

Catalytic, enantioselective fluorination of alkene

Literature Seminar

2018/4/28

Takahiro Watanabe

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1. Introduction

2. Difluorination of alkene

2-1. 1-2 difluorination

2-2. 1-1 difluorination

3. Fluoroamination of alkene

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1. Introduction

2. Difluorination of alkene

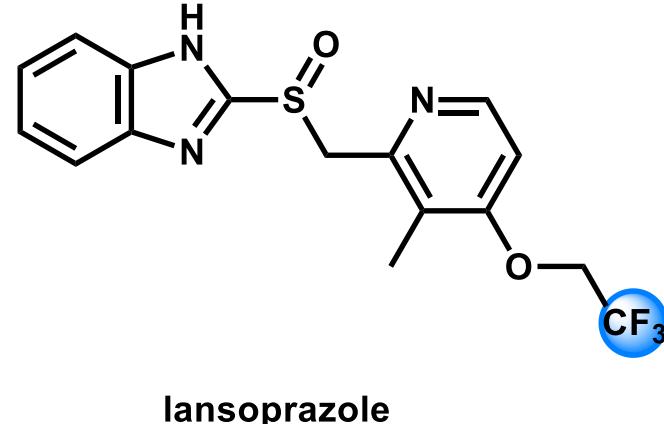
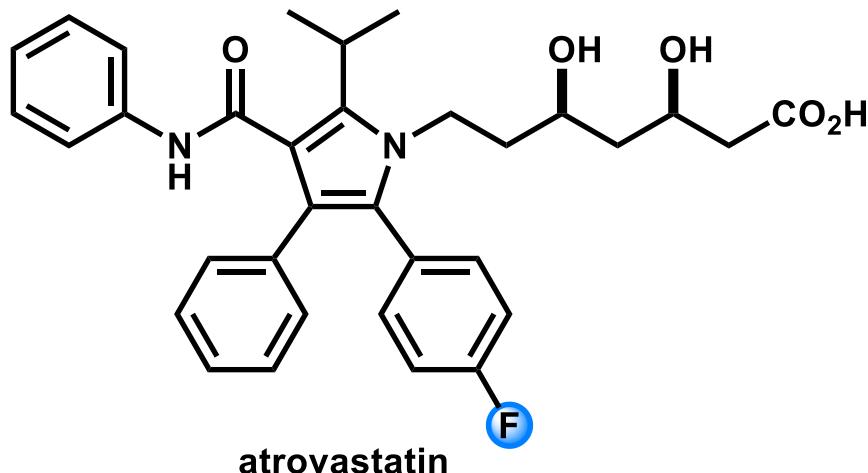
2-1. 1-2 difluorination

2-2. 1-1 difluorination

3. Fluoroamination of alkene

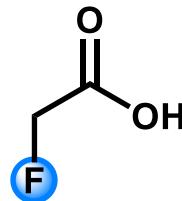
Fluorine-containing molecules

artificially synthesized: ex. medicine

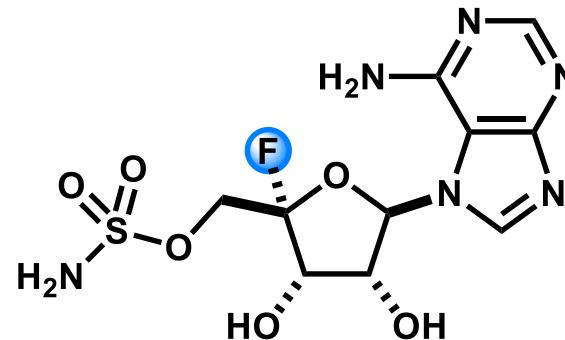


... Over 150 medicines have fluorine atom.¹⁾

natural products



fluoroacetic acid



nucleocidin

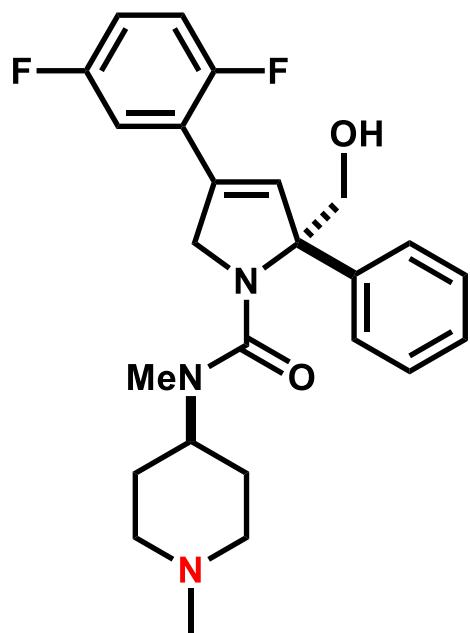
... Only six discrete fluorinated natural products have been isolated.²⁾

(excluding the fatty acid homologues)

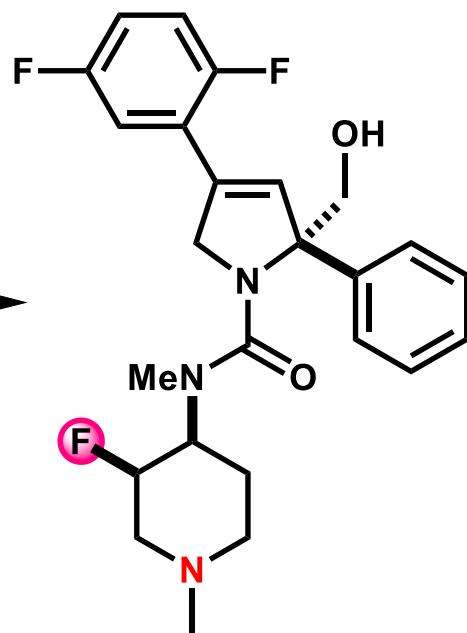
1) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, 317, 1881.

2) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, 100, 127.

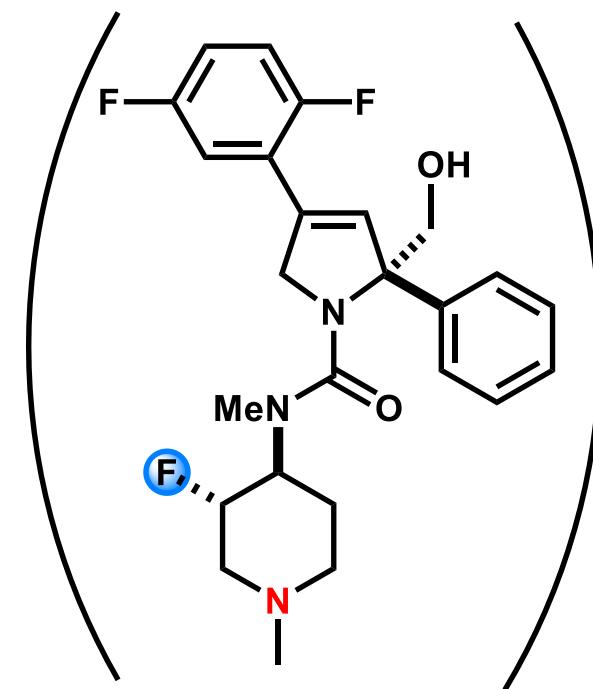
Effect of introduction of fluorine atom



pKa = 8.8



MK-0731
(axial F atom)
pKa = 7.6



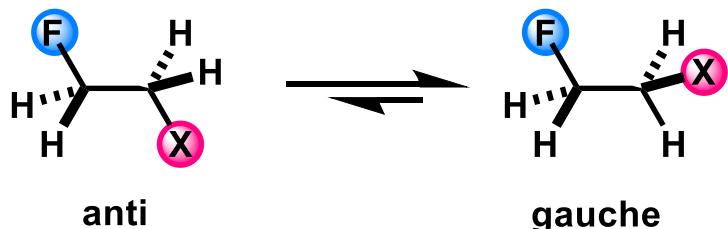
(equatorial F atom)
pKa = 6.6

Decrease of basicity of piperidine nitrogen

→ Improvement of metabolic stability

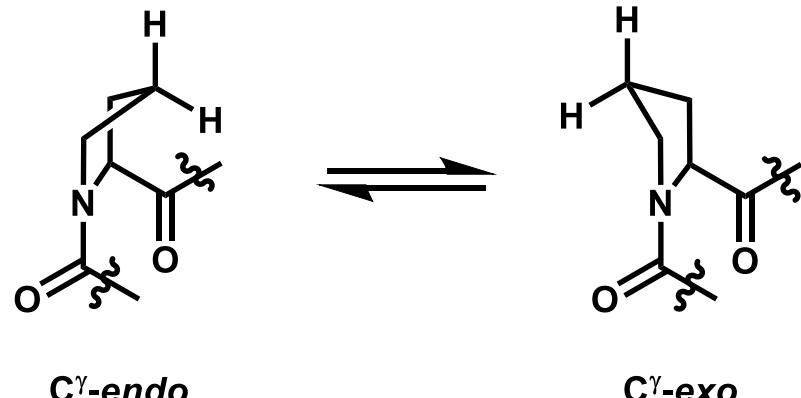
Conformational control by introducing fluorine

