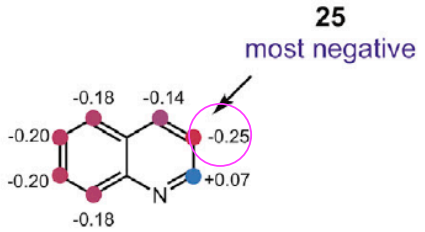


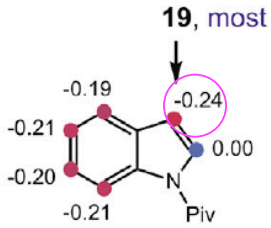


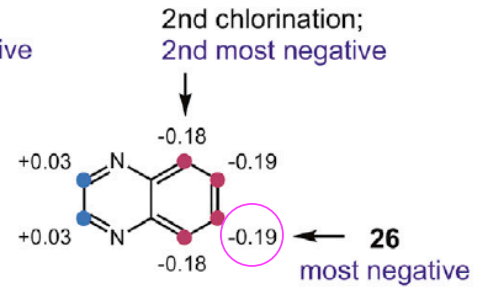


heteroarenes: partial charges predict selectivity





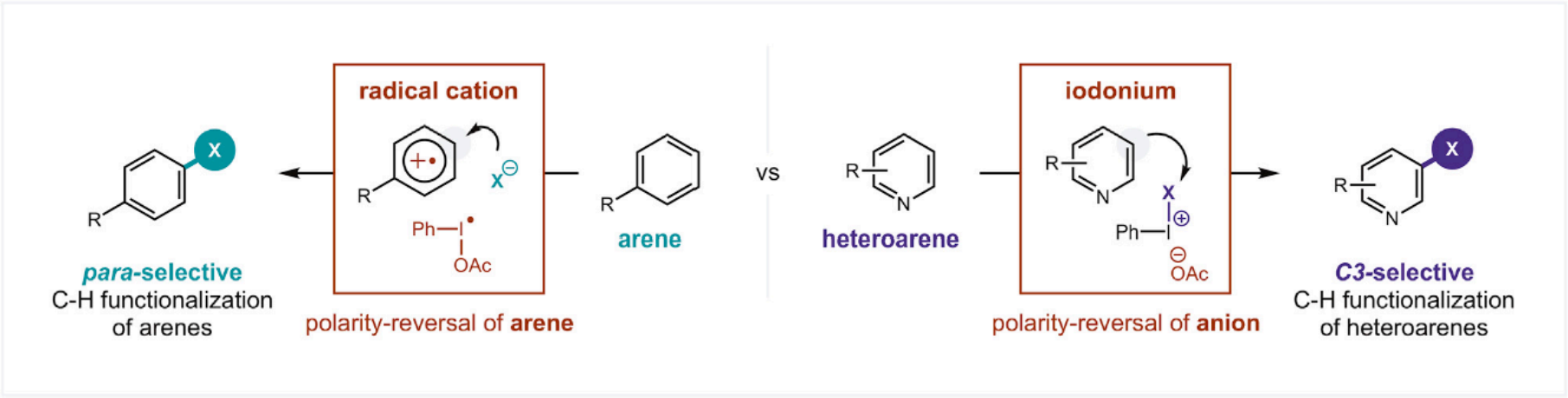




Actual reaction point

9-3. Background : Chlorination of (hetero)arenes

Proposed Reaction Mechanism



Demerits of these method

–Expensive chlorinating reagents

–Harsh conditions

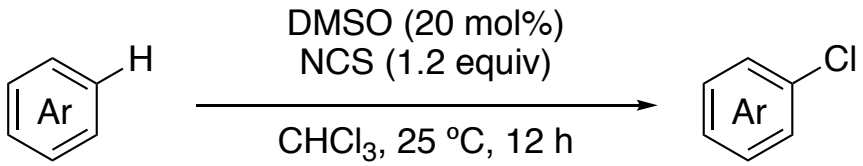
– A lack of a simple, selective and practical catalytic protocol for late-stage chlorination

