Dearomative halogenation

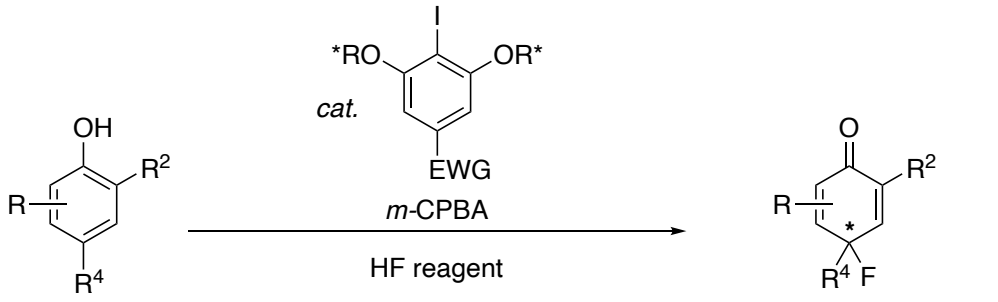
2022/11/25

Shogo YAMAMOTO

Contents

My Researh Projects

Enantioselective Oxidative Dearomative Fluorination of Arenols

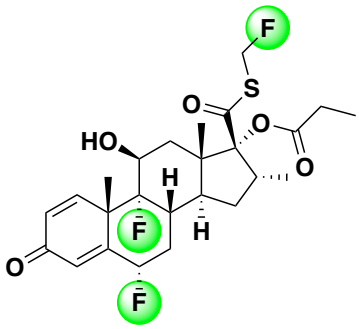


high yield, moderate ee

1. Introduction

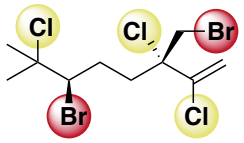
1-1. Organohalogen compounds

1-1-1. Artificial or Natural compounds



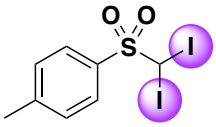
Fluticasone
(anti-inflammatory)

Artificial



Halomon
(antiumor agent)

Natural

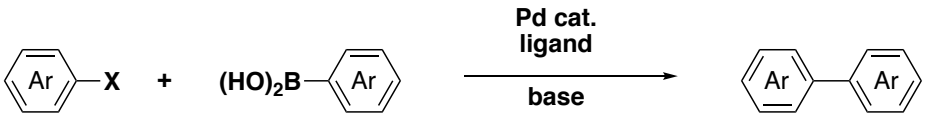


DMTS
(antifungal agent)

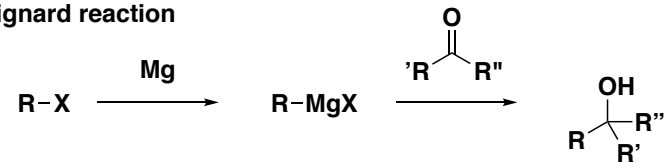
Artificial

1-1-2. Organohalogen compounds as synthetic intermediate

- Suzuki-Miyaura Coupling (SMC)

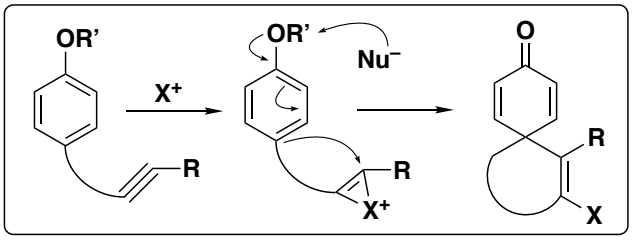


- Grignard reaction

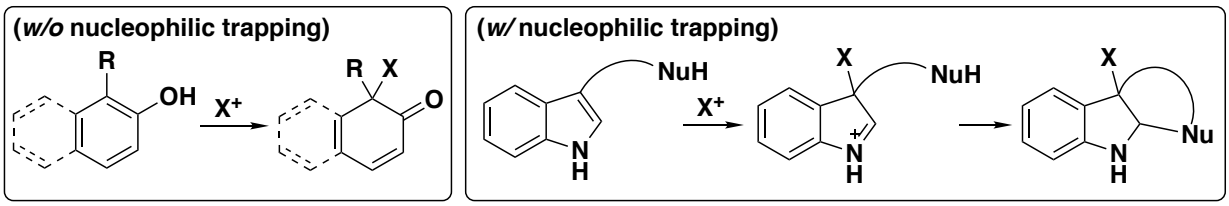


1-2. Dearomatizative halogenation – general strategies

Halogenation at alkynes (chapter 2)



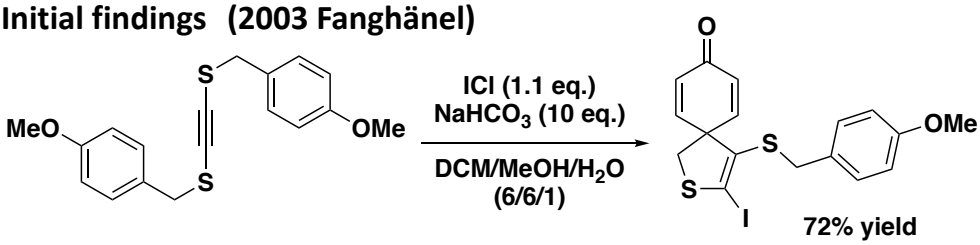
Halogenation at arenes (chapter 3)



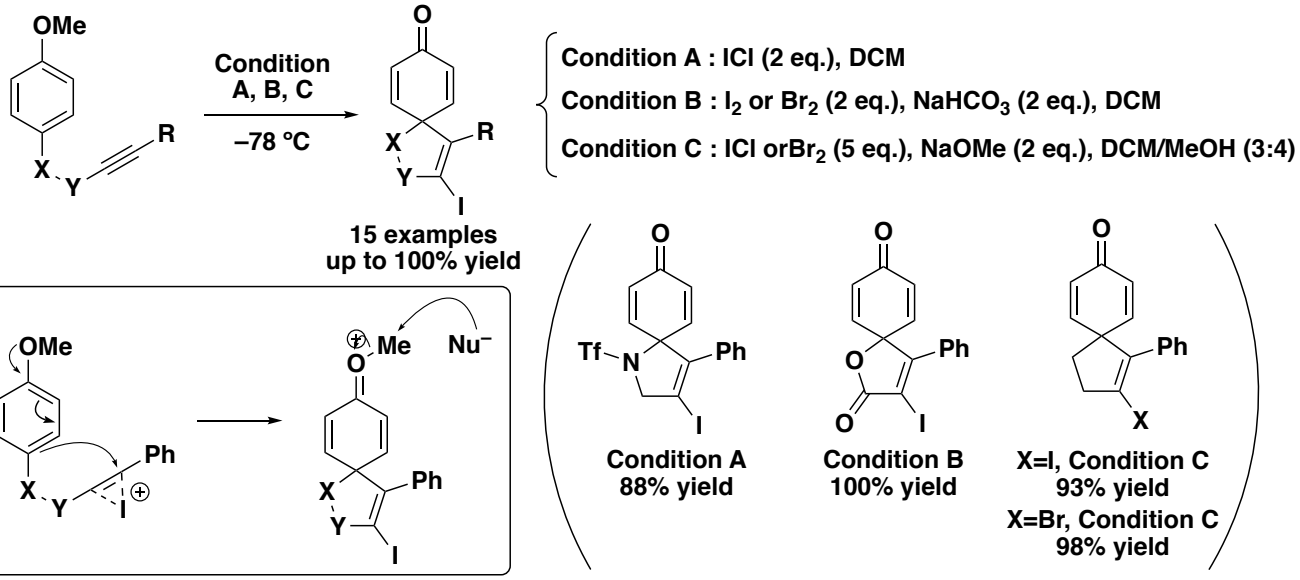
1) You. *et. al. Chem. Eur. J.* **2016**, *22*, 11918.

