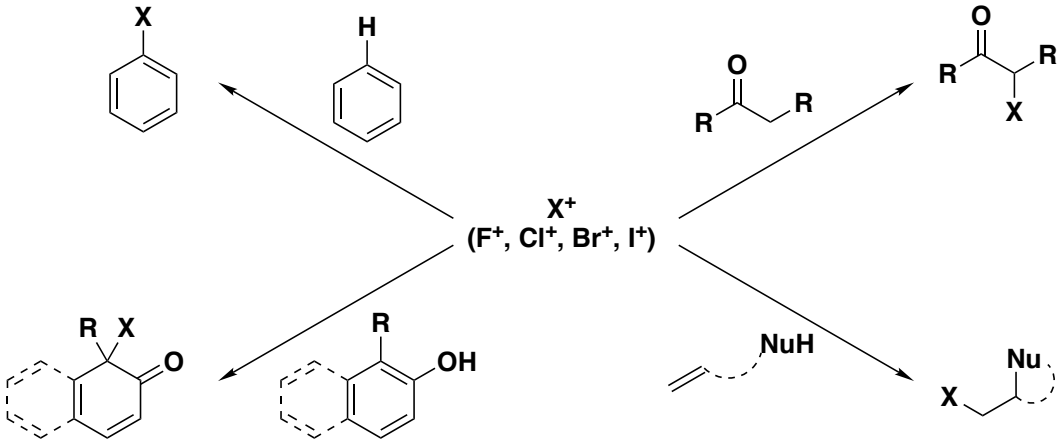
Electrophilic halogenation



2023/11/25

Yuto Fujii

Contents

1. Introduction

2. EnantioselectiveHalogenation using Metal Cat.

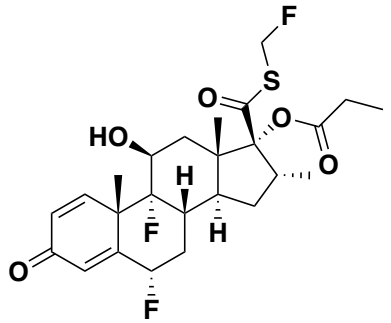
3. Enantioselective halogenation using Organocatalyst

4. Proposal

1. Introduction

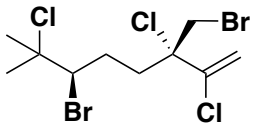
1-1. Organohalogen compounds

1-1-1. Artificial or Natural compounds



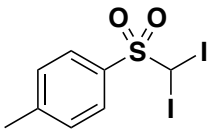
Fluticasone
(anti-inflammatory)

Artificial



Halomon
(antiumor agent)

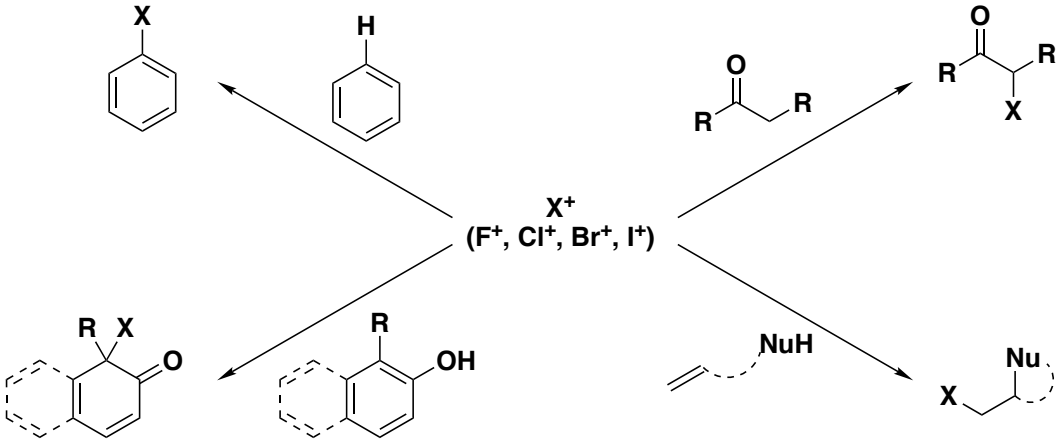
Natural



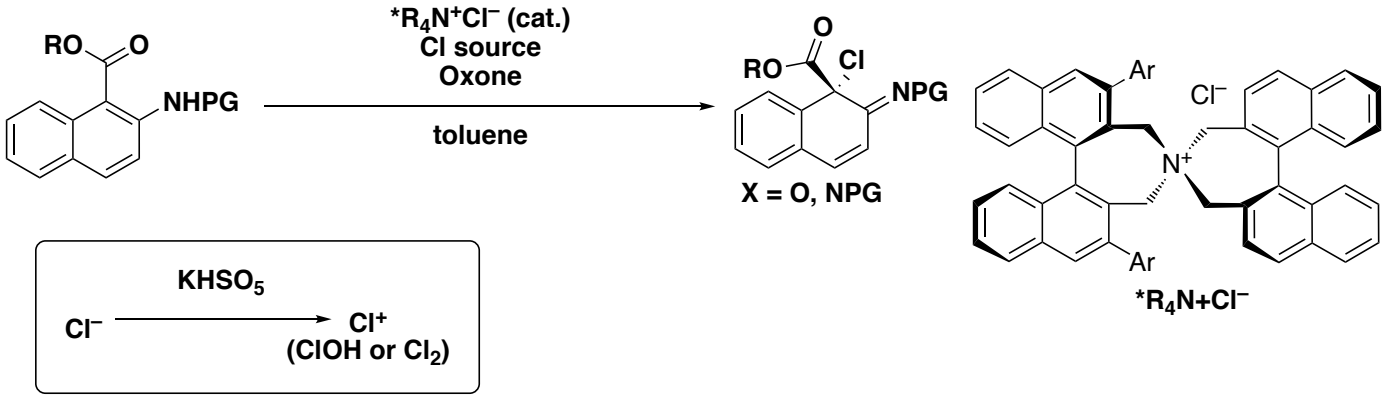
DMTS
(antifungal agent)