gauche effect



X= F, OCOR, NHCOR

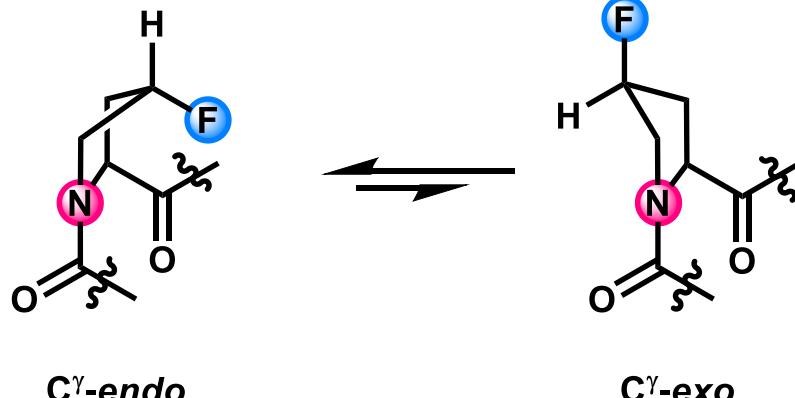
Pro residue



ex. **Collagen** is composed by about 300 repeats of the sequence of X_{aa}Y_{aa}Gly.

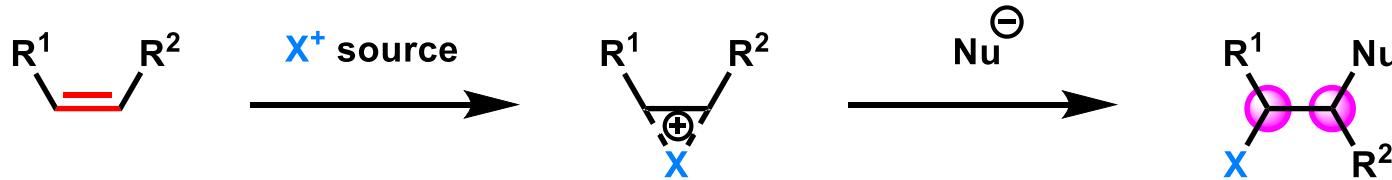
→ In most cases, X_{aa} and Y_{aa} are (2S)-proline (Pro) and (2S,4R)-4-hydroxyproline (4R-Hyp).

(2S,4S)-fluoroproline residue



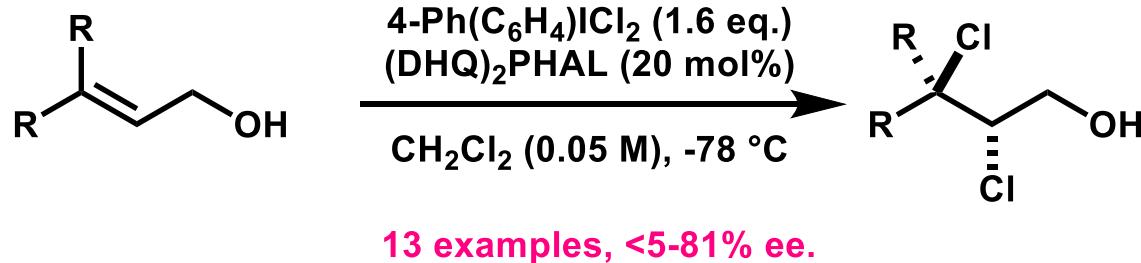
→ This conformational restriction affects helix stability.

Halogenation of alkene

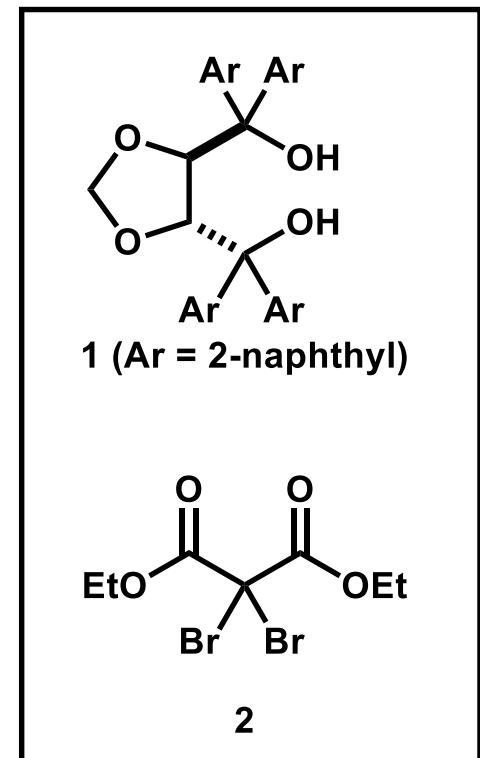
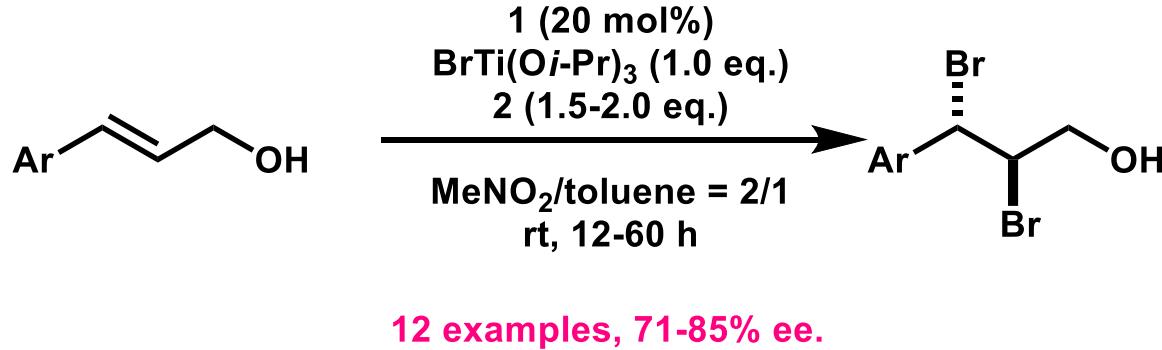


Halogenation of alkene is fundamental reaction to introduce halogene atoms.

For catalytic enantioselective dichlorination ¹⁾:

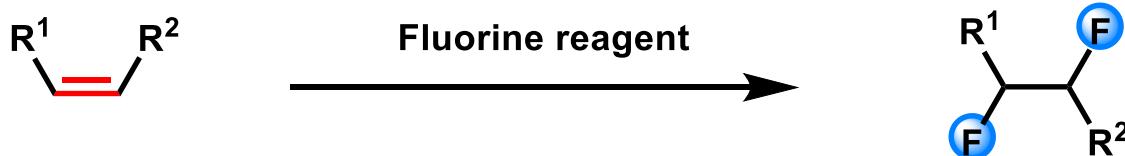


For catalytic enantioselective dibromination ²⁾:



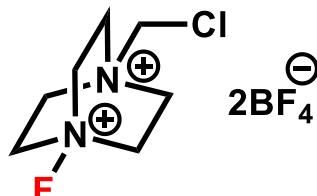
1) Nicolaou *et al.* *J. Am. Chem. Soc.* **2011**, *133*, 8134. 2) Burns *et al.* *J. Am. Chem. Soc.* **2013**, *135*, 12960.