10-1. DMSO-catalysed late-stage chlorination of (hetero)arenes

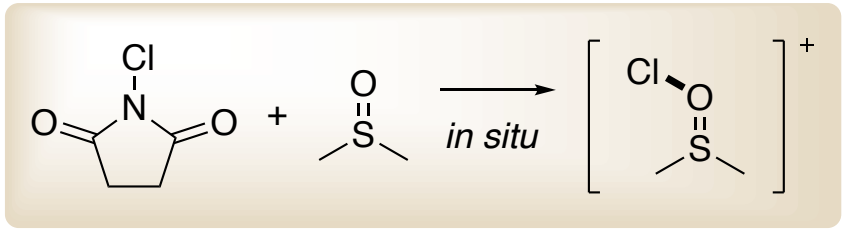
Type III : Lewis Base

DMSO-catalysed late-stage chlorination of (hetero)arenes

Song S. *et al. Nat. Catal.* **2020**, 107



- up to 99% yield
- 51 examples
- including 9 drugs, 30 (hetero)arenes, 6 natural products, 5 peptides



– Simple DMSO as catalyst

– Efficient, pratical, scalable and low cost

– Late stage chlorination of bioactive molecules

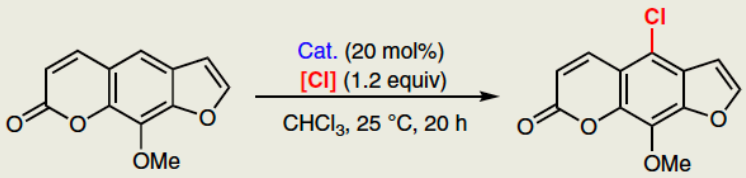
– Readily available NCS reagents

– Broad heteroarene scopes

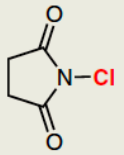
– Direct chlorination of tyrosine residue

10-2. DMSO-catalysed late-stage chlorination of (hetero)arenes

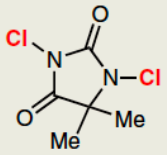
Optimization



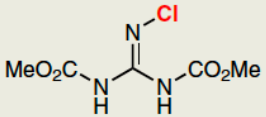
xanthotoxin — Cl-xanthotoxin



NCS



DCDMH

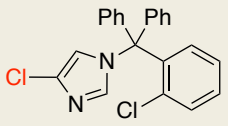


Palau'chlor

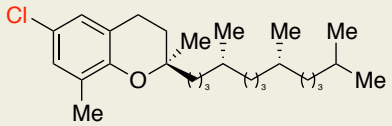
Entry	[Cl]	Cat.	Yield	Entry	[Cl]	Cat.	Yield
1	NCS	-	3%	8	DCDMH	$Ph_3P{=}S$	62%
2	NCS	- (70 °C)	11%[a]	9	DCDMH	DMSO	90%
3	NCS	DMSO	90%	10	Palau'chlor	-	48%
4	NCS	Py *N*-oxide	trace	11	Palau'chlor	$Ph_3P{=}S$	55%
5	NCS	$PhNO_2$	trace	12	Palau'chlor	DMSO	91%
6	NCS	$Ph_3P{=}S$	40%	13	NCS	DMSO as solvent	trace
7	DCDMH	-	45%	14	HCl[b]	DMSO as solvent	trace

Reactions were conducted in 0.25 M $CHCl_3$ at 25 °C for 20 h at the 0.25 mmol scale catalysed by 20 mol% catalyst. Isolated yields. [a]At 70 °C for 48 h. [b]Aqueous HCl (2 equiv., 37%) was employed.

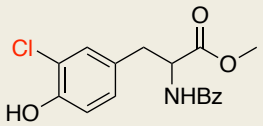
Scope



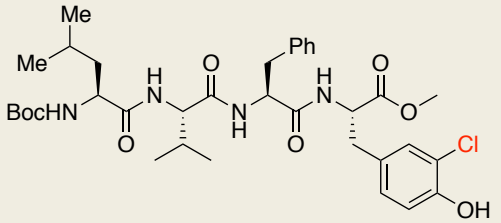
Cl-Clotrimazole
(drug)
49% yield



Cl-Deoxtgen-δ-tocopherol
(natural product)
92% yield



Cl-Bz-Tyr-OMe
(natural product)
86% yield

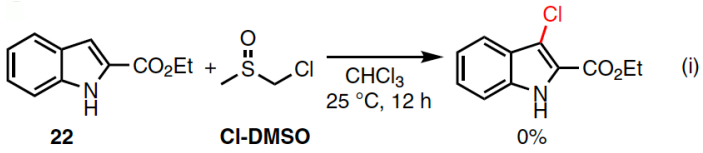


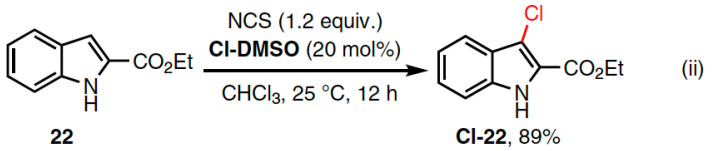
Cl-Boc-Leu-Val-Phe-Tyr-OMe
(peptide)
75% yield