Artificial

1-1-2. Electrophilic Halogenation Reactions



1-2. My Work

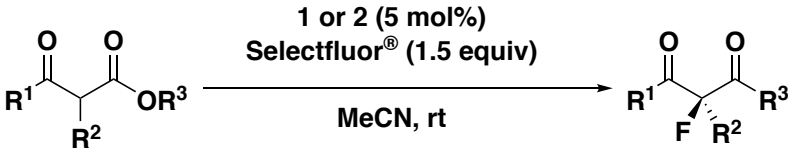


2. EnantioselectiveHalogenation using Metal Cat.

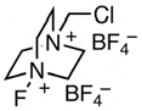
2-1. First Catalytic EnantioselectiveHalogenation

Enantioselective Halogenation of β-Keto Esters (2000 Togni)

Enantioselective Fluorination of β-Keto Esters (2000 Togni)

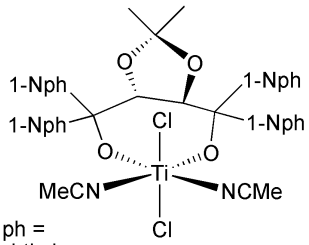


8 examples
up to 89% yield
up to 91 % ee



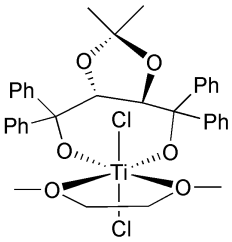
Selectfluor®

A. Togni
(1956-)

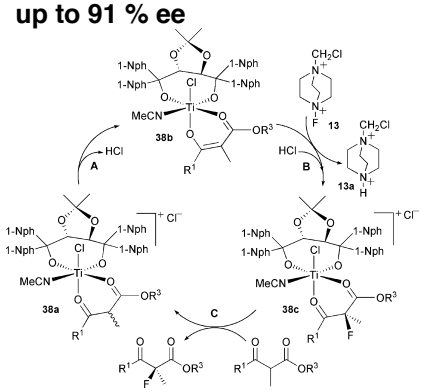


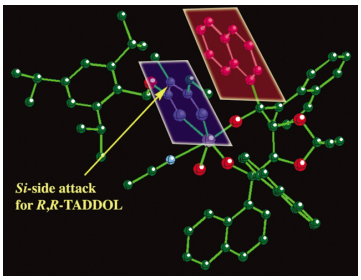
1-Nph =
1-naphthyl

1

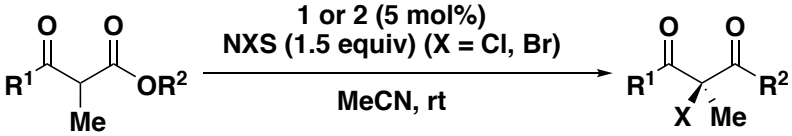


2





Enantioselective Chlorination and Bromination of β-Keto Esters (2000 Togni)

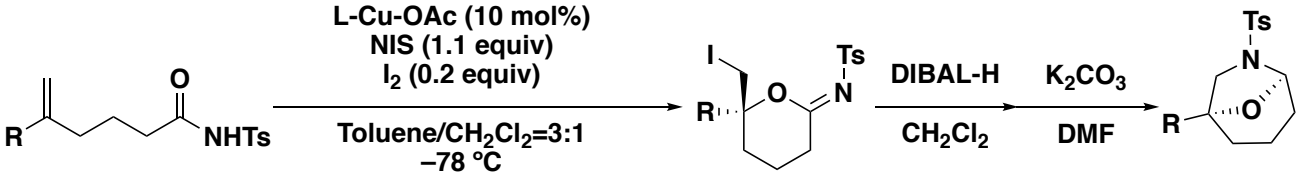


X = Cl
up to 97% yield
up to 88 % ee

X = Br
up to 90% yield
up to 23 % ee

2-2. Recent Catalytic Enantioselective Halogenation

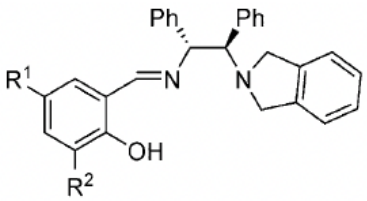
Enantioselective Iodocyclization of *N*-Tosyl Alkenamides (2015 Yamanaka)



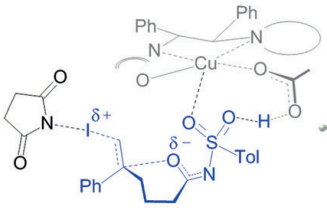
R = Ar, $(CH_2)_7CH_3$, Cy

12 examples
up to 98% yield
up to 94% ee

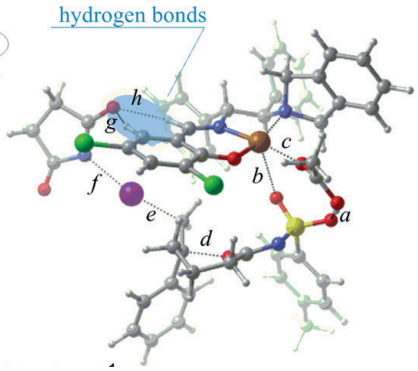
w/o loss of ee



Ligand
R^1 = Br, R^2 = Br



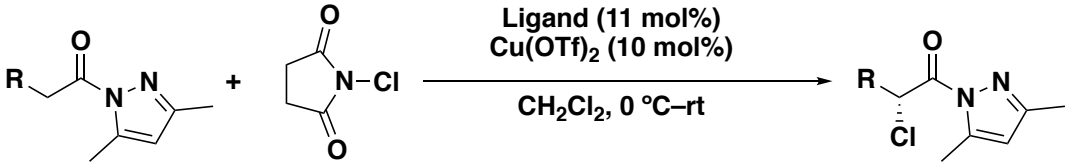
a : 1.683 *f* : 2.452
b : 3.098 *g* : 2.163
c : 1.986 *h* : 2.313
d : 1.889
e : 2.326