2. Halogenation at alkynes or alkenes

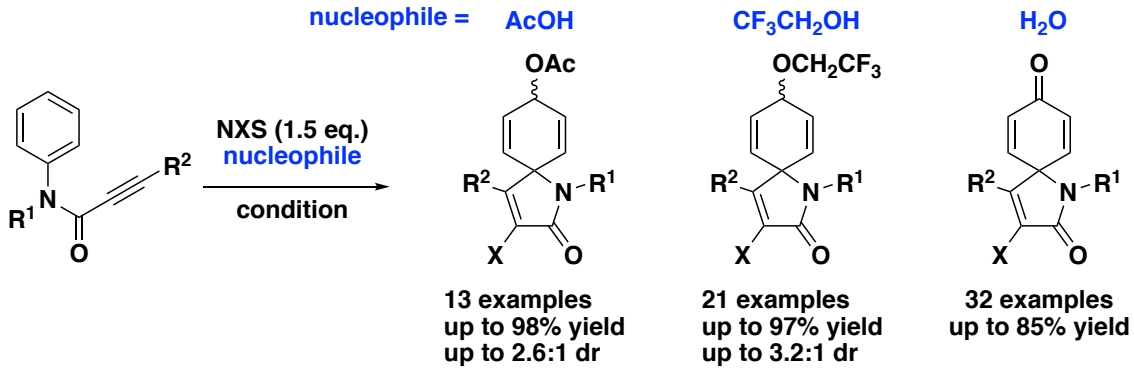
Initial findings (2003 Fanghänel)

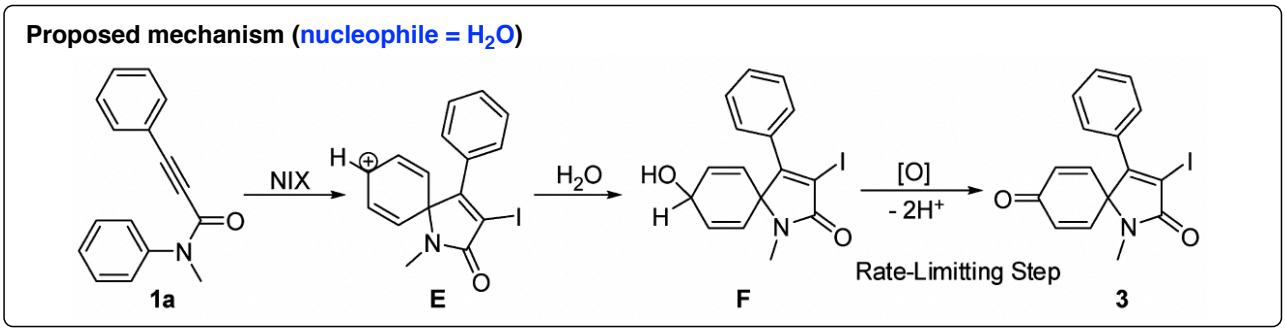


General protocols (2005 Larock)



No activating arenes (2008, 2009, 2012 Li)





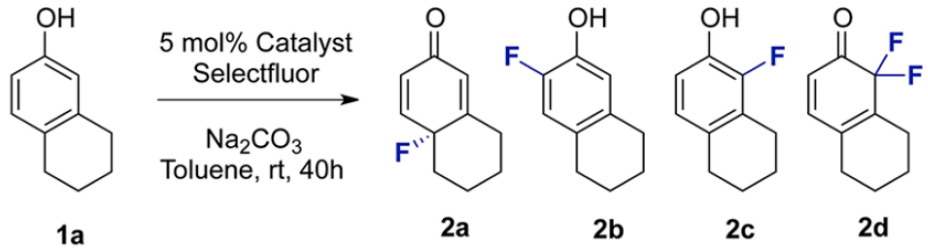
1) Fanghänel. *et. al. Eur. J. Org. Chem.* **2003**, *1*, 47.
2) Larock. *et. al. J. Am. Chem. Soc.* **2005**, *127*, 12230.
3) Li. *et. al. Org. Lett.* **2008**, *10*, 1063.; *Synthesis,* **2009**, *6*, 891.; *J. Org. Chem.* **2012**, *77*, 2837.

3. Halogenation at arenes without nucleophilic trapping

3-1. Fluorination

Enantioselective reactions of phenols (2013 Toste)

Initial findings

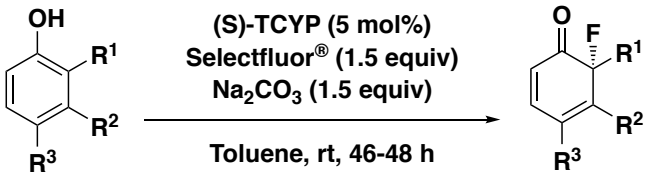


1a → 2a, 2b, 2c, 2d

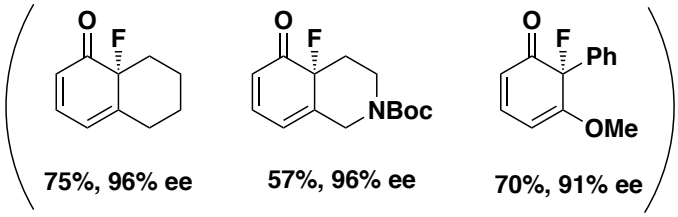
Catalyst	Ratio 2a:2b:2c:2d	Net *para:ortho*	Yield 2a (% conv)	*ee* 2a
(*S*)-TCYP	1 : 0.19 : 0.51 : 0.32	1.0 : 1	41% (>95)	63%
none	1 : 0.11 : 0.23 : 0.00	2.9 : 1	17%[c] (23)	--

F. Dean Toste (1971-)

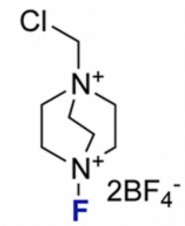
***ortho*-selective fluorinative dearomatization**