10-3. DMSO-catalysed late-stage chlorination of (hetero)arenes

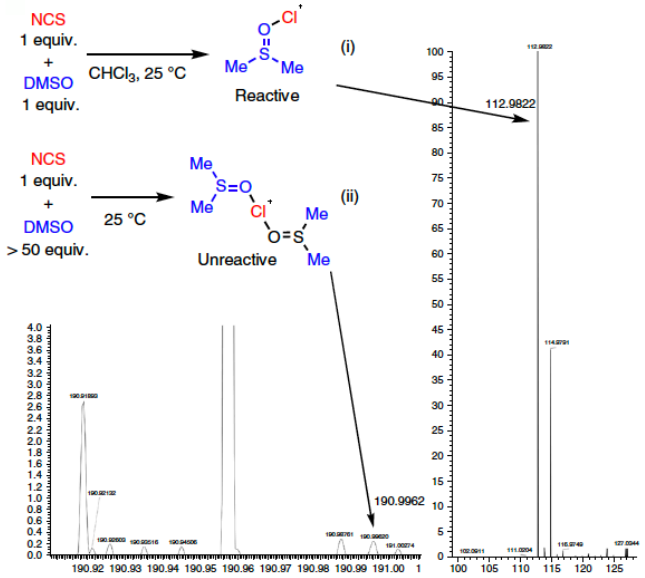
K.ISHIHARA GROUP green catalysis

a. Control Experiments

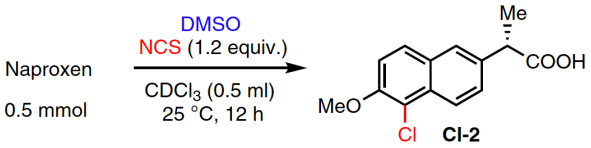




b. The detection of intermediates

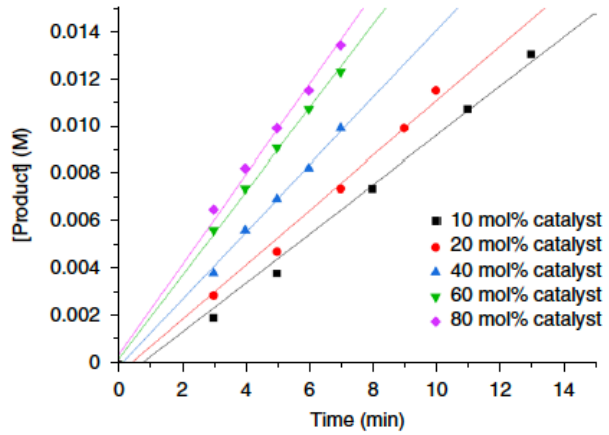


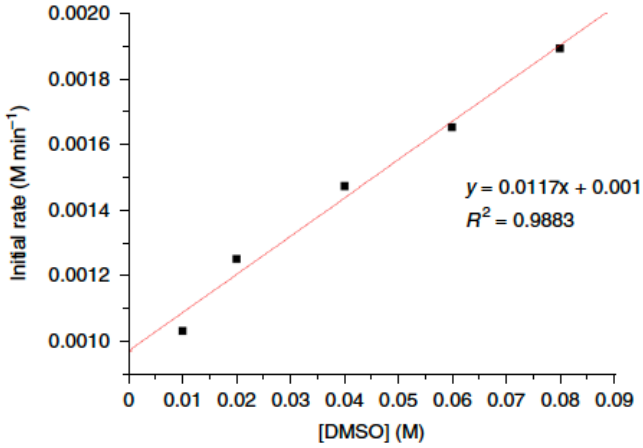
c. The dependence of reaction rate on [DMSO cat.]