Reagent type of fluorination



F^+ source

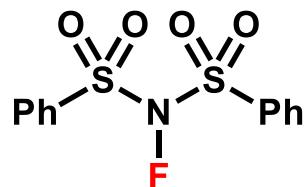
F_2



2BF_4^-

XeF_2

(Selectfluor®)
-> See 160827_LS_
Masaki_KOSHIMIZU



(*N*-fluorobenzenesulfonimide)

F^- source

$\text{HF}\cdot\text{py} (\text{/Ar-I}/m\text{CPBA})$

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Eric N. Jacobsen



**1978-1982: B.S. New York University
(Prof. Yorke E. Rhodes)**

**1982-1986: Ph.D. University of California
(Prof. Robert G. Bergman)**

**1986-1988: Postdoc. Massachusetts Institute of Technology
(Prof. K. Barry Sharpless)**

1988-1991: Assistant Prof. University of Illinois at Urbana-Champaign

1991-1993: Associate Prof. University of Illinois at Urbana-Champaign

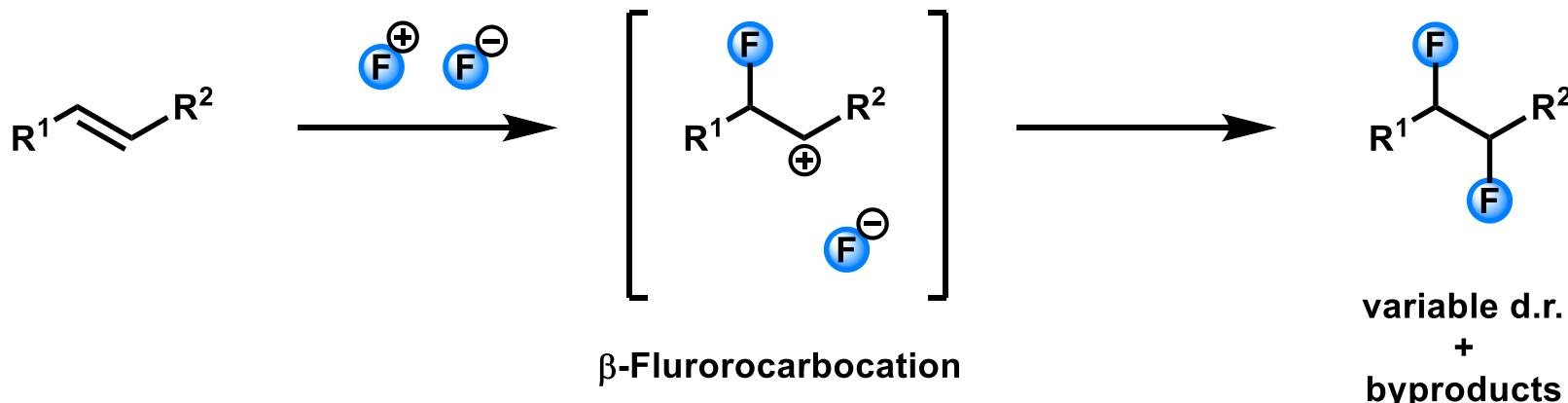
1993-present: Prof. Harvard University

Research Interests:

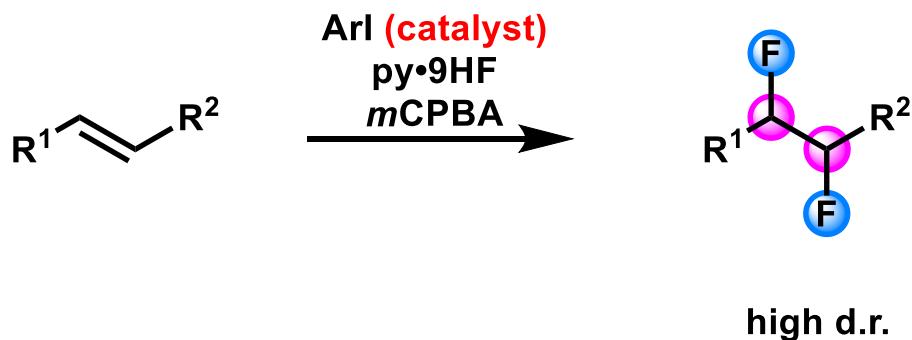
- 1. Development of new catalytic reactions**
- 2. Physical-organic studies of reactivity and recognition phenomena in homogeneous catalysis**
- 3. Enantioselective synthesis of natural products and pharmaceutical compounds**

Challenges for stereocontrol (1,2-difluorination)

Prior work



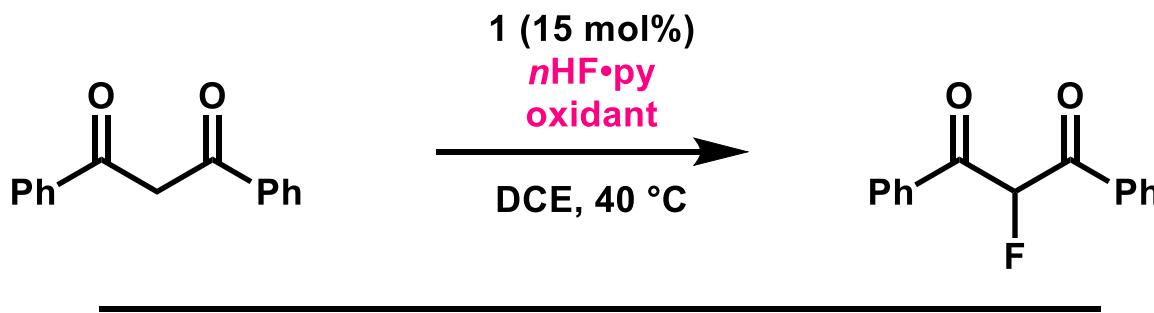
Jacobsen's work



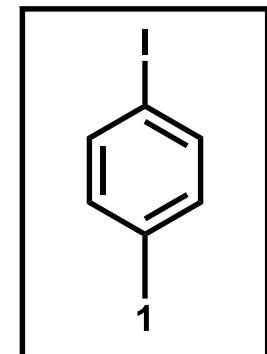
Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 5000.

Arl-py·HF-*m*CPBA system

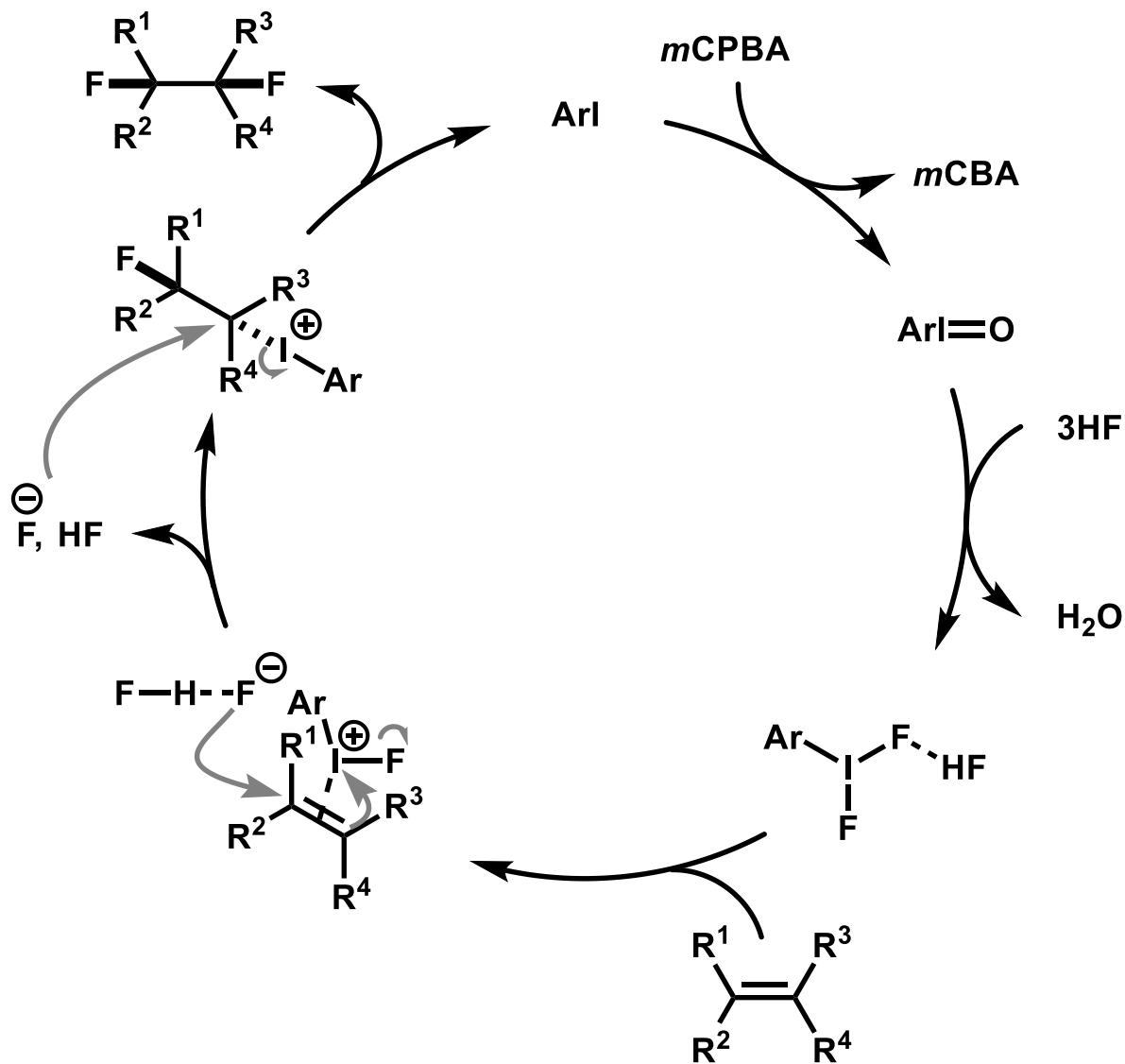
Shibata et al.