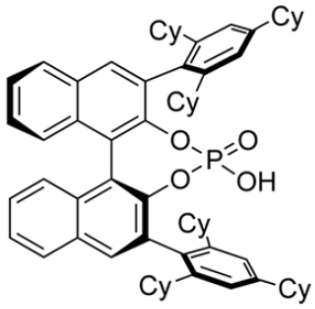
9 examples



75%, 96% ee | 57%, 96% ee | 70%, 91% ee

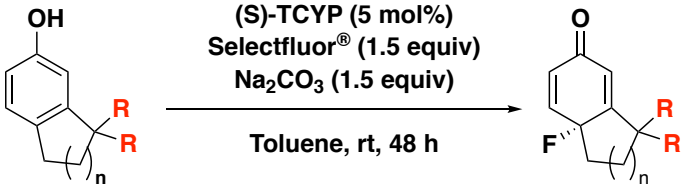


Selectfluor

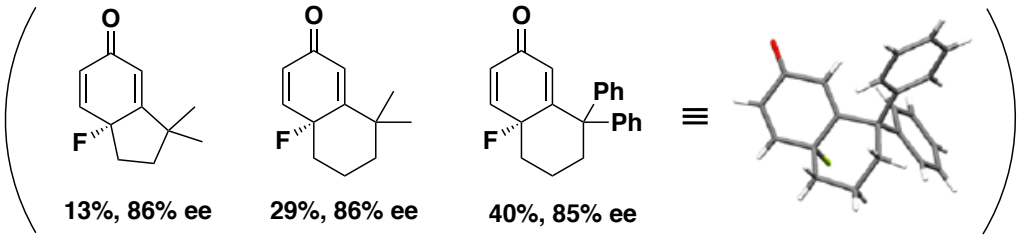


(S)-TCYP

***para*-selective fuluorinative dearomatization**

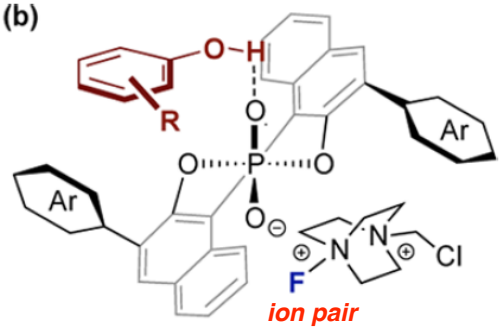


3 examples



13%, 86% ee | 29%, 86% ee | 40%, 85% ee

(b)



ion pair

Plausible interaction

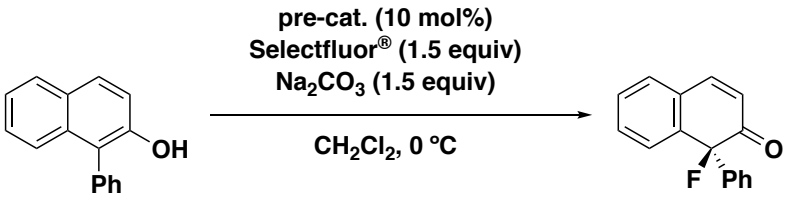
1) Toste. *et. al. J. Am. Chem. Soc.* **2013**, *135*, 1268.

3. Halogenation at arenes without nucleophilic trapping

3-1. Fluorination

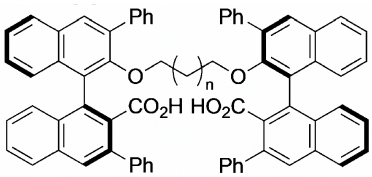
Enantioselective reactions of 2-naphthols (2020 Hamashima)

Optimization of catalyst

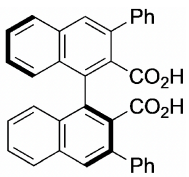


Y. Hamashima (1974-)

pre-Cat.	Time	Yield	Ee
1	18 h	quant.	93%
5	36 h	89%	–61%
6	36 h	81%	24%
7	36 h	78%	–15%

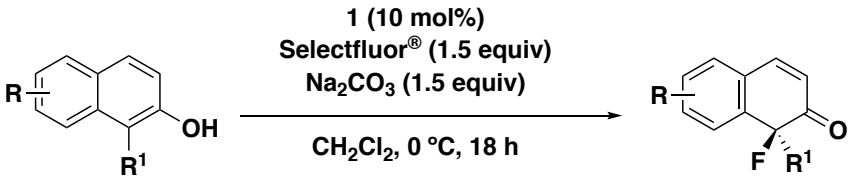


1: n = 1, **5**: n = 2, **6**: n = 3

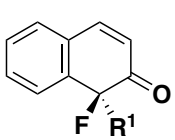


7

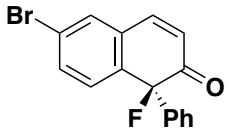
Substrate scope



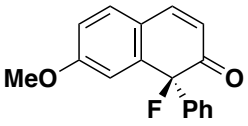
21 examples
up to >99% yield
up to 94 % ee



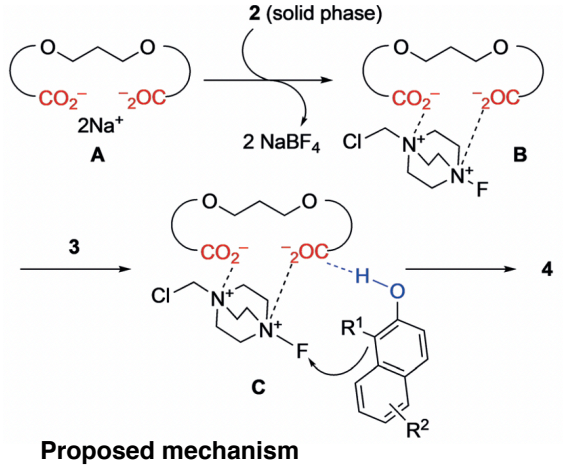
R^1 = Me 92%, 81% ee
R^1 = allyl 95%, 83% ee
R^1 = 3-thiophenyl 90%, 92% ee



90%, 88% ee

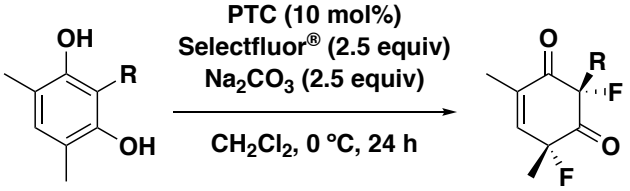


98%, 94% ee

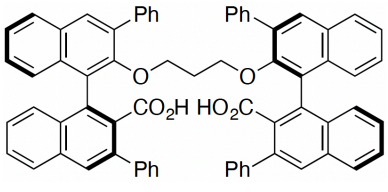


Proposed mechanism

Enantioselective reactions of resorcinols (2021 Hamashima)



7 examples
up to >99% yield
up to 16:1 dr
up to 95 % ee



PTC

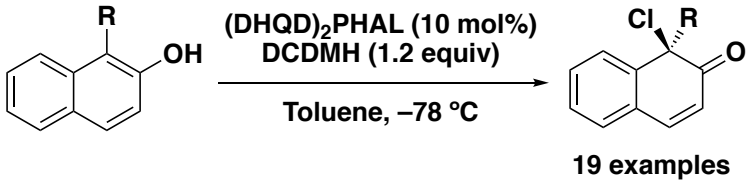
1) Hamashima. *et. al. Angew. Chem. Int. Ed.* **2020**, *59*, 14101.
2) Hamashima. *et. al. Tetrahedron.* **2021**, *96*, 132355.