Entry	DMSO	Yield of **Cl-2**	NL value in HRMS	Relative concertration of DMSO·Cl⁺ in HRMS
1	0	Trace		
2	0.2 equiv.	97%		
3	0.5 equiv.	96%		
4	1 equiv.	94%	5.05×10^6	1
5	2.0 equiv.	76%	1.32×10^6	0.26
6	5.0 equiv.	35%	2.12×10^5	0.042
7	10.0 equiv.	17%	6.02×10^4	0.012
8	50.0 equiv.	Trace	2.49×10^3	49×10^{-4}

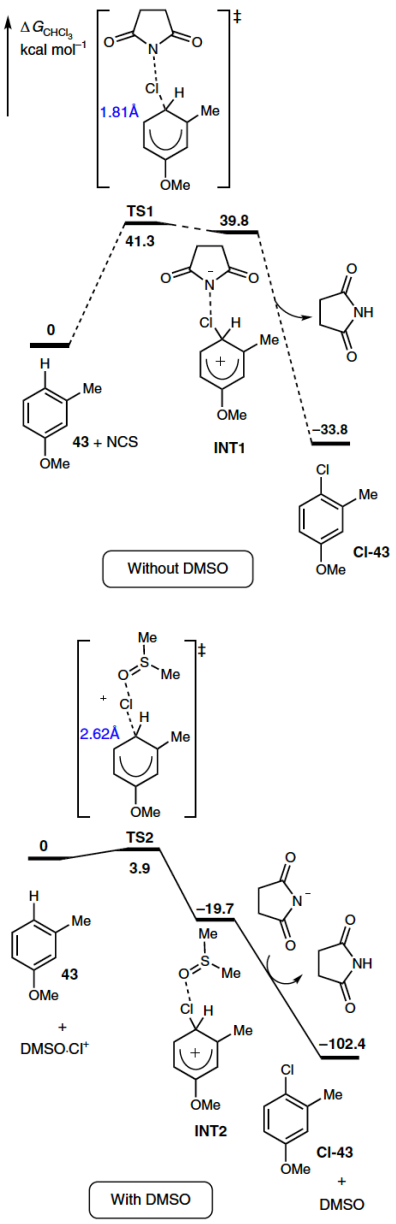
d. Reaction rate vs. [DMSO]