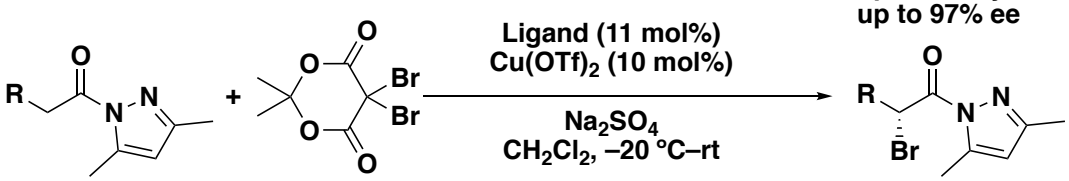


1) Togni. *et. al. Angew. Chem. Int. Ed.* **2000**, *39*, No. 23.
2) Togni. *et. al. Helv. Chim. Acta.* **2000**, *83*, 2425–2435.
3) Togni. *et. al. Chem. Comm.* **2004**, 1147–1155.
4) Yamanaka. *et. al. Angew. Chem. Int. Ed.* **2015**, *54*, 12767–12771.

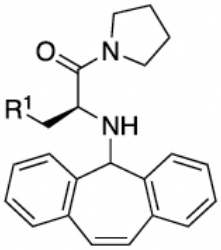
2. EnantioselectiveHalogenation using Metal Cat.

Enantioselective α-Halogenation of *N*-Acyl-3,5-dimethylpyrazoles (2022 Ishihara)

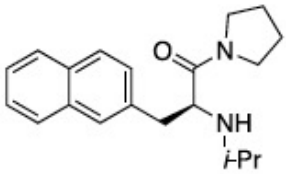




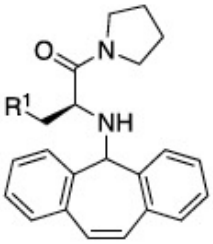
K. Ishihara
(1963-)



Ligand
R^1 = 2-naphthyl

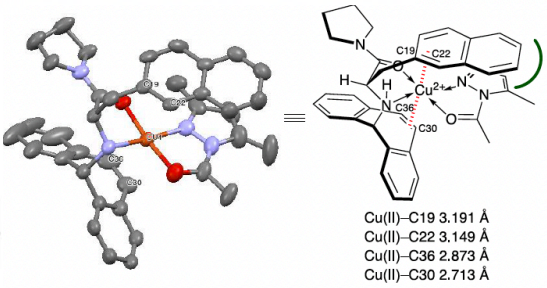


L1

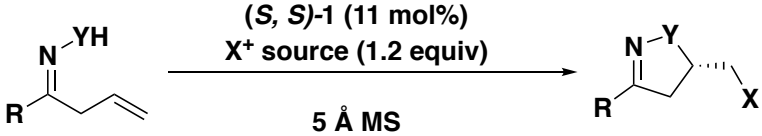


L2

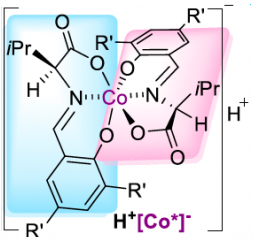
entry	ligand (R^1)	2b yield (%)[b]	2b ee (%)[c]
1[d]	L1 w/2,6-lutidine	8	38
2	L1 w/o base	54	32
5	L2 (2-naphthyl) w/o base	90 (71)[g]	96 (94)[g]



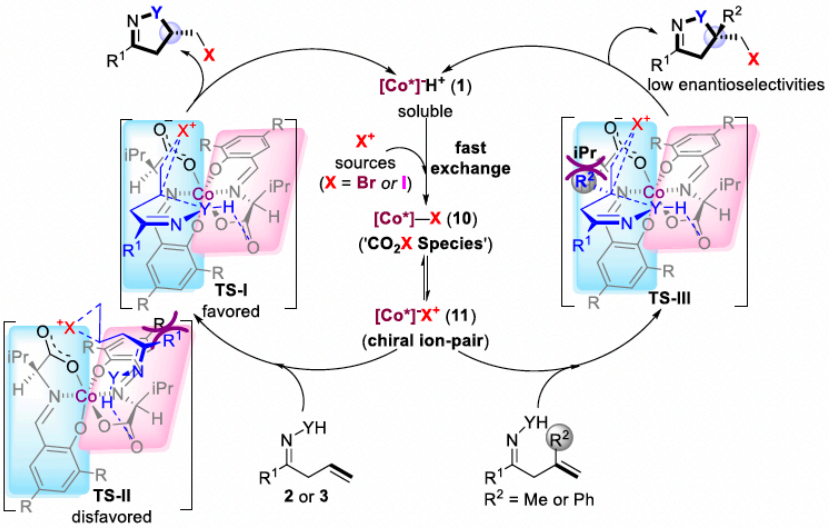
Anionic Chiral CO(III) Complexes Mediated Asymmrtric Halocyclization (2021 Yu)



Y = NPG, O
X = Br, I
up to 99% yield
up to 94% ee



(*S, S*)-1

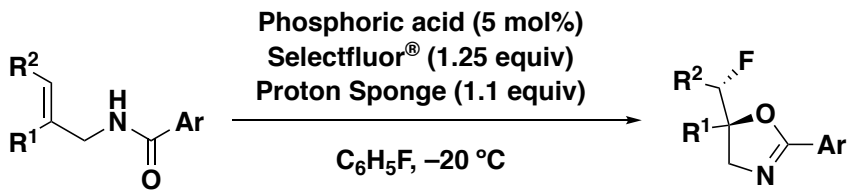


1) Ishihara. *et. al. Acs. Catal.* **2022**, *12*, 1012–1017.
2) Yu. *et. al. Org. Lett.* **2021**, *23*, 9134–9139.