entry	oxidant	yield
1	NaIO_4	N.R.
2	$t\text{BuOOH}$	0%
3	$\text{Na}_2\text{S}_2\text{O}_8$	25%
4	Oxone®	12%
5	50% H_2O_2	N.R.
6	<i>m</i> CPBA	80%

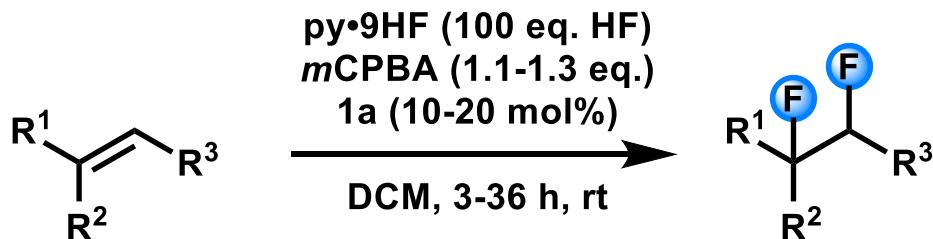


Proposed catalyst cycle

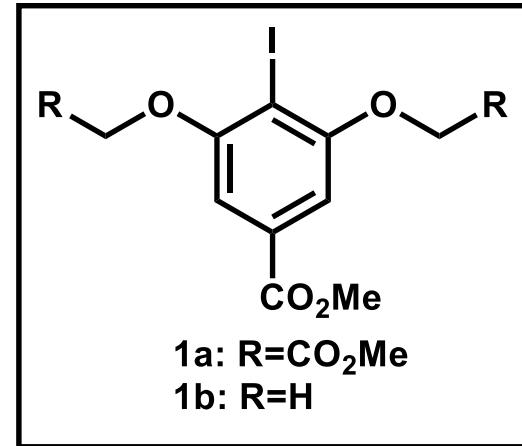
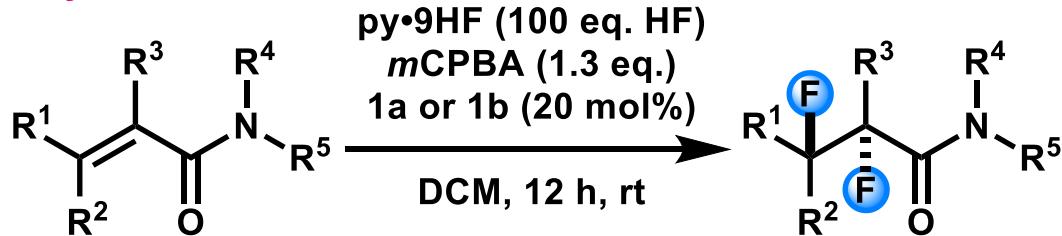


Diastereoselective 1,2-Difluorination by Jacobsen's group

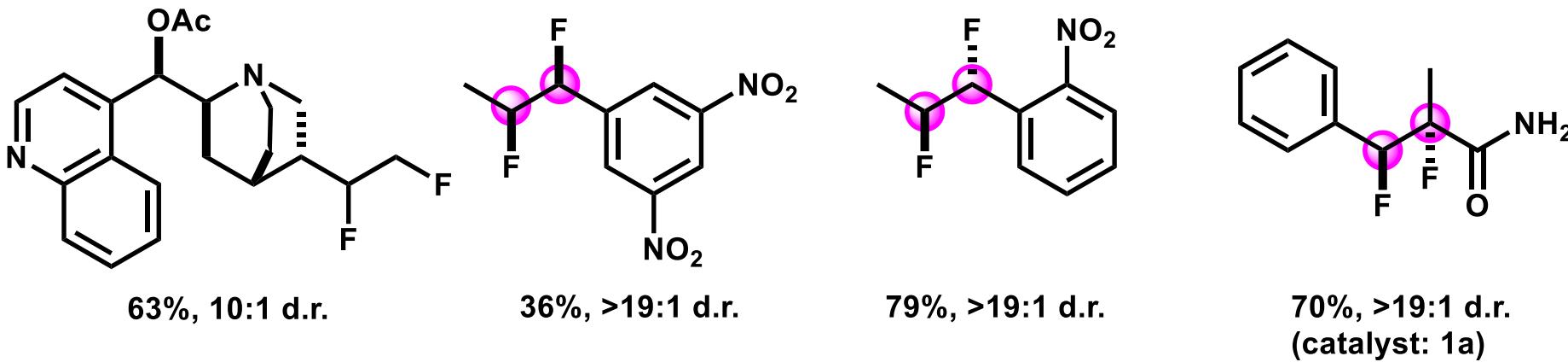
Terminal ($R^2, R^3=H$), Internal alkene



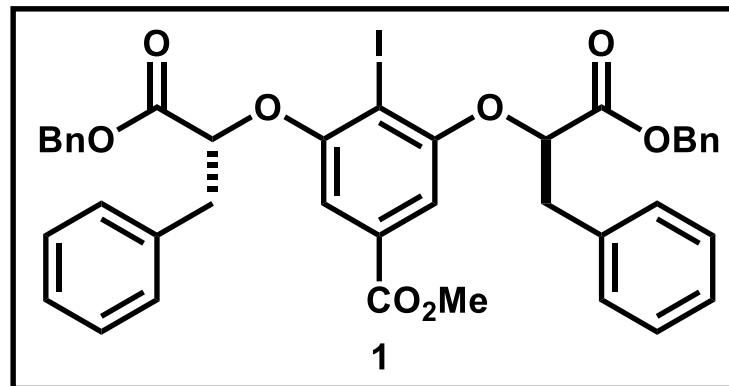
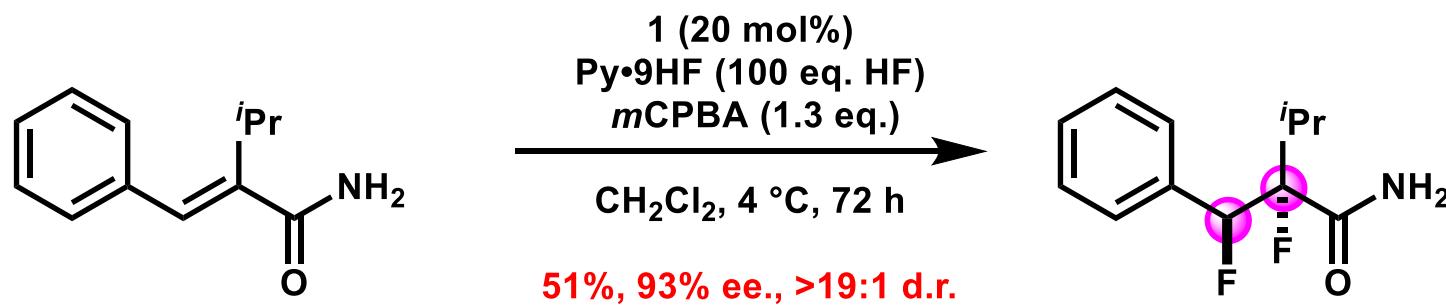
Acrylamide



(scope, part)



Enantioselective 1,2-Difluorination by Jacobsen's group



Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 5000.