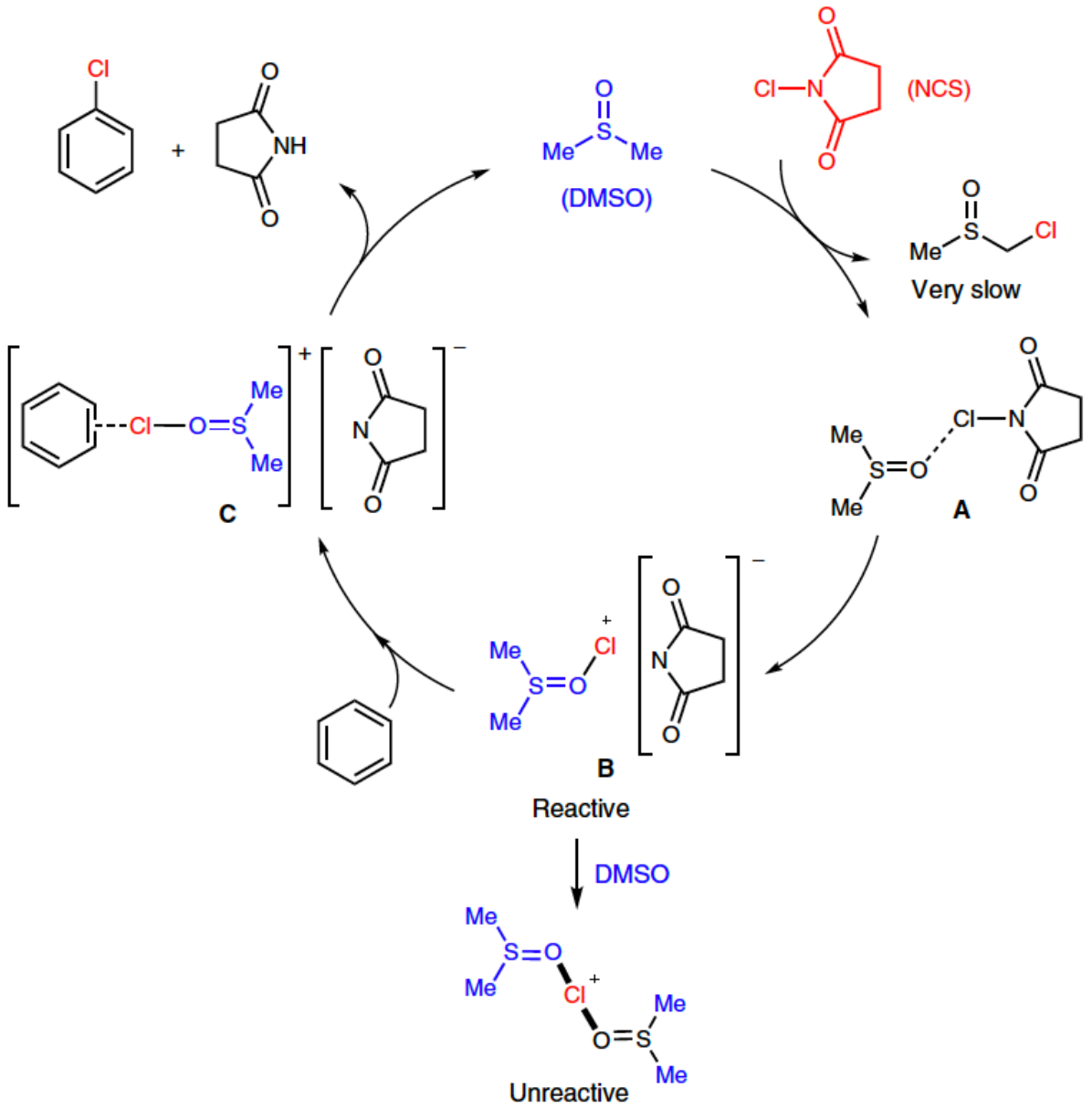


10-4. DMSO-catalysed late-stage chlorination of (hetero)arenes

e. DFT caluculation



f. Reaction mechanism

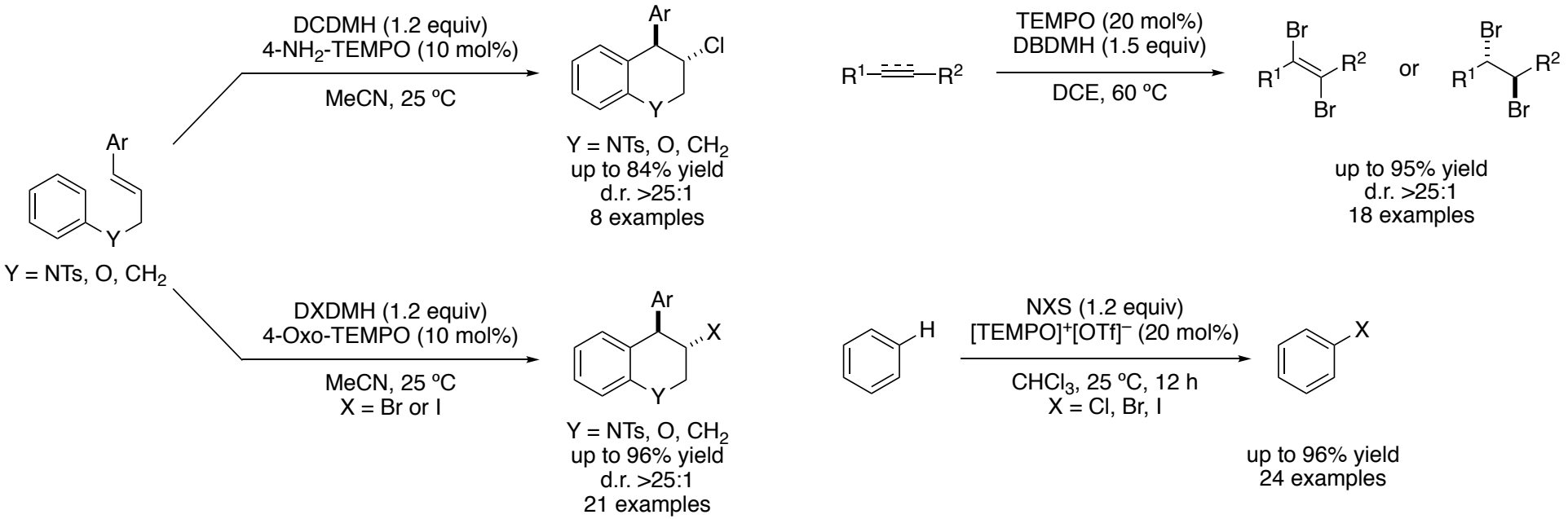


11-1. Selective Halogenation of Olefins, Alkynes, Aromatics

Type II : Lewis Acid

Oxoammonium salts are catalysing efficient and selective halogenation of olefins, alkynes and aromatics