3. Enantioselective halogenation using Organocatalyst

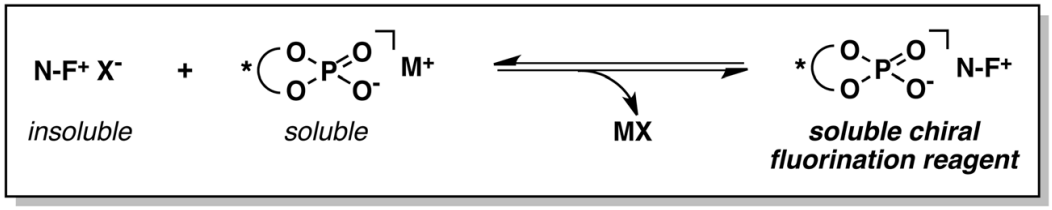
3-1. Enantioselective halogenation using Anionic PTC

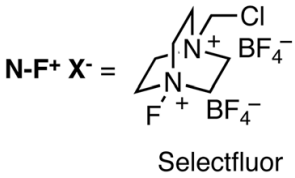
3-1-1. First Example of Asymmetric Fluorination using Anionic PTC (2011 Toste)

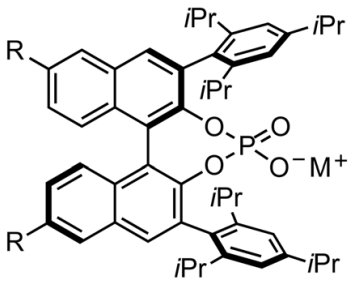


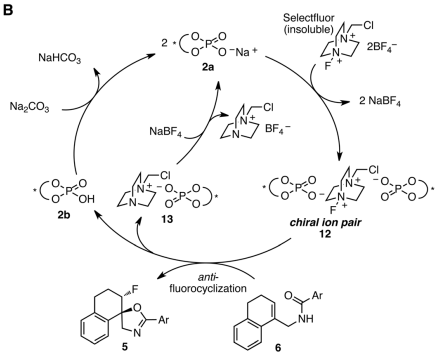
up to 95% yield
up to 97% ee

F. Dean Toste
(1971-)

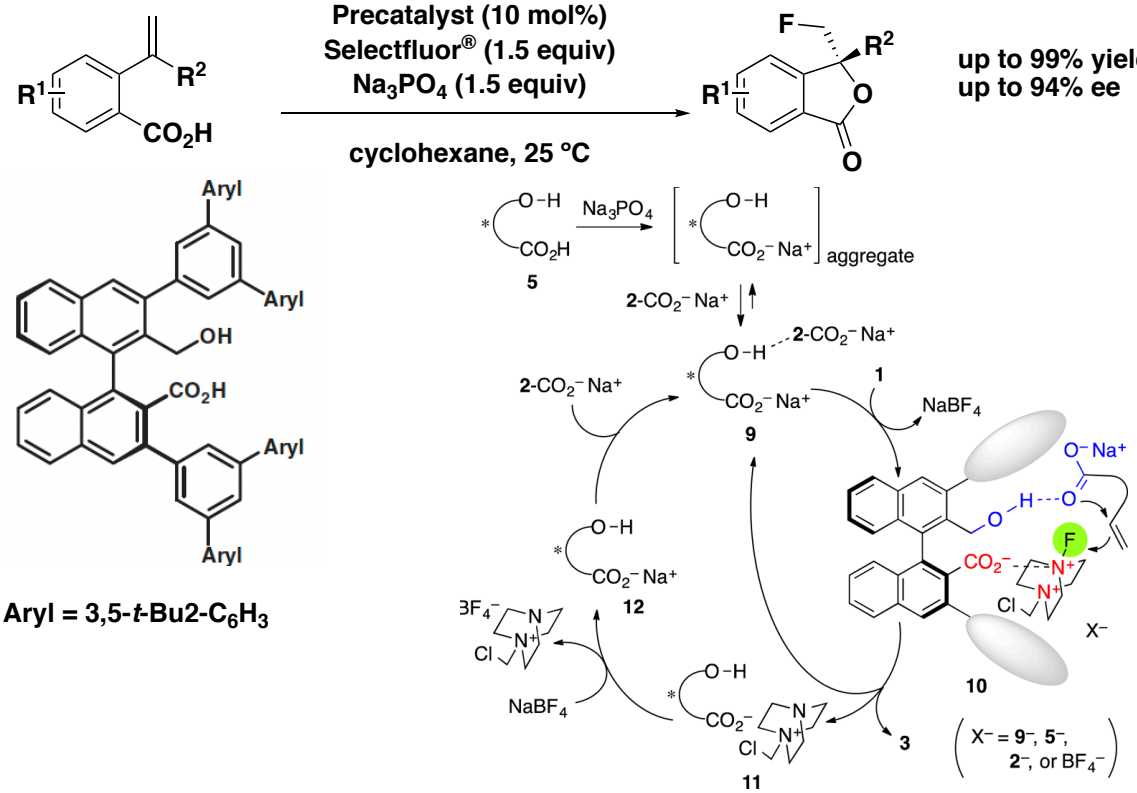








3-1-2. Asymmetric Fluorolactonization with a Bifuctional Hydroxyl Carboxylate Catalyst (2015 Hamashima)



up to 99% yield
up to 94% ee

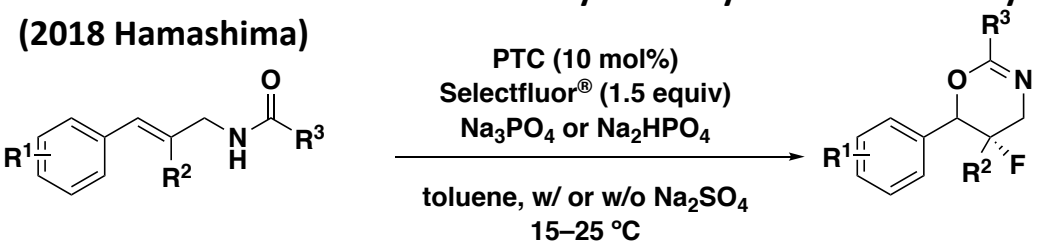
Y. Hamashima
(1974-)