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REPORTS

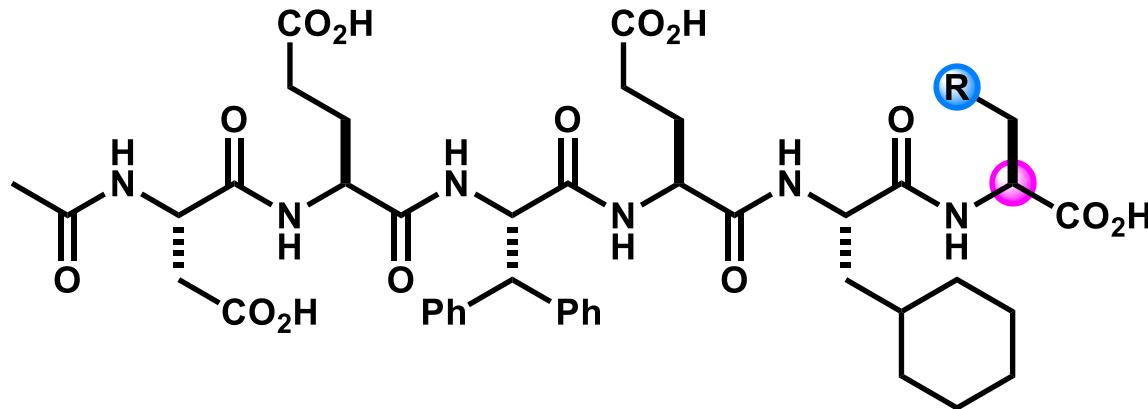
ORGANIC CHEMISTRY

Catalytic, asymmetric difluorination of alkenes to generate difluoromethylated stereocenters

Steven M. Banik, Jonathan William Medley, Eric N. Jacobsen*

CHF₂ group

ex. RCHF₂ as thiol mimic



R = SH (inhibitor of HCV NS₃ protease) :

K_i = 40 nM

R = CHF₂:

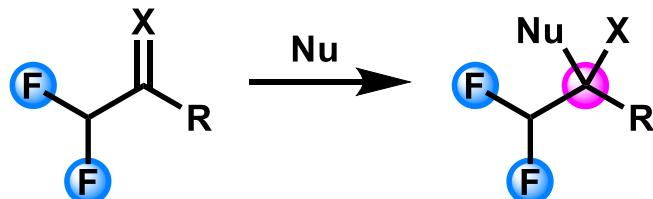
K_i = 30 nM

- Similar Van der Waals surfaces (HCF₂CH₃ = 46.7 Å, HSCH₃ = 47.1 Å)
- Similar electrostatic potential

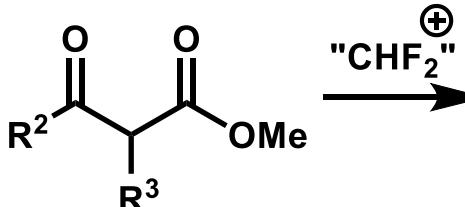
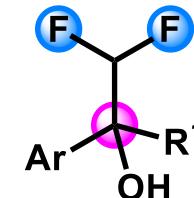
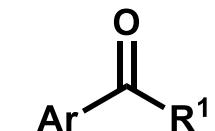
Also, CHF₂ group works as a **hydrogen bond donor/acceptor**

Introduction of difluoromethylated stereocenters

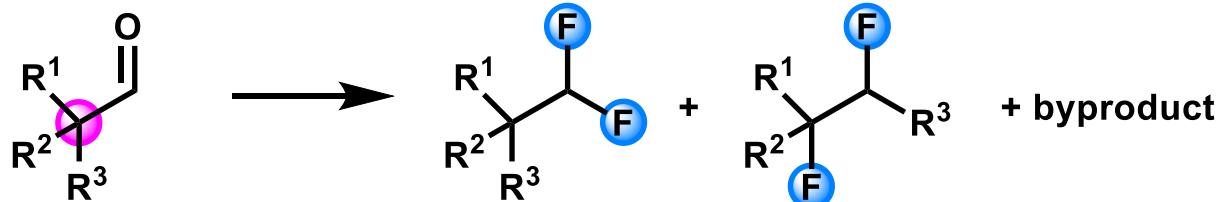
Pre-installation of CHF_2



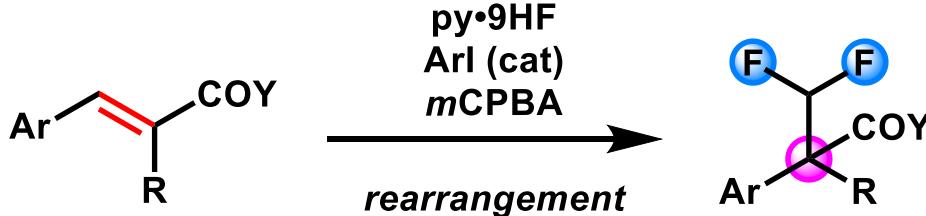
CHF_2 equivalents



Deoxyfluorination



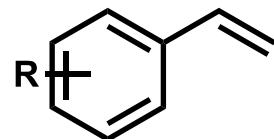
This work



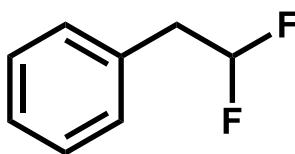
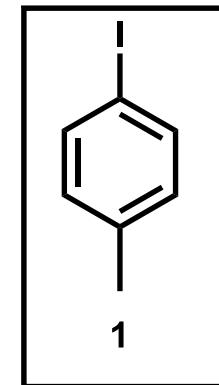
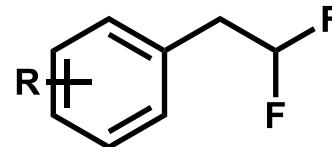
$\text{COY} = \text{ester or amide}$
 $\text{R} = \text{H or alkyl}$

High enantioselectivity

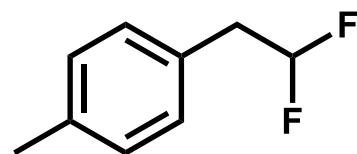
1,1-Difluorination with iodoarene catalyst



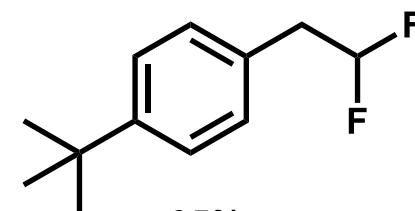
1 (20 mol%)
Py·HF (20 eq. HF)
*m*CPBA (1.5 eq.)
CH₂Cl₂, rt, 0.5 h