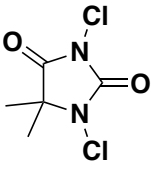
3. Halogenation at arenes without nucleophilic trapping

3-2. Chlorination

Enantioselective reactions of naphthols (2015 You)

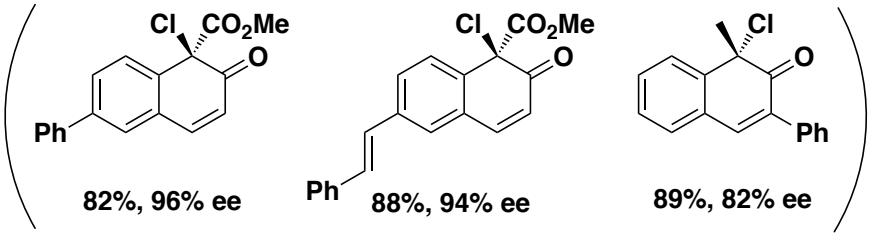
Scope of 2-naphthols

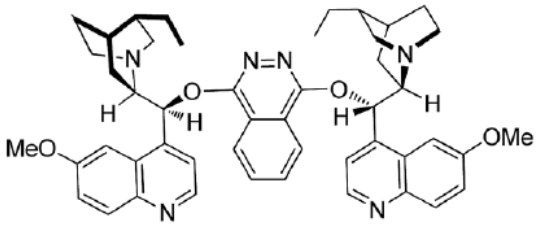




DCDMH

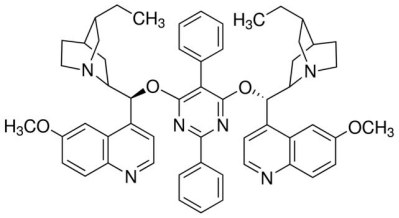
Shu-Li You
(1975-)

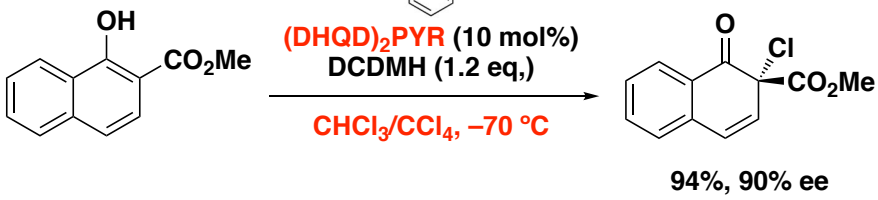




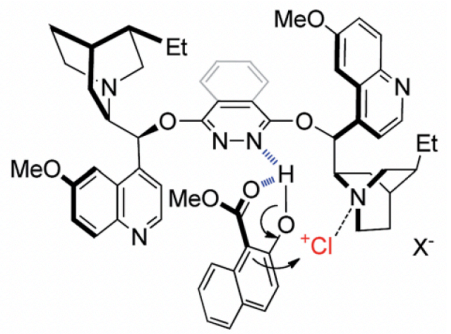
(DHQD)$_2$PHAL

Investigation of 1-naphthols



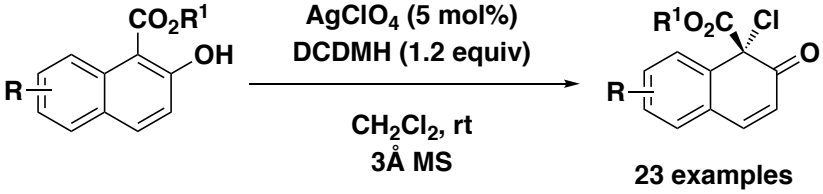


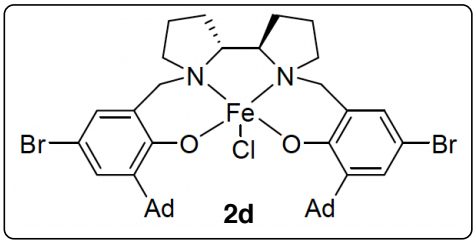
94%, 90% ee

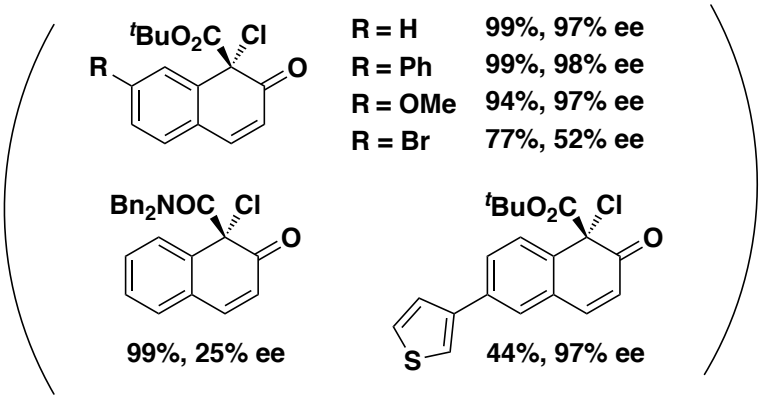


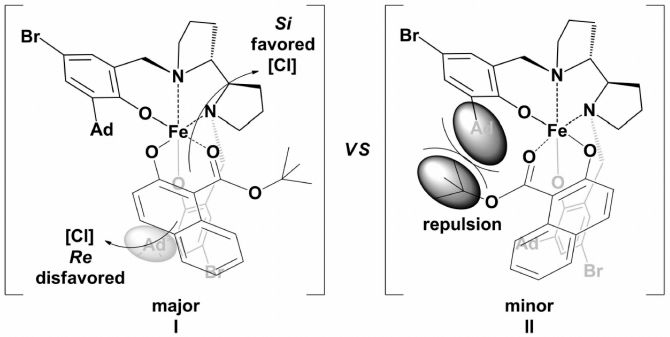
Proposed working model

Enantioselective reactions of 2-naphthols (2021 Che)









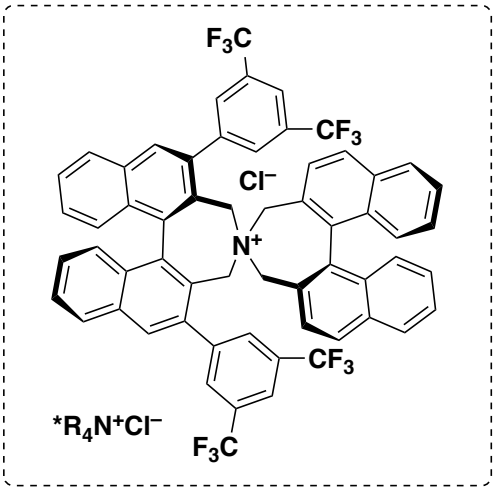
Plausible intermediates

1) You. *et. al. Chem. Sci.* **2015**, *6*, 4179.
2) Che. *et. al. Asian. J. Org. Chem.* **2021**, *10*, 674.

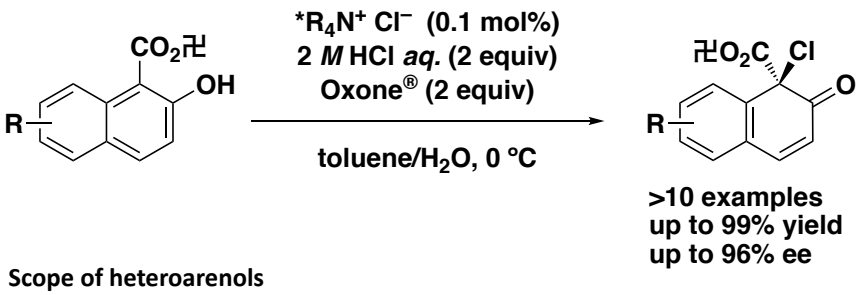
3. Halogenation at arenes without nucleophilic trapping

3-2. Chlorination

Enantioselective reactions of (hetero)arenols (Our lab.)