Aryl = 3,5-*t*-Bu2-C_6H_3

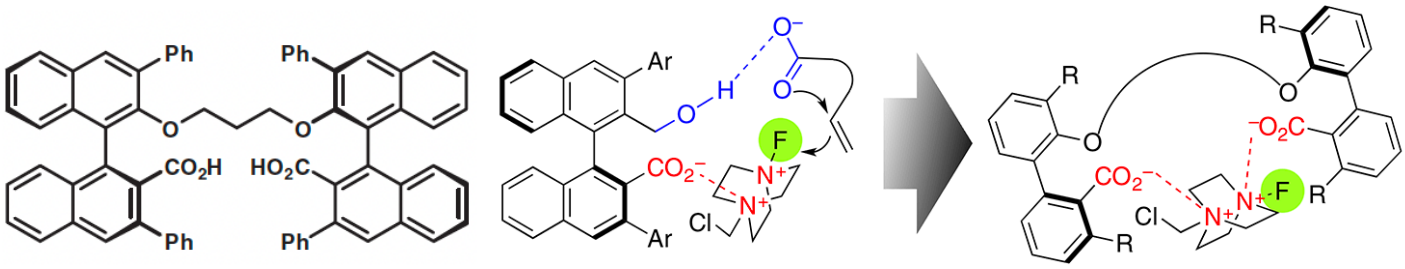
1) Toste. *et. al. Science.* **2011**, *334*, 1681.
2) Hamashima. *et. al. J. Am. Chem. Soc.* **2015**, *137*, 10132–10135.

3. Enantioselective halogenation using Organocatalyst

3-1-3.Dianionic Phase-Transfer Catalyst for Asymmetric Fluoro-cyclization (2018 Hamashima)



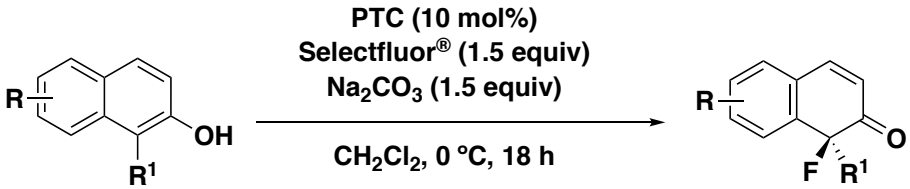
up to 80% yield
up to 99% ee



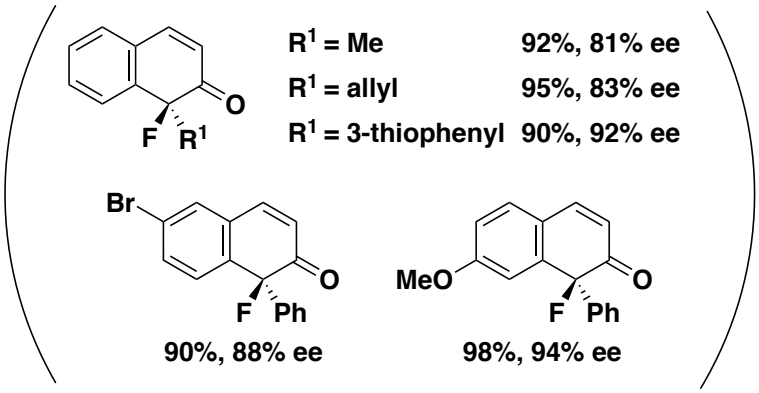
PTC

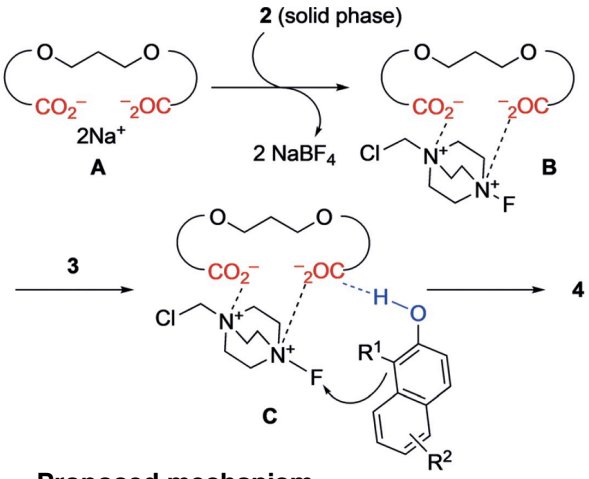
Phase-transfer activity
mono-anion < formal di-anion

3-1-4. Enantioselective reactions of 2-naphthols (2020 Hamashima)



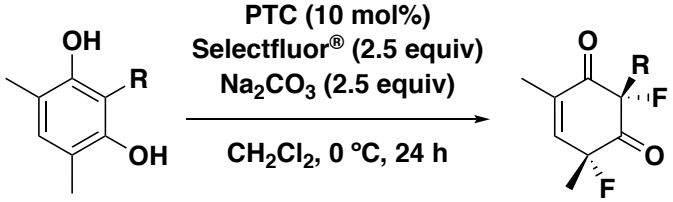
21 examples
up to >99% yield
up to 94 % ee





Proposed mechanism

3-1-5. Enantioselective reactions of resorcinols (2021 Hamashima)



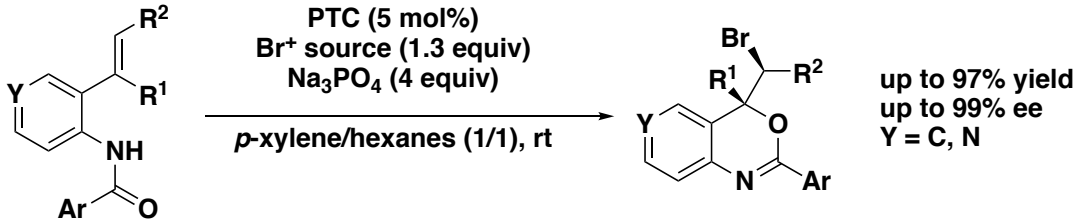
7 examples
up to >99% yield
up to 16:1 dr
up to 95 % ee

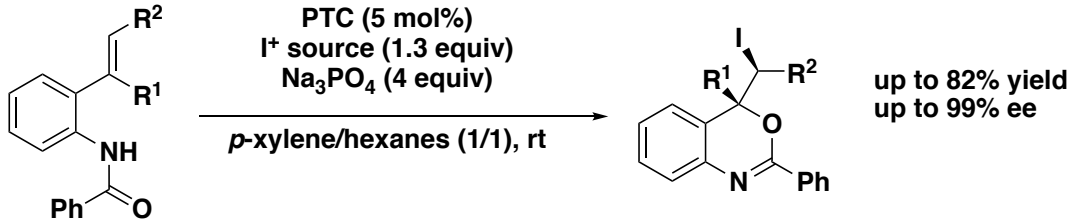
1) Hamashima. *et. al. J. Am. Chem. Soc.* **2015**, *137*, 10132–10135.
2) Hamashima. *et. al. Angew. Chem. Int. Ed.* **2020**, *59*, 14101.
3) Hamashima. *et. al. Tetrahedron.* **2021**, *96*, 132355.