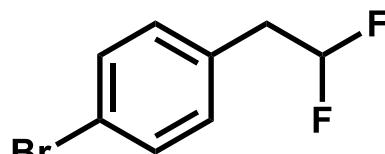
34%



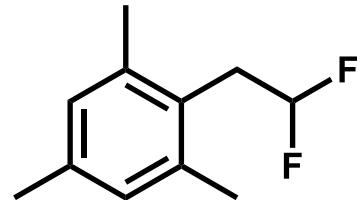
31%



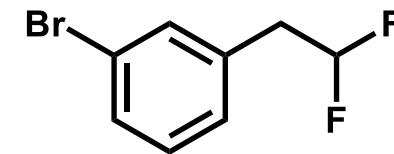
35%



50%

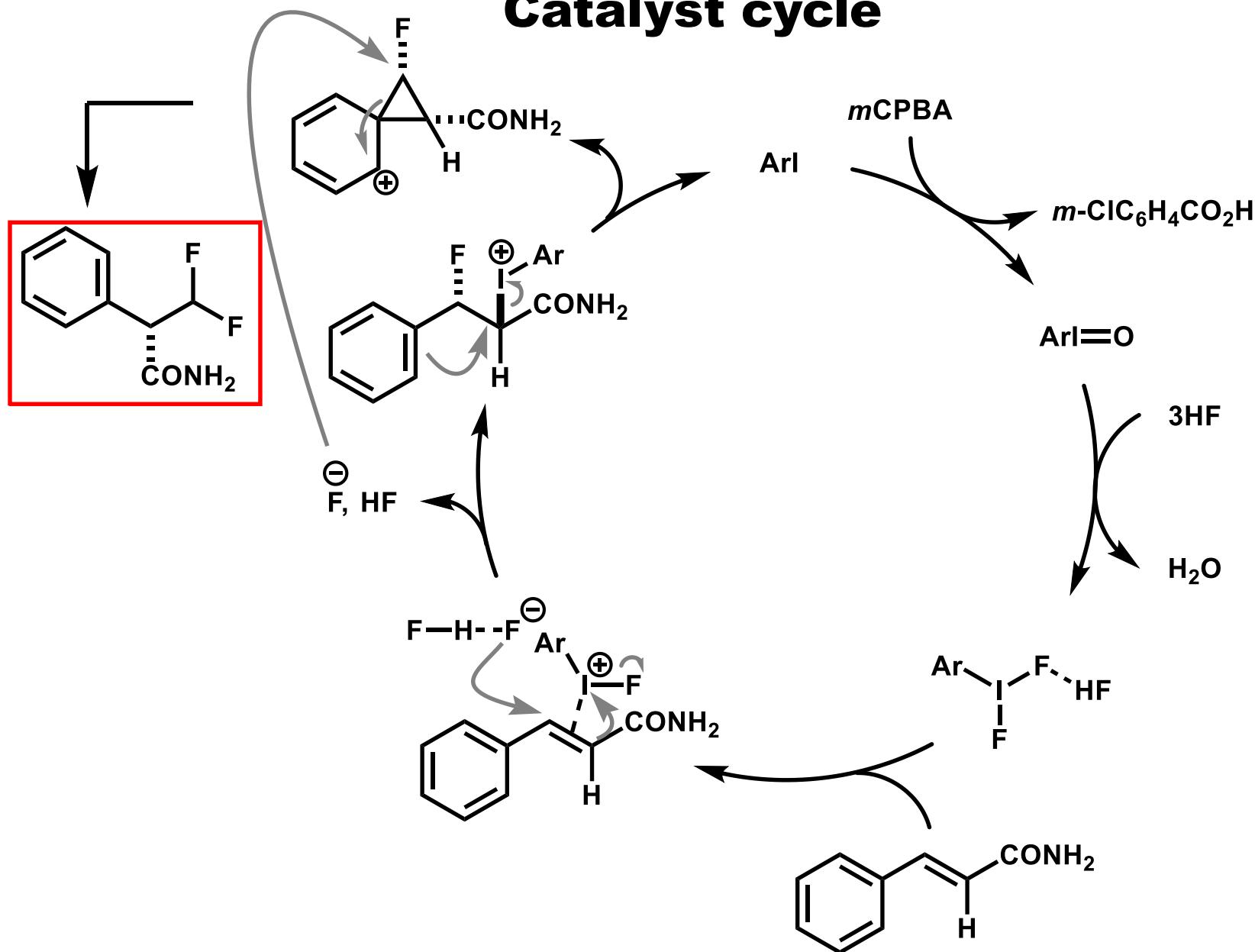


66%

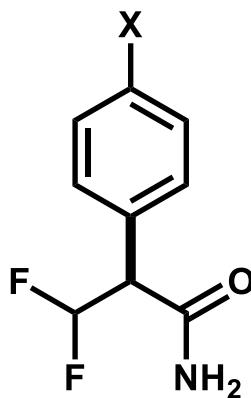
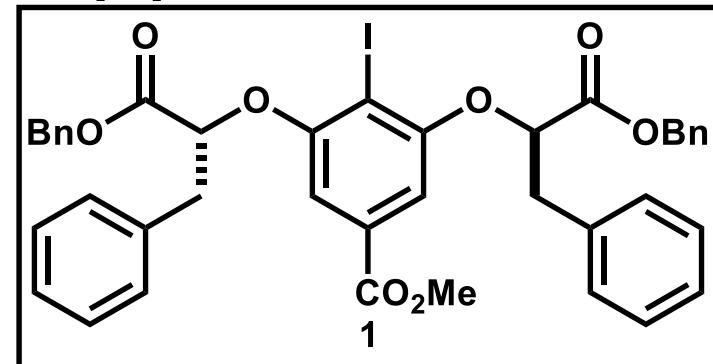
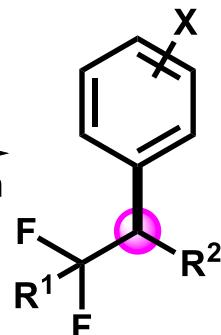
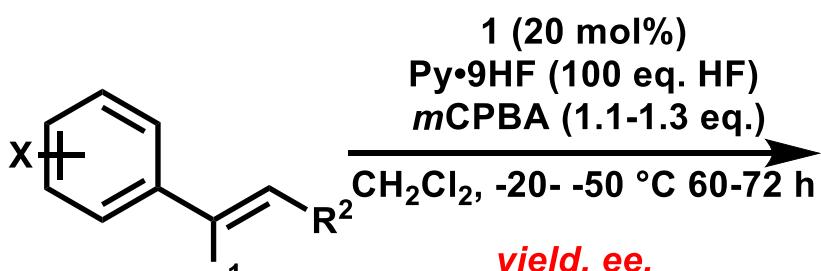


46%

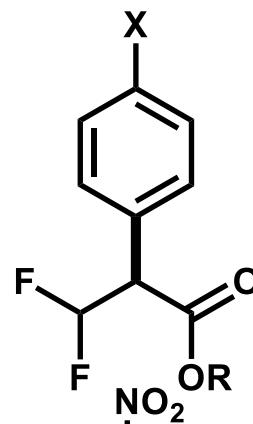
Catalyst cycle



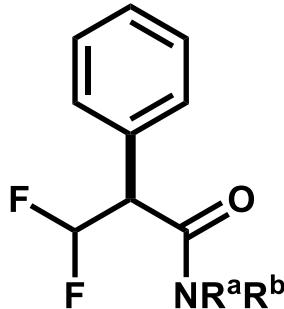
Substrate scope (1)



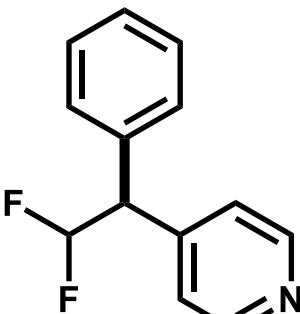
$X=H$: 67%, 92% ee.
 $X=Cl$: 63%, 92% ee.
 $X=F$: 76%, 91% ee.
 $X=iBu$: 80%, 83% ee.
 $X=Me$: 83%, 84% ee.
 $X=NPhth$: 94% ee.



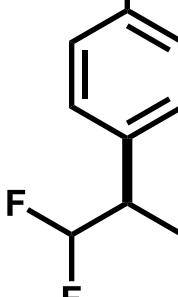
$X=H$, $R=Me$: 49%, 84% ee.
 $X=Cl$, $R=Me$: 62%, 87% ee.
 $X=Br$, $R=Me$: 45%, 87% ee.
 $X=H$, $R=iPr$: 63%, 85% ee.



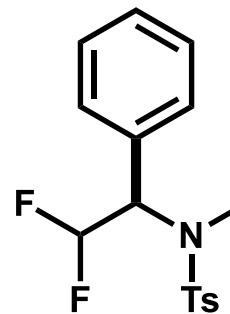
$R^a=H$, $R^b=Me$: 67%, 90% ee.



$R^a=Me$, $R^b=Me$: 28%, 96% ee. 74%, 71% ee.