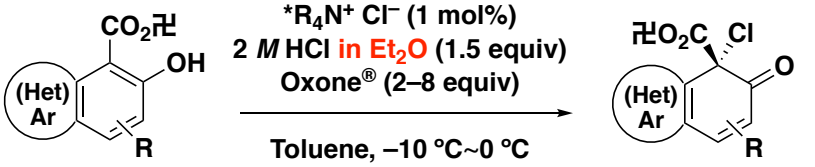


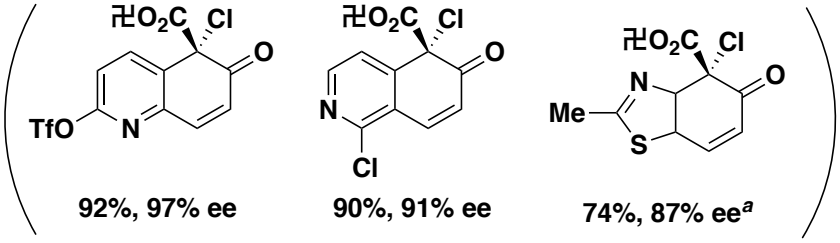
Scope of 2-naphthols



>10 examples
up to 99% yield
up to 96% ee

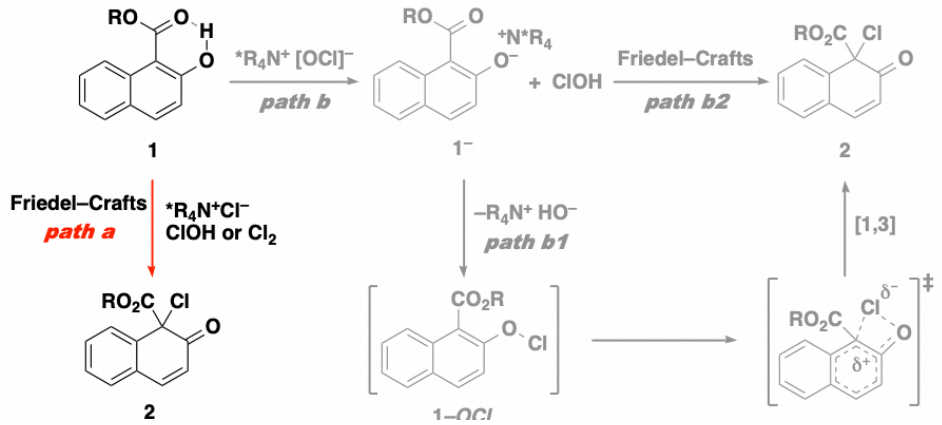
Scope of heteroarenols





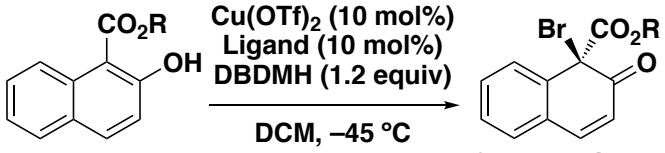
92%, 97% ee | 90%, 91% ee | 74%, 87% ee[a]

[a] 2 *M* HCl *aq.* (3 equiv) was used.

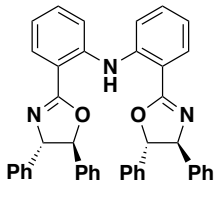


3-3. Bromination

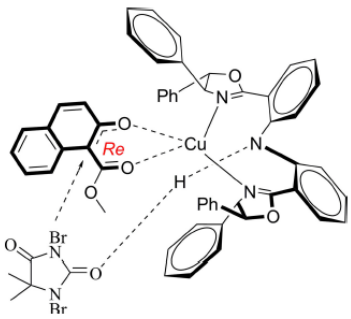
Enantioselective reactions (2018 Xu)



24 examples
up to 96% yield
up to 95% ee



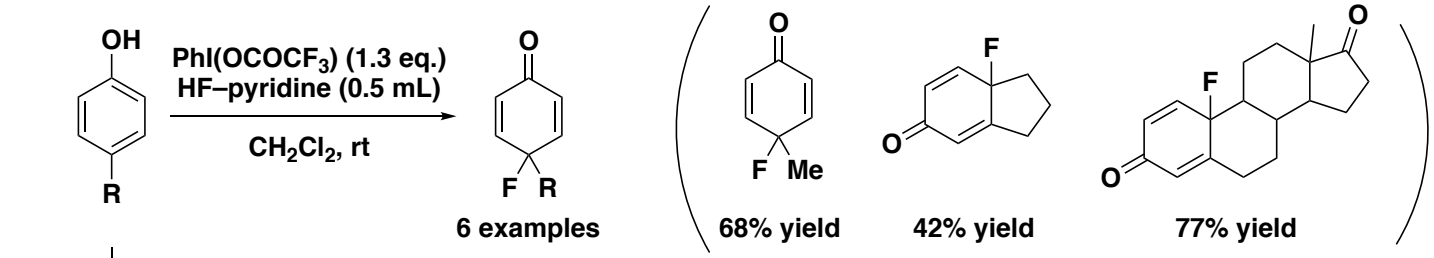
Ligand

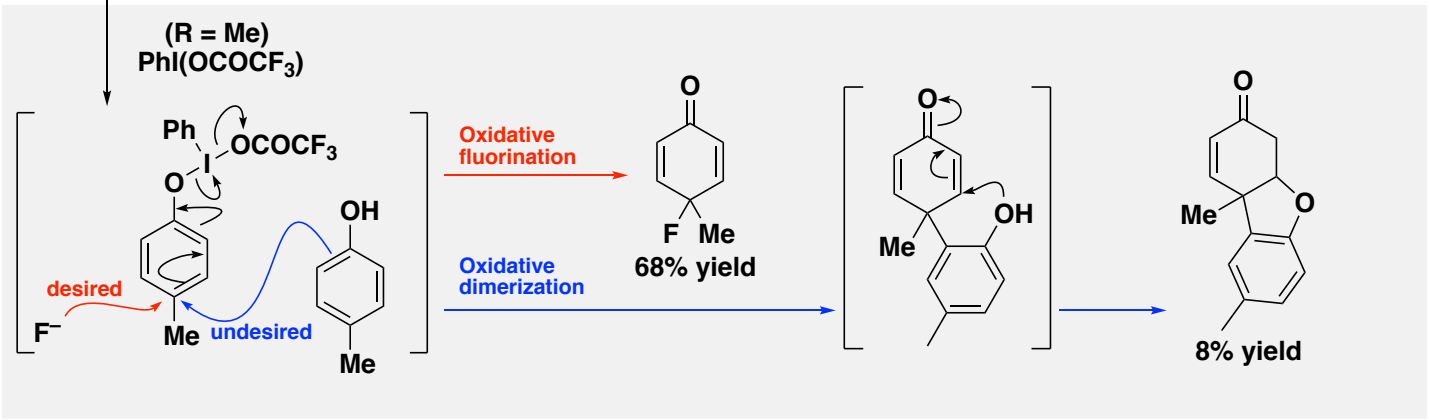


1) Xu. *et. al. Adv. Synth. Catal.* **2018**, *360*, 2285.