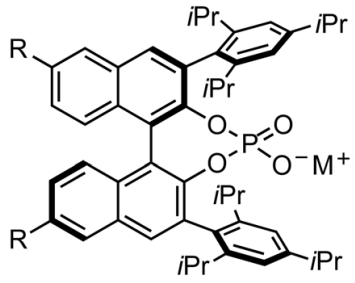
3. Enantioselective halogenation using Organocatalyst

Asymmetric Electrophililic Bromination/Iodination Using an Anionic Chiral PTC

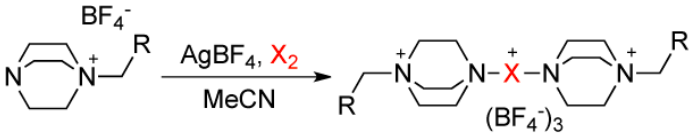
3-1-6. Enantioselective Halocyclization Using Reagents Tailored for Chiral Anion PTC (2012 Toste)







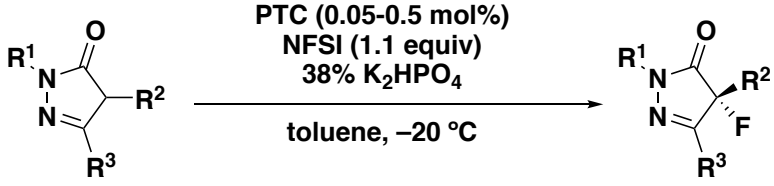
PTC
R = *i*-Pr_3Si



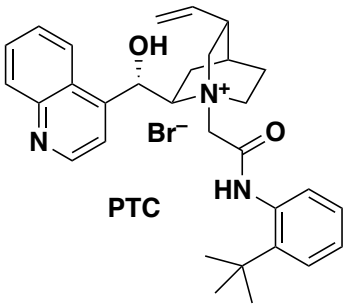
X^+ source
X = Br, I

3-2. Enantioselective halogenation using Cationic PTC

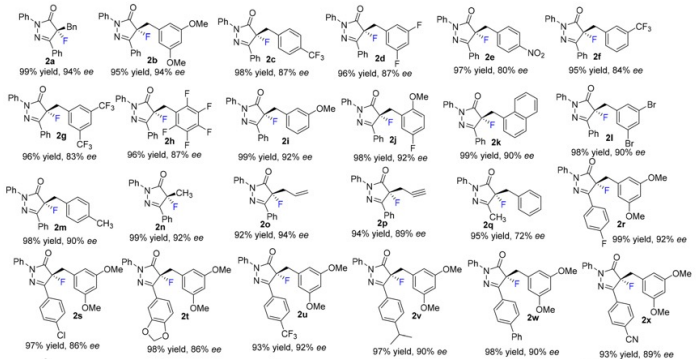
3-2-1. Enantioselective Fluorination of 4-Substituted Pyrazolones (2023 Wang)

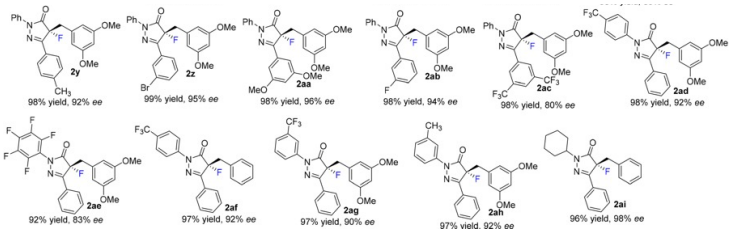


35 examples
up to 99% yield
up to 98% ee



PTC

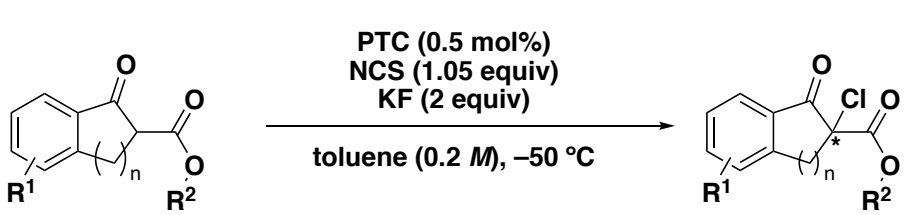


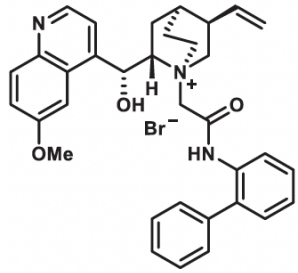


1) Toste. *et. al. J. Am. Chem. Soc.* **2012**, *134*, 12928–12931.
2) Wang. *et. al. Org. Chem. Front.* **2023**, *10*, 2226–2233.