Song S. *et al. Nat. Commun.* **2021**, 3873



DMSO-catalysed System

– Inactive for bromination and iodinaion

– Inactive for alkenes

This System

– Commercially available, stable catalysts

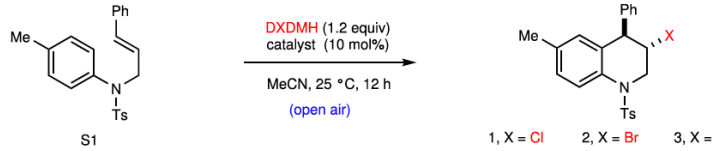
– Activation of Cl^+, Br^+ and I^+

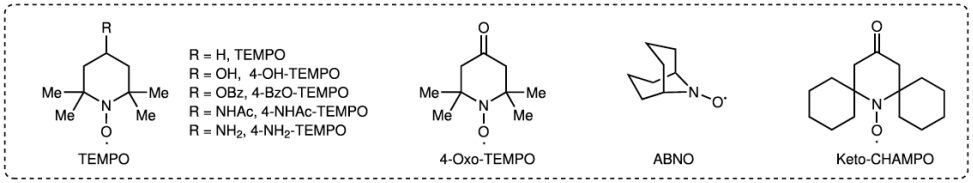
– Halogenation of olefins, alkynes and aromatics

– Exellent regio- and diastereoselective

11-2. Selective Halogenation of Olefins, Alkynes, Aromatics

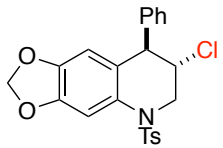
Optimization



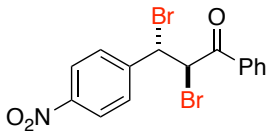


Entry	X	catalyst	Yield	Entry	X	catalyst	Yield
1	Cl	-	trace	16	Cl	Quinoline N-oxide	38%
2	Cl	$2,4,6\text{-}(Me)_3PhNH_2$	44%	17	Cl	TEMPO	64%
3	Cl	$Ph_3P{=}S$	38%	18	Cl	4-OH-TEMPO	61%
4	Cl	$(Me_2N)_2C{=}S$	33%	19	Cl	4-BzO-TEMPO	55%
5	Cl	Ph_2S	35%	20	Cl	4-Oxo-TEMPO	63%
6	Cl	Ph_2Se	29%	21	Cl	4-NHAc-TEMPO	70%
7	Cl	nBu_3P	48%	22	Cl	$4\text{-}NH_2\text{-}TEMPO$	75% (74%)[b]
8	Cl	TMSOTf	trace	23	Cl	ABNO	57%
9	Cl	TfOH	trace	24	Cl	Keto-CHAMPO	40%
10	Cl	DMSO	35%	25	Br	4-Oxo-TEMPO	92% (88%)[b]
11	Cl	$Ph_2S{=}O$	47%	26	Br	$4\text{-}NH_2\text{-}TEMPO$	72%
12	Cl	$Bn_2S{=}O$	40%	27	Br	ABNO	78%
13	Cl	$MeNO_2$	10%	28	Br	Keto-CHAMPO	60%
14	Cl	Py N-oxide	42%	29	I	4-Oxo-TEMPO	62% (60%)[b]
15	Cl	$4\text{-}NO_2Py$ N-oxide	37%	30	I	$4\text{-}NH_2\text{-}TEMPO$	43%

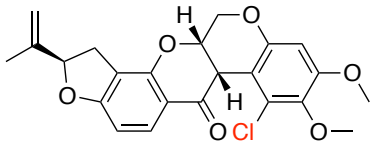
Scope



from alkene
65% yield
d.r. >25:1

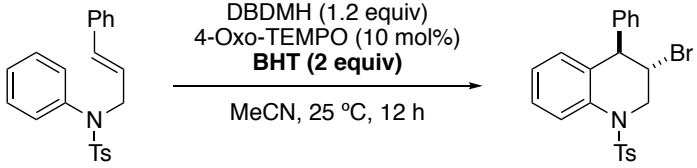


from alkene
89% yield
d.r. >25:1

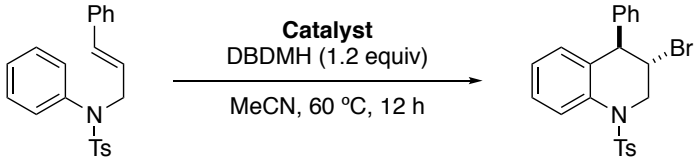


w/ [TEMPO][OTf]
62% yield
(DMSO cat. : trace)