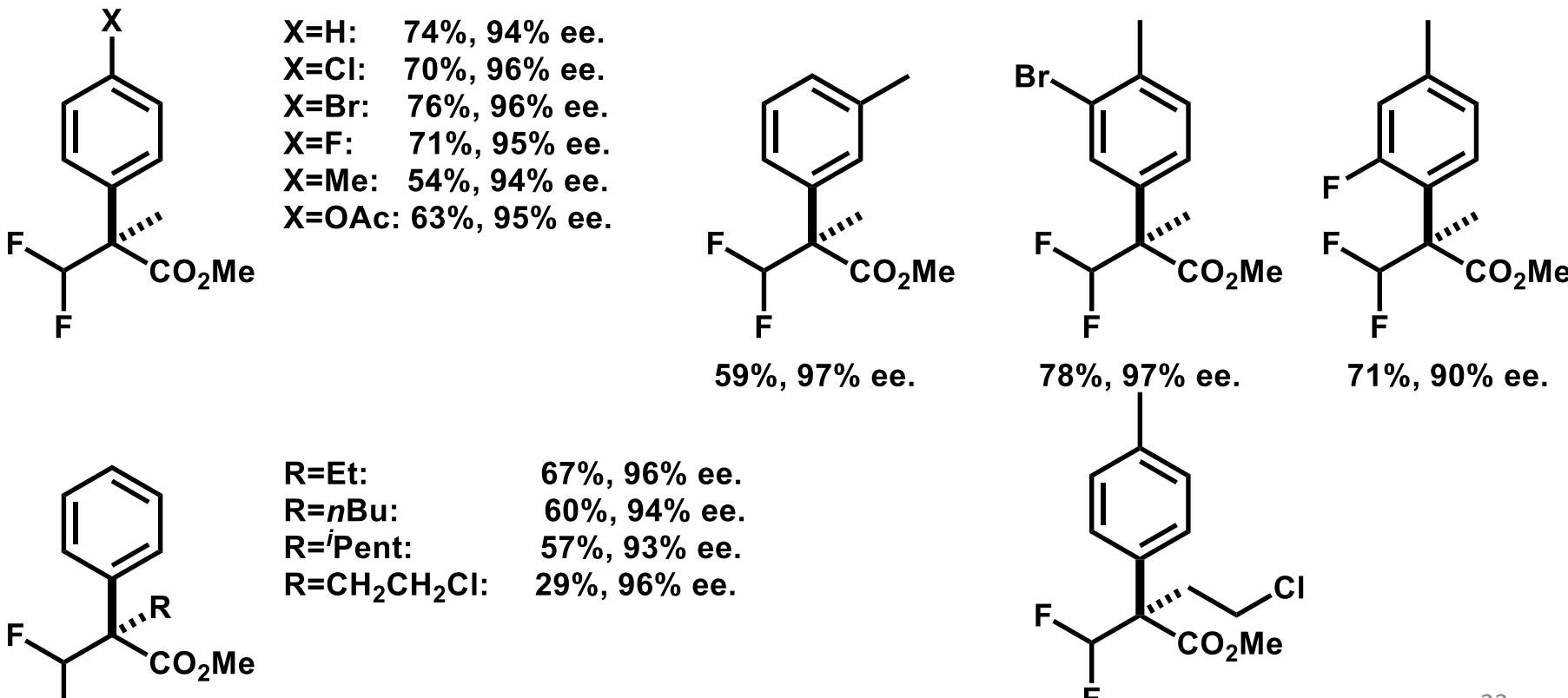
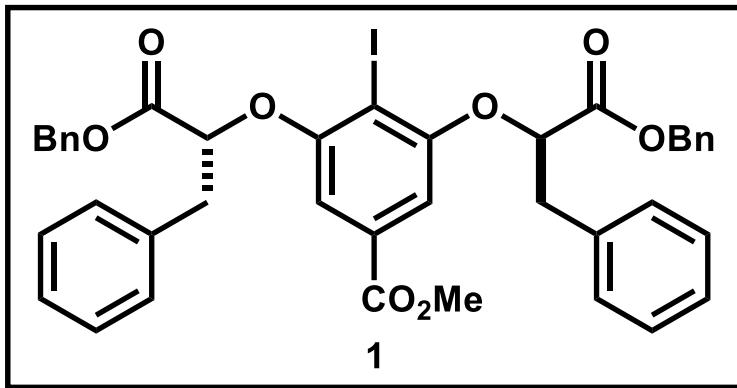
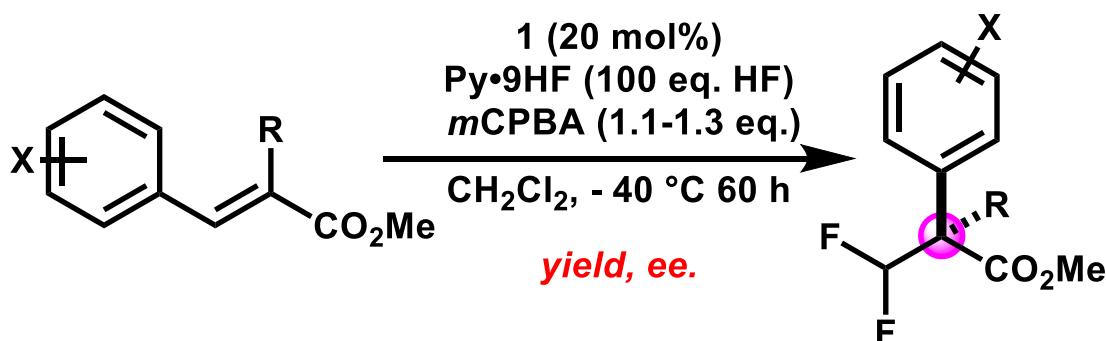


52%, 74% ee. 72%, 64% ee.



93%, 76% ee.

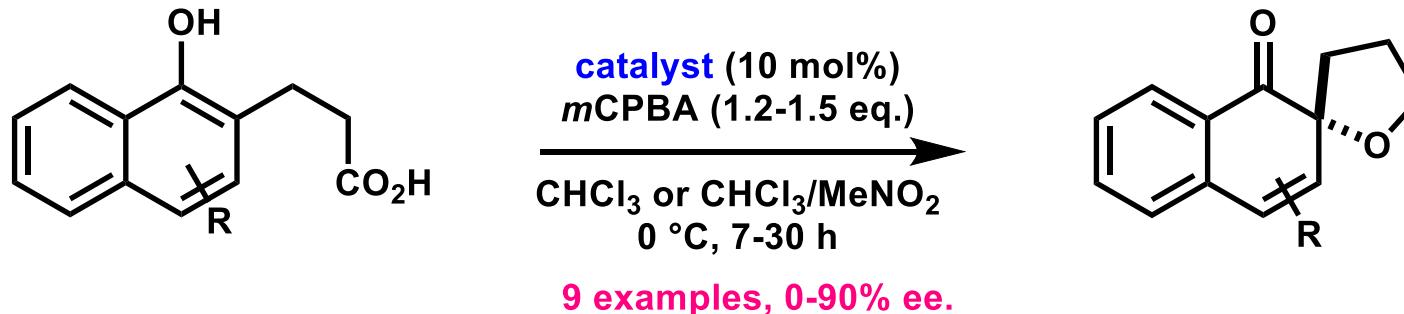
Substrate scope (2)



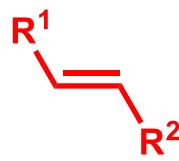
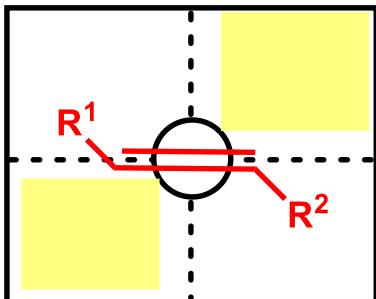
C_2 -symmetric chiral iodine catalyst

Oxidative spirolactonization

Ishihara et al. (2010)



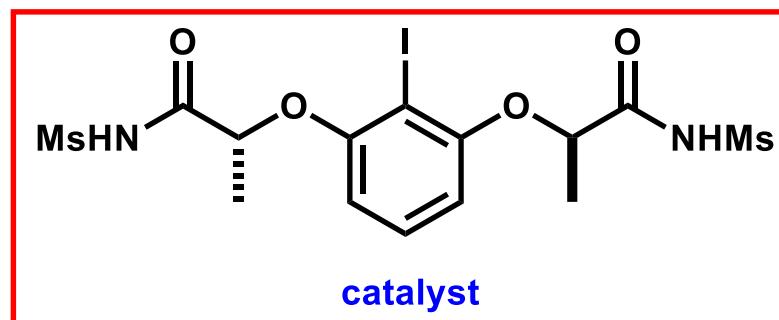
quadrant diagram



: Metal of C_2 -symmetric catalyst



: Occupied area by ligands
(the first and third quadrant)



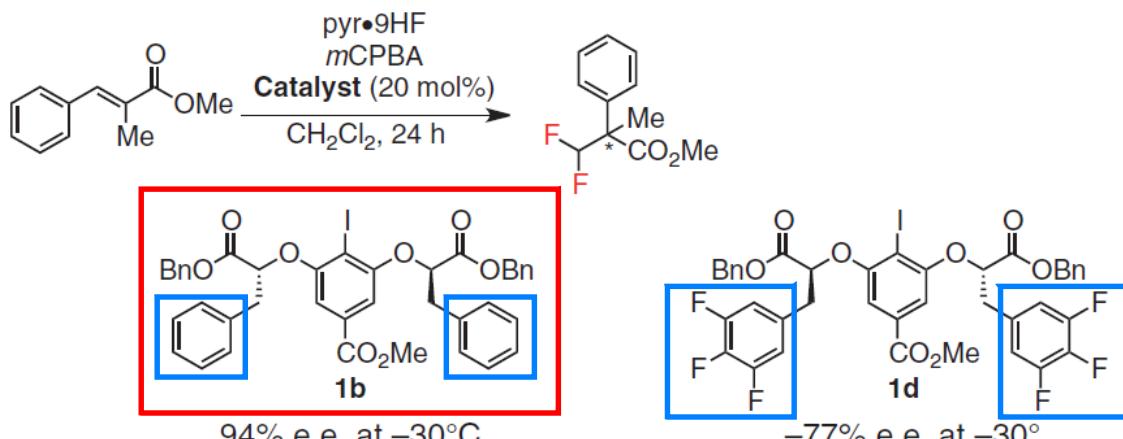
Generally speaking, when ligands occupy the first and third quadrant, conformation of alkene is more favorable when substituent R¹ and R² positions at the second and fourth quadrant.
→ Induction of asymmetry

Uyanik, K.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* 2010, 49, 2175.