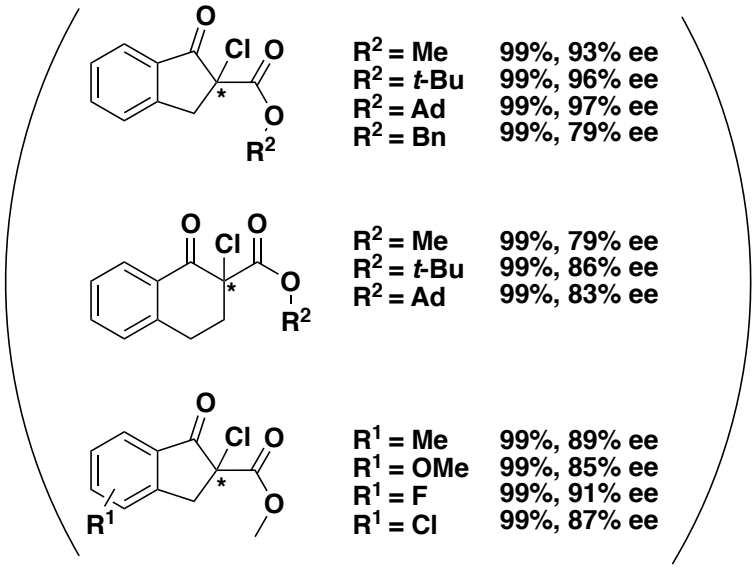
3. Enantioselective halogenation using Organocatalyst

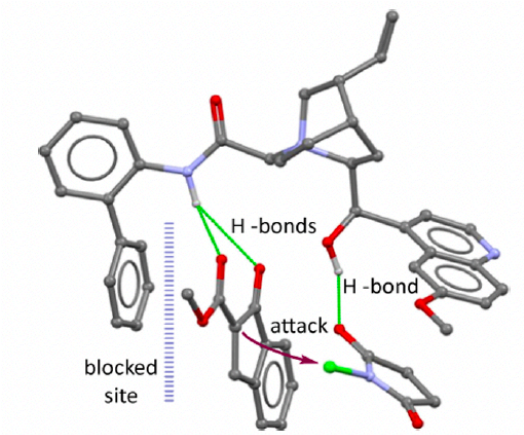
3-2-2. Enantioselective α-Chlorination of β-Keto Esters (2021 Jurczak)





PTC

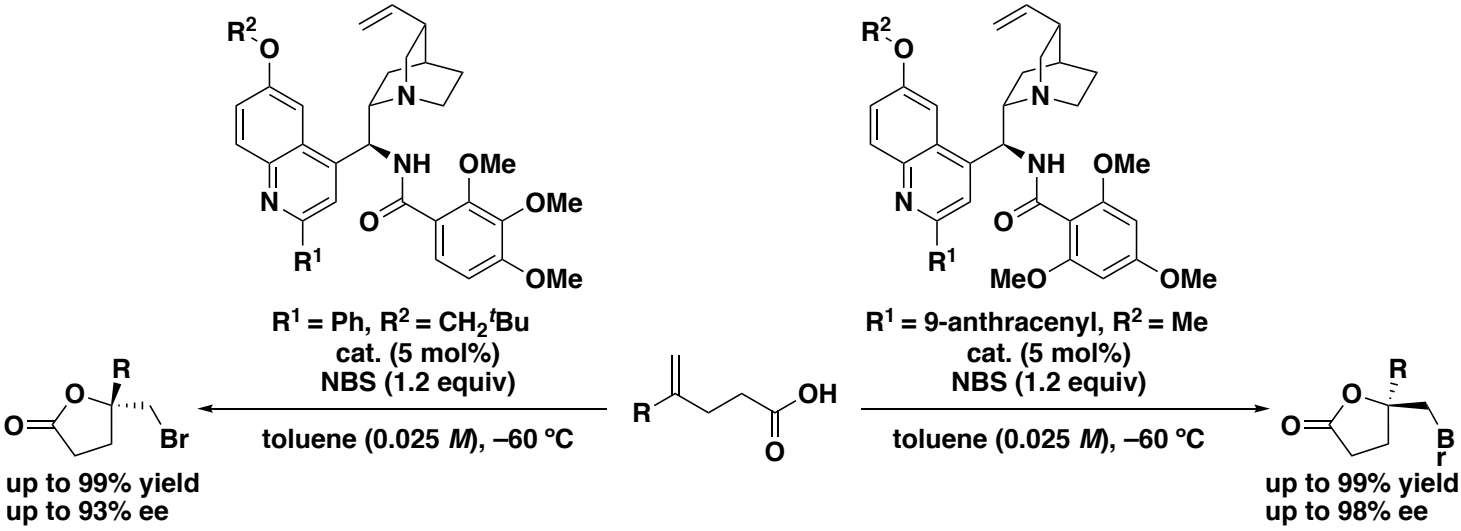


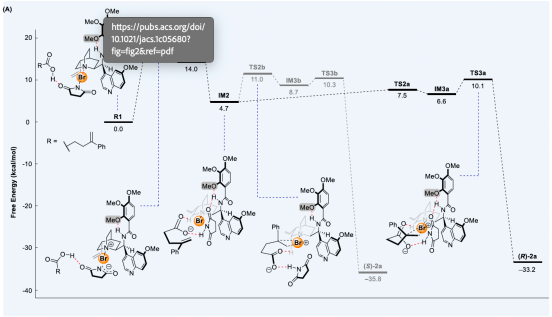


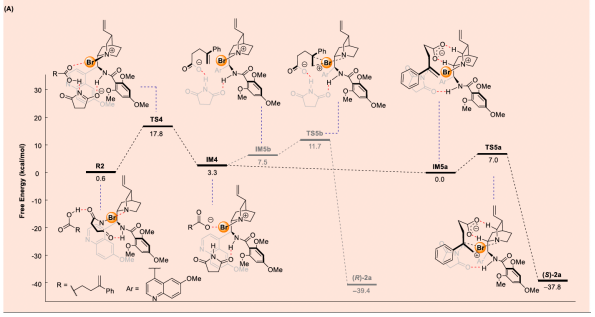
Proposed transition state model

3-3. Enantioselective halogenation using Organocatalyst

3-3-1. Enantiodivergent Bromolactonization (2021 Yeung)





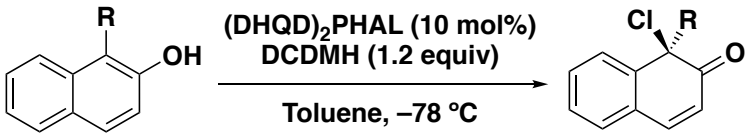


1) Jurczak. *et. al. J. Org. Chem.* **2021**, *86*, 995–1001.
2) Yeung. *et. al. J. Am. Chem. Soc.* **2021**, *143*, 12745–12754.