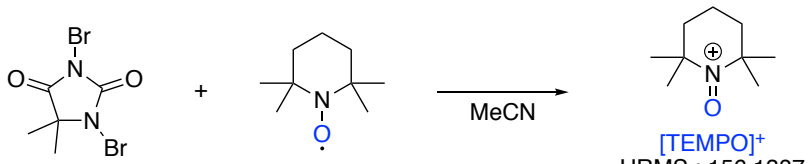
Control experiments



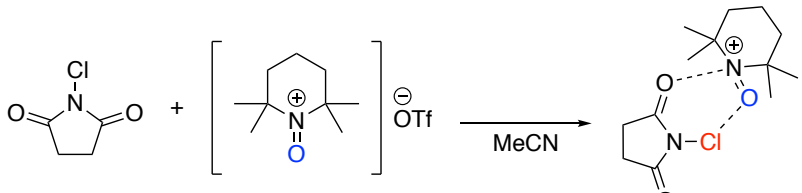
70% yield



10 mol% TEMPO : 68% yield
2 mol% [TEMPO][OTf] : 88% yield



[TEMPO]+
HRMS : 156.1387

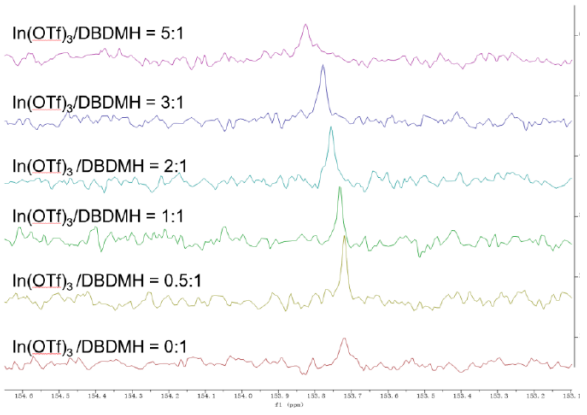


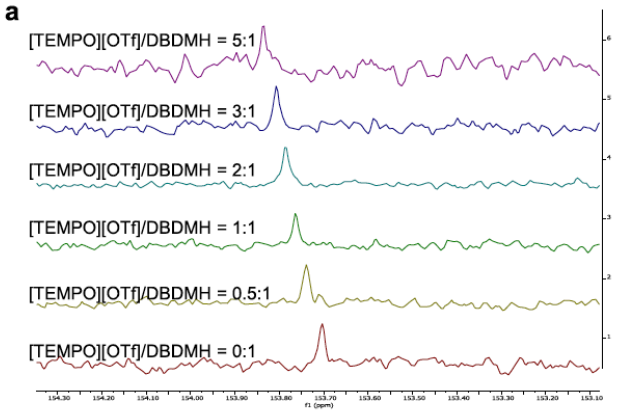
[TEMPO][OTf]

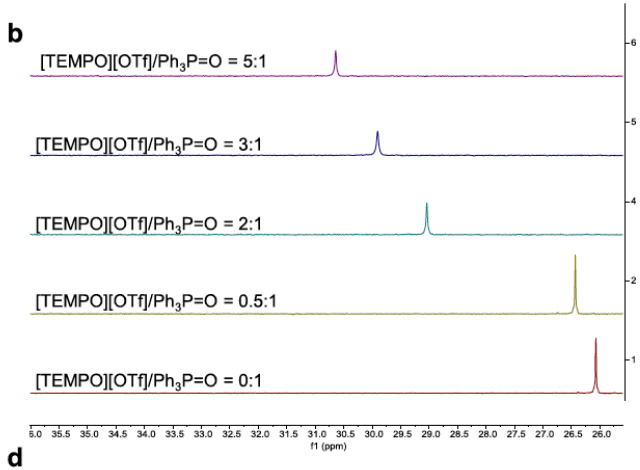
[TEMPO•NCS]+
HRMS : 289.1317

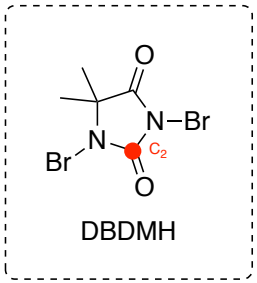
11-3. Selective Halogenation of Olefins, Alkynes, Aromatics