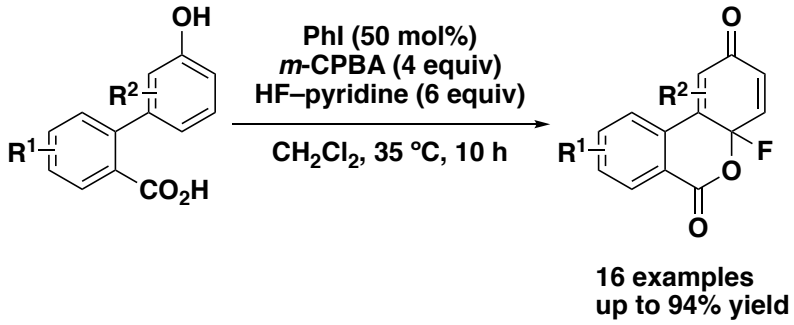
3-4. Nucleophilic fluorination

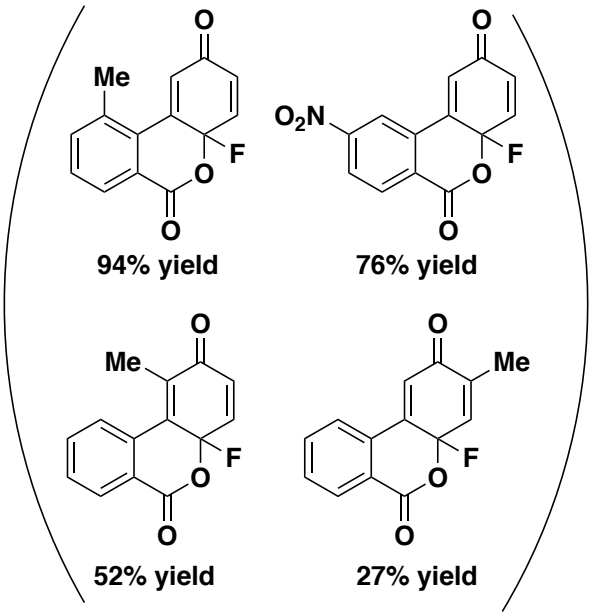
Stoichiometric reaction of phenols (1994 Jouannetaud)

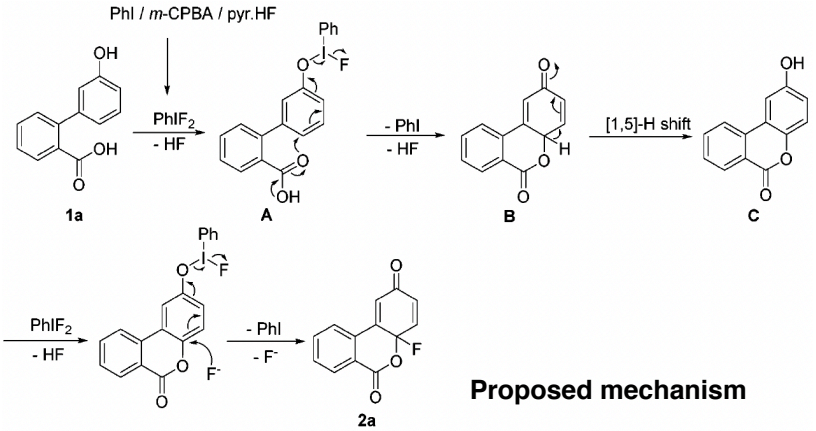




Catalytic reaction of phenols (2022 Xiong)



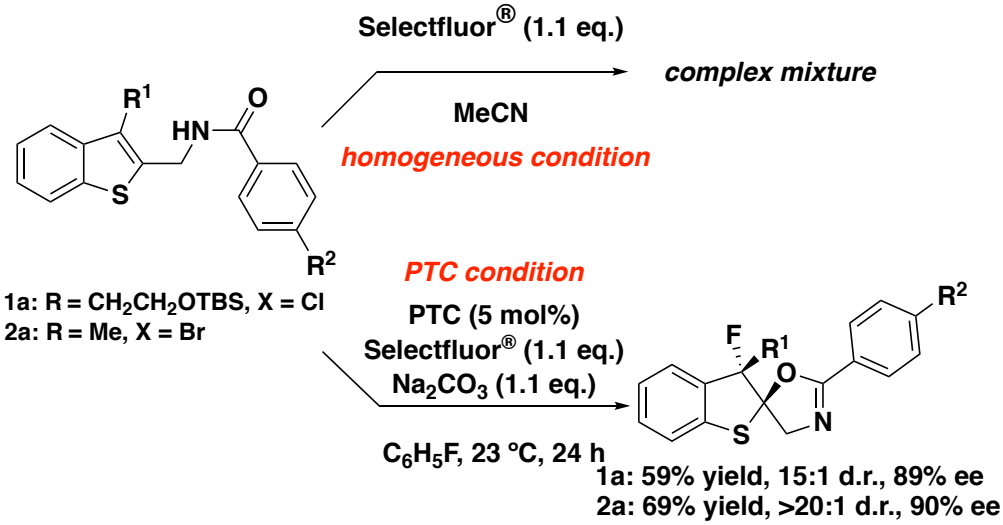


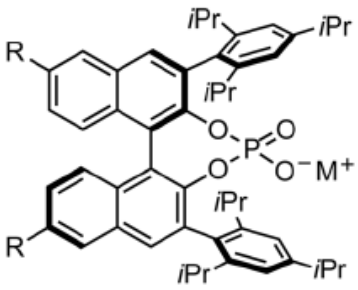


1) Jouannetaud. *et. al. Tetrahedron lett.* **1994**, *35*, 2541.
2) Xiong. *et. al. Org. Biomol. Chem.* **2022**, Advance article

4. Halogenation at arenes with nucleophilic trapping

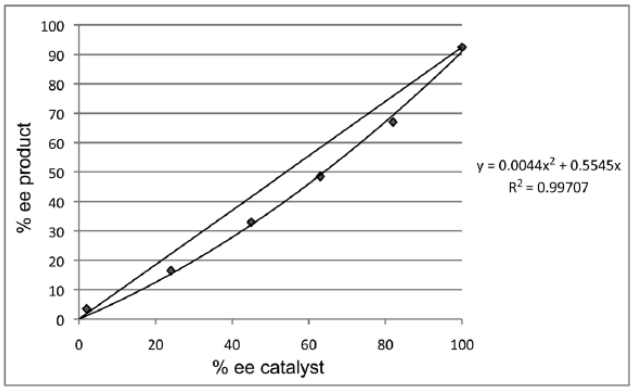
4-1. Fluorination of benzothiophene derivatives (2011 Toste)





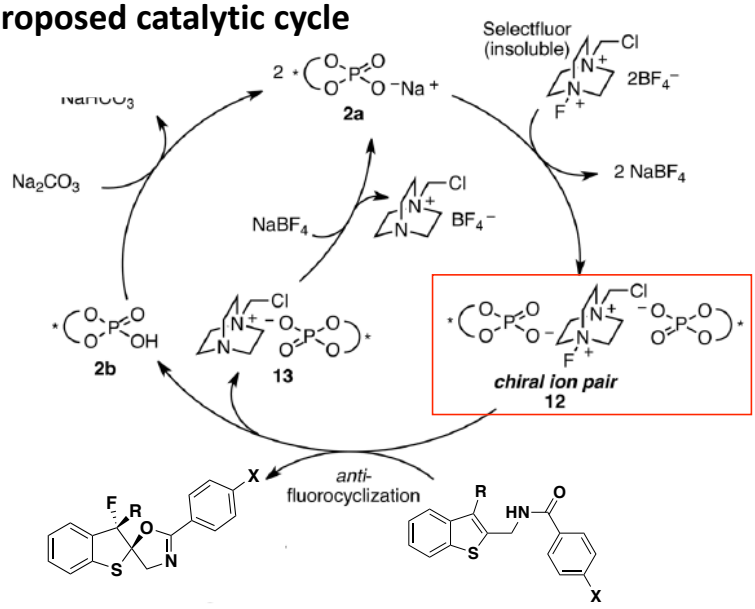
1a: 59% yield, 15:1 d.r., 89% ee
2a: 69% yield, >20:1 d.r., 90% ee