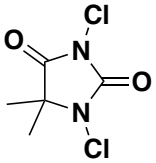
3. Enantioselective halogenation using Organocatalyst

3-3-2. Enantioselective reactions of naphthols (2015 You)

Scope of 2-naphthols

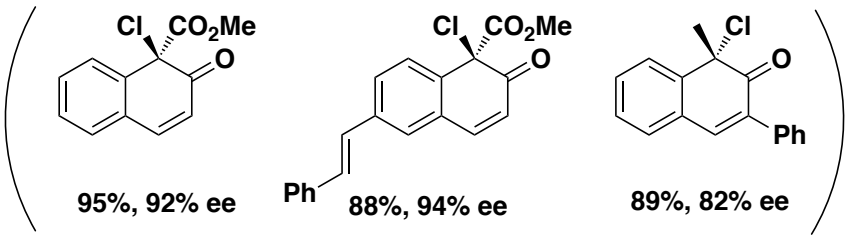


19 examples



DCDMH

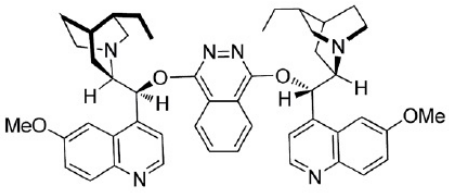
Shu-Li You
(1975-)



95%, 92% ee

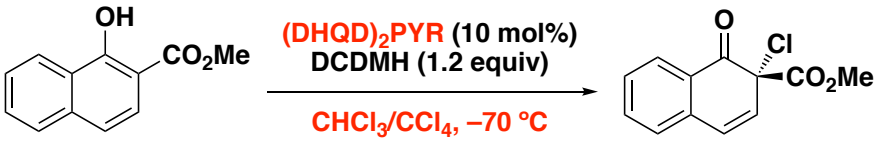
88%, 94% ee

89%, 82% ee

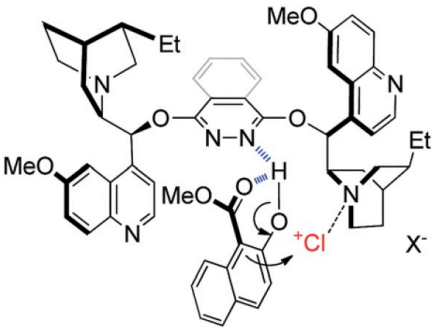


(DHQD)2PHAL

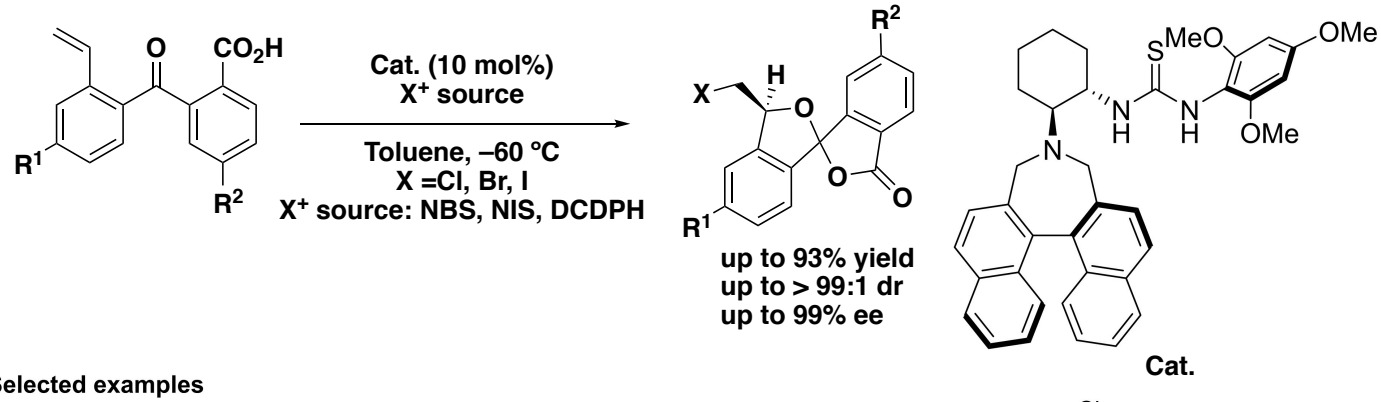
Investigation of 1-naphthols



94%, 90% ee



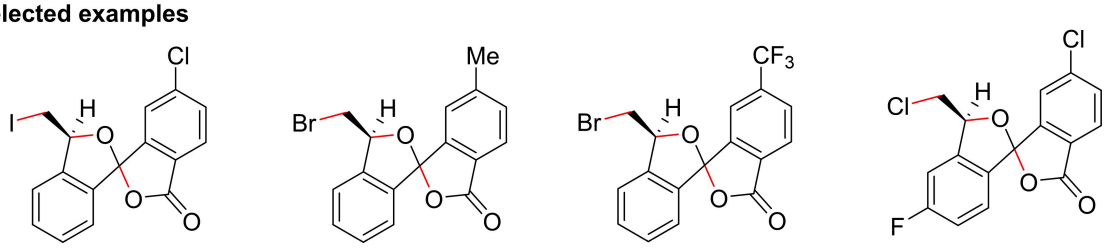
3-3-3. Enantio- and Diastereoselective Domino Halocyclization (2020 Yeung)



up to 93% yield
up to > 99:1 dr
up to 99% ee

Cat.

Selected examples



98a
71% yield
99% ee, 44:1 dr

98b
93% yield
99% ee, 44:1 dr

98c
90% yield
>99% ee, 53:1 dr

98d
77% yield
96% ee, 44:1 dr

1) You. *et. al. Chem. Sci.* **2015**, *6*, 4179.
2) Yeung. *et. al. Nat. Catal.* **2020**, *3*, 993–1001.