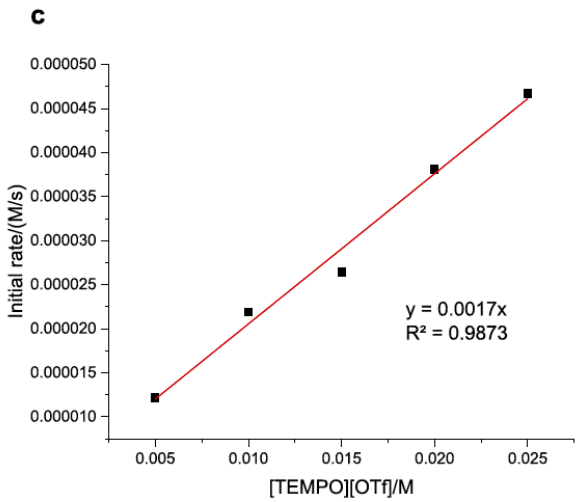
Mechanistic studies

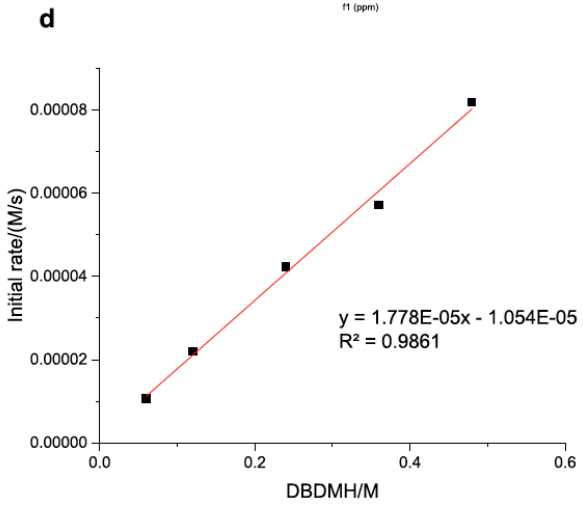












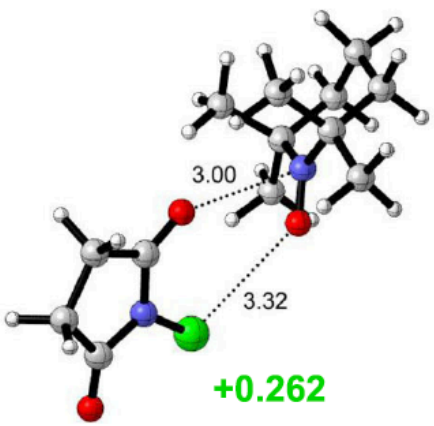
– TEMPO$^+$ functioned as a potential Lewis acid

– [TEMPO][OTf] was involved in the activation of DBDMH

11-4. Selective Halogenation of Olefins, Alkynes, Aromatics

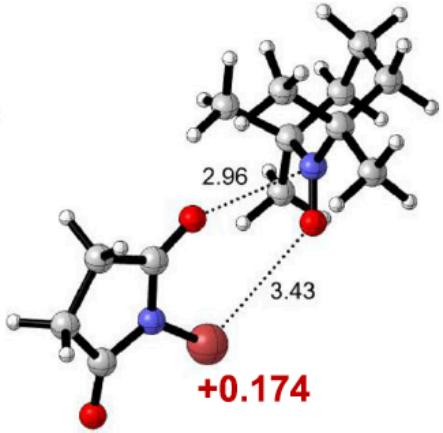
K.ISHIHARA GROUP
green catalysis

DFT calculations



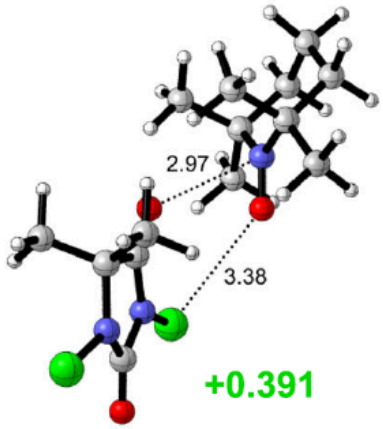
NCS-TEMPO⁺

ΔE_{CHCl3} = -5.9



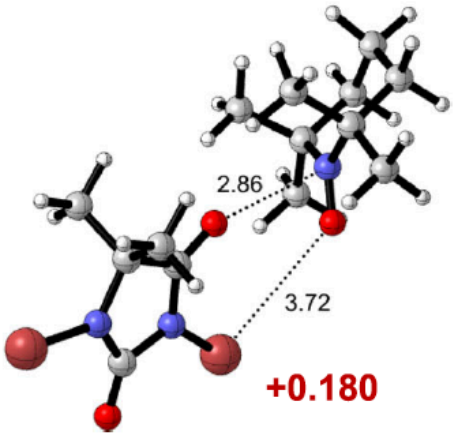
NBS-TEMPO⁺

-7.1



DCDMH -TEMPO⁺

ΔE_{MeCN} = -5.2



DBDMH -TEMPO⁺

-5.8

Reaction mechanism