nonlinear effect



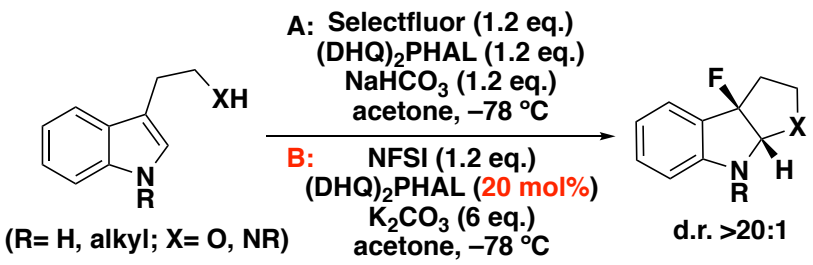
Supporting a pathway in which both BF_4^- are exchanged for chiral phosphate

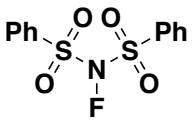
proposed catalytic cycle



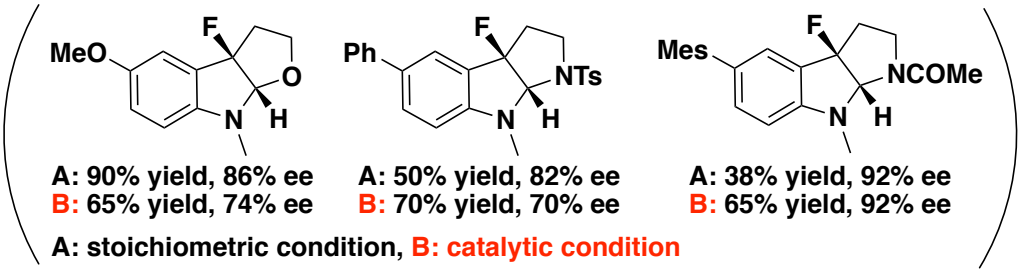
4-2. Fluorination of indole derivatives

Stoichometric & catalytic reaction (2011 Gouverneur)

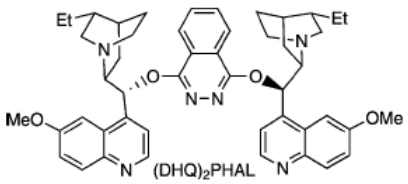




V. Gouverneur (1964-)



A: stoichiometric condition, B: catalytic condition

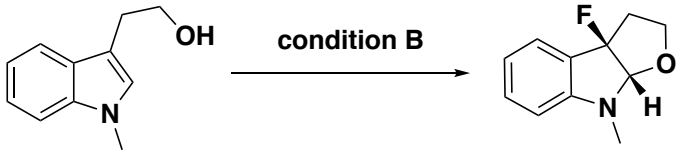


1) Toste. *et. al. Science* **2011**, *334*, 1681.
2) Gouverneur. *et. al. Angew. Chem. Int. Ed.* **2011**, *50*, 8105.

4. Halogenation at arenes with nucleophilic trapping

4-2 Fluorination of indole derivatives

Stoichometric & catalytic reaction (2011 Gouverneur)



w/ premix.: 66% ee
w/o premix.: 50% ee

d.r. >20:1

^{19}F NMR experiment

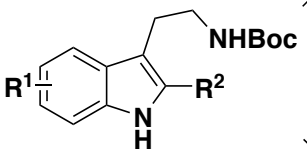
NFSI + $(DHQ)_2PHAL$ → RT → fully transfer to $[F(DHQ)_2PHAL]^+$

NFSI + $(DHQ)_2PHAL$ → –78 °C → $[F(DHQ)_2PHAL]^+$ trace (<2%)

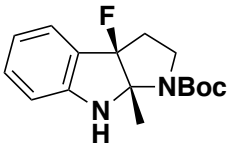
Procedure

NFSI + K_2CO_3 + $(DHQ)_2PHAL$ (20 mol%) → premix. RT, 1 h → SM –78 °C → product

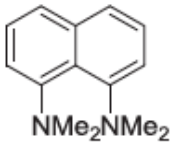
Catalytic reaction (2017 You)



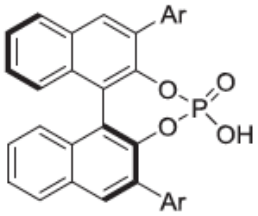
(*S*)-CPA (10 mol%)
Selectfluor® (1.1 eq.)
PS (1.1 eq.)
CH_3CN, 0 °C, 10 min
homogeneous condition



78%, 47% ee

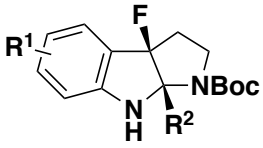


PS
(Proton Sponge)

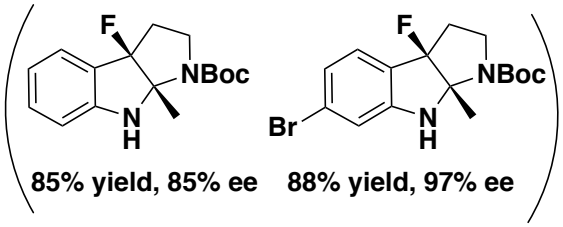


(*S*)-CPA
Ar = 9-anthryl

(*S*)-CPA (5–10 mol%)
Selectfluor® (1.1 eq.)
PS (1.1 eq.)
C_6H_5F/CH_3CN, –60 °C
PTC condition

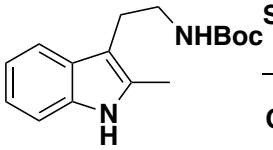


24 examples
up to 92% yield
up to 97% ee

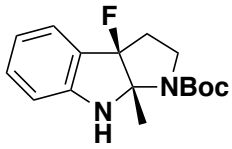


85% yield, 85% ee
88% yield, 97% ee

Control experiment

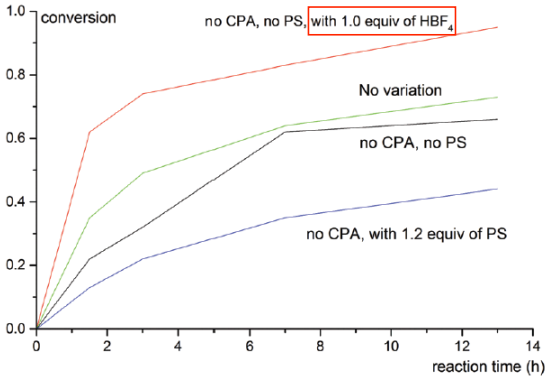


(*S*)-CPA (5-10 mol%)
Selectfluor® (1.1 eq.)
PS (1.1 eq.)
C_6H_5F/MeCN, –60 °C



HBF_4 *accelerate the reaction*

in situ generated from Selectfluor®



Correlation between conversion with reaction time

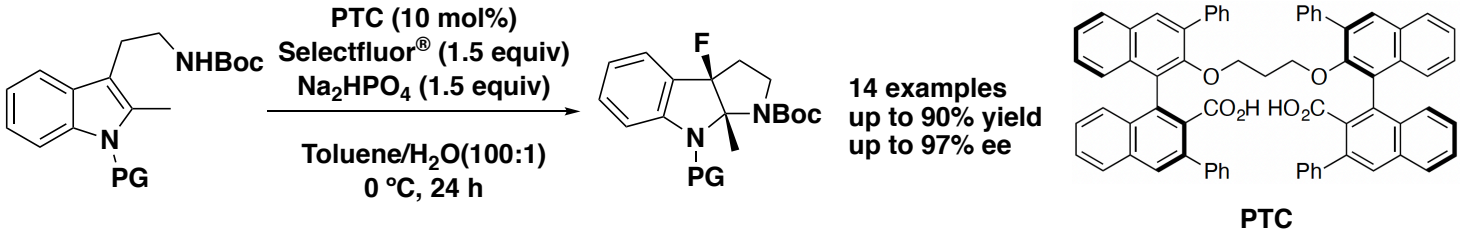
The role of PS … neutralize HBF_4 generated *in situ*
inhibit the strong racemic background reaction

1) You. *et. al. Chem. Commun.* **2017**, *53*, 5531.

4. Halogenation at arenes with nucleophilic trapping

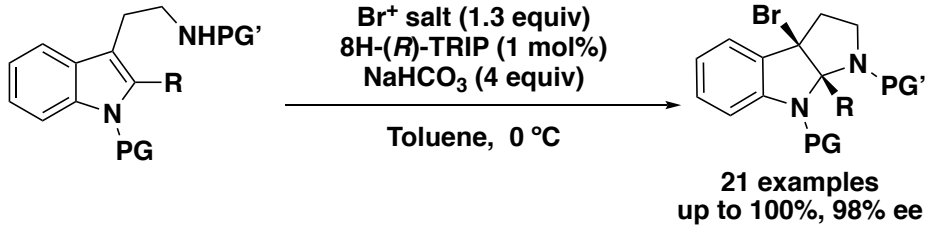
4-2. Fluorination of indole derivatives

Catalytic reaction (2020 Hamashima)

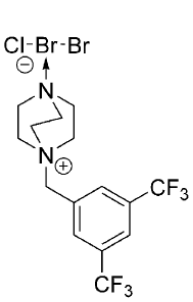


PTC

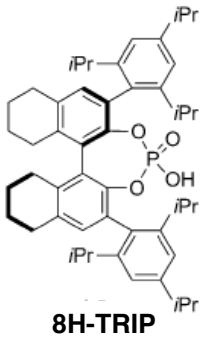
4-3. Bromination of indole derivatives (2013 Ma)



21 examples
up to 100%, 98% ee

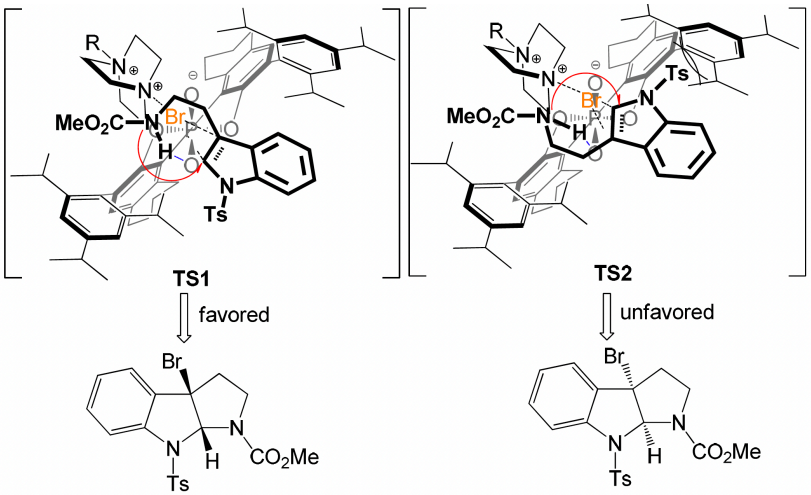


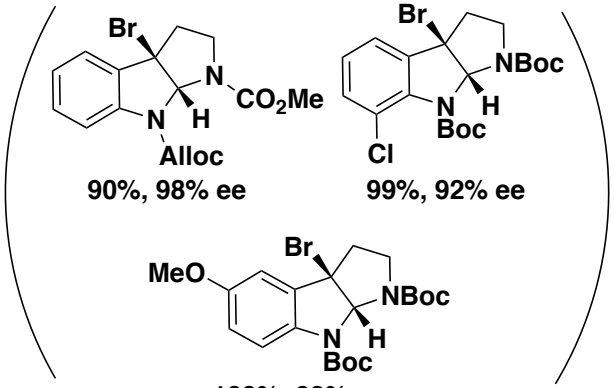
Br+ salt



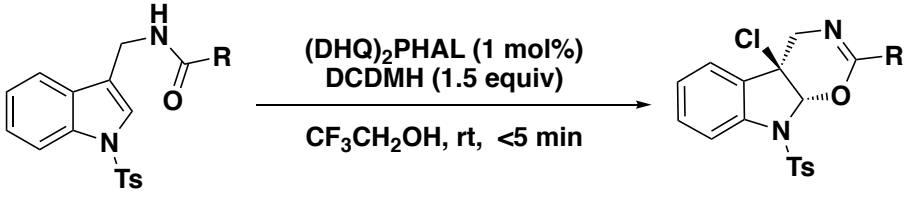
8H-TRIP

Proposed transition states

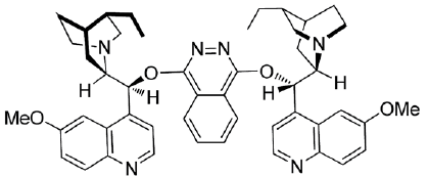




4-4. Chlorination of indole derivatives (2014 You)

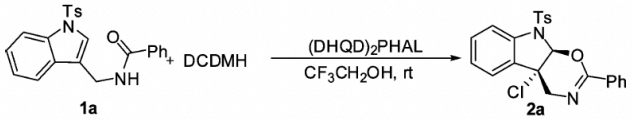


14 examples
up to 98%, >99% ee

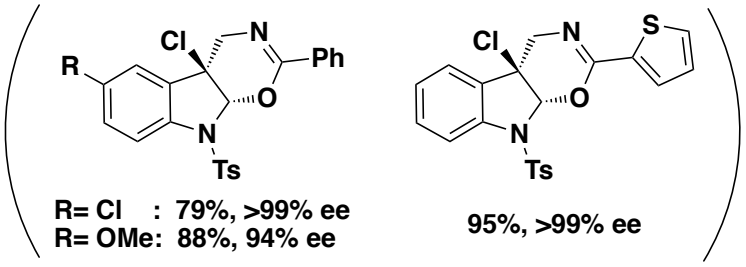


(DHQD)2PHAL

Evaluation of the catalyst loading



entry	catalyst loading	time	yield (%)[b]	ee (%)[c]
1	5 mol %	<5 min	92	>99
2	1 mol %	<5 min	93	>99
3	0.5 mol %	5 min	92	99
4	0.1 mol %	10 min	73	94
5	0.01 mol %	1 h	37	90



1) Hamashima. *et. al. Org. Lett.* **2020**, *22*, 5656.
2) Ma. *et. al. Angew. Chem. Int. Ed.* **2013**, *52*, 12924.
3) You. *et. al. Org. Lett.* **2014**, *16*, 2426.