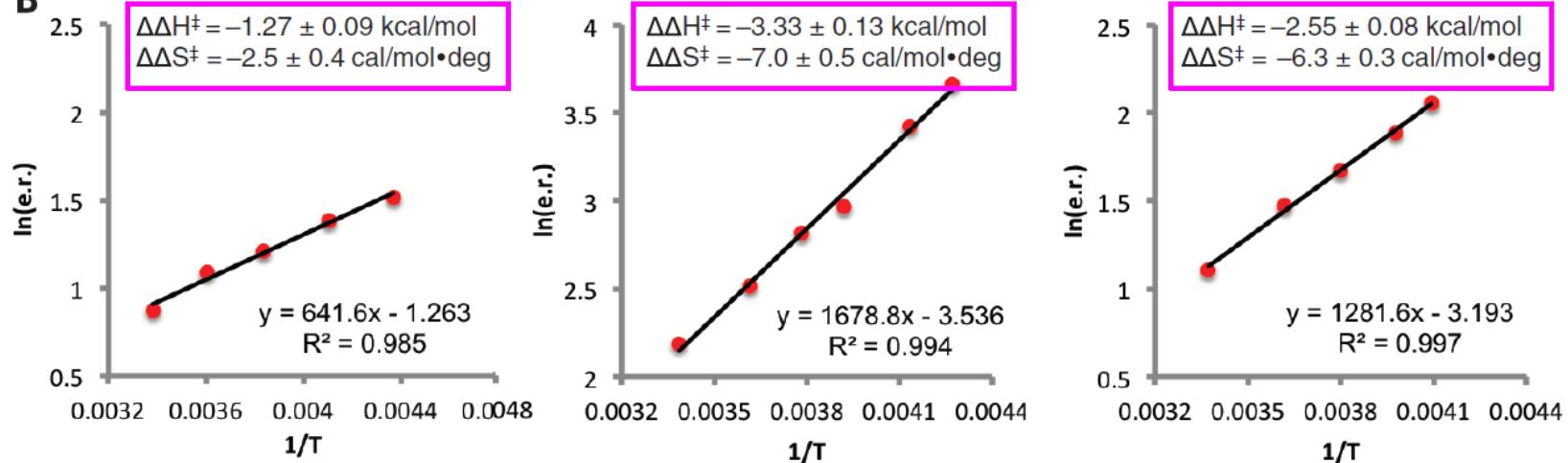
ハートwig有機遷移金属化学(下) p524-525

Catalyst substituent effects on enantioselectivity

A



B



1b (center): original catalyst (substituent: phenyl)

1c (left), 1d (right): substituents are cyclohexyl and 3,4,5-trifluorophenyl, respectively.

$$\ln(\text{e.r.}) = -\frac{\Delta\Delta H^\ddagger}{RT} + \frac{\Delta\Delta S^\ddagger}{R}^{24}$$

Interpretation of the result of Eyring analysis

entry	substituents of catalyst	ee. of products at -30 °C (%)	$\Delta\Delta H^\ddagger$ (kcal/mol)	$\Delta\Delta S^\ddagger$ (cal/mol·deg)
1		-60	-1.27±0.09	-2.5±0.4
2		94	-3.33±0.13	-7.0±0.5
3		-77	-2.55±0.08	-6.3±0.3

cation-π interaction might contribute the selective stabilization of high-energy cationic intermediated and/or transition structures.



Eyring analysis, $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ were calculated.

Significant difference of $\Delta\Delta H^\ddagger$ between entry 1 and entry 2 was observed.

→ difficult to ascribe steric effects alone

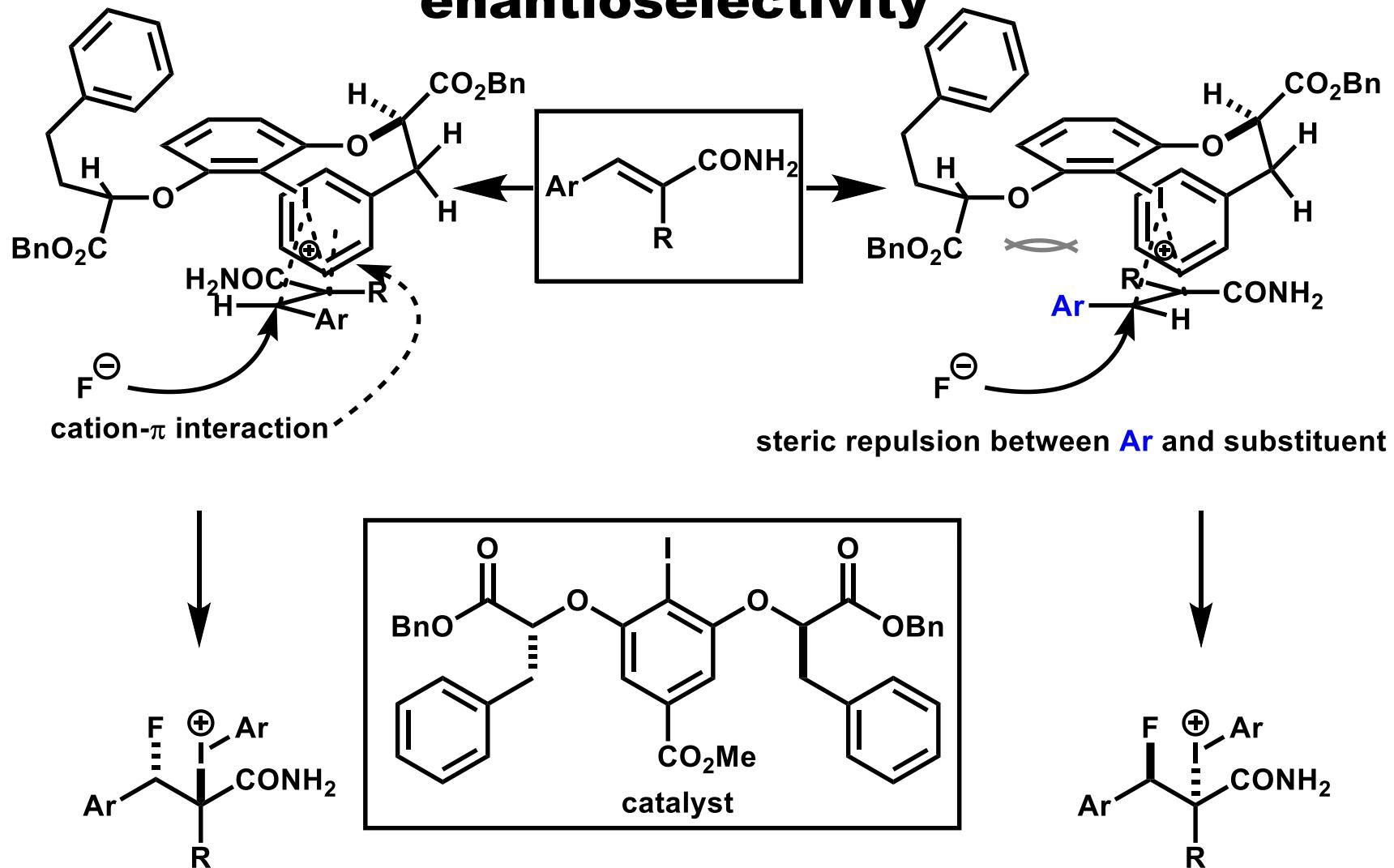
→ selective stabilization of the transition state leading to major enantiomer was suggested.

$\Delta\Delta H^\ddagger$ of entry 3 was rather similar to that of entry 1.

→ consistent with more electron-donating π surface contributing high enantioselectivity.

supporting for cation-π interaction playing role for enhancement in enantioselectivity

My proposal for induction of enantioselectivity



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Cite This: *J. Am. Chem. Soc.* 2018, 140, 4797–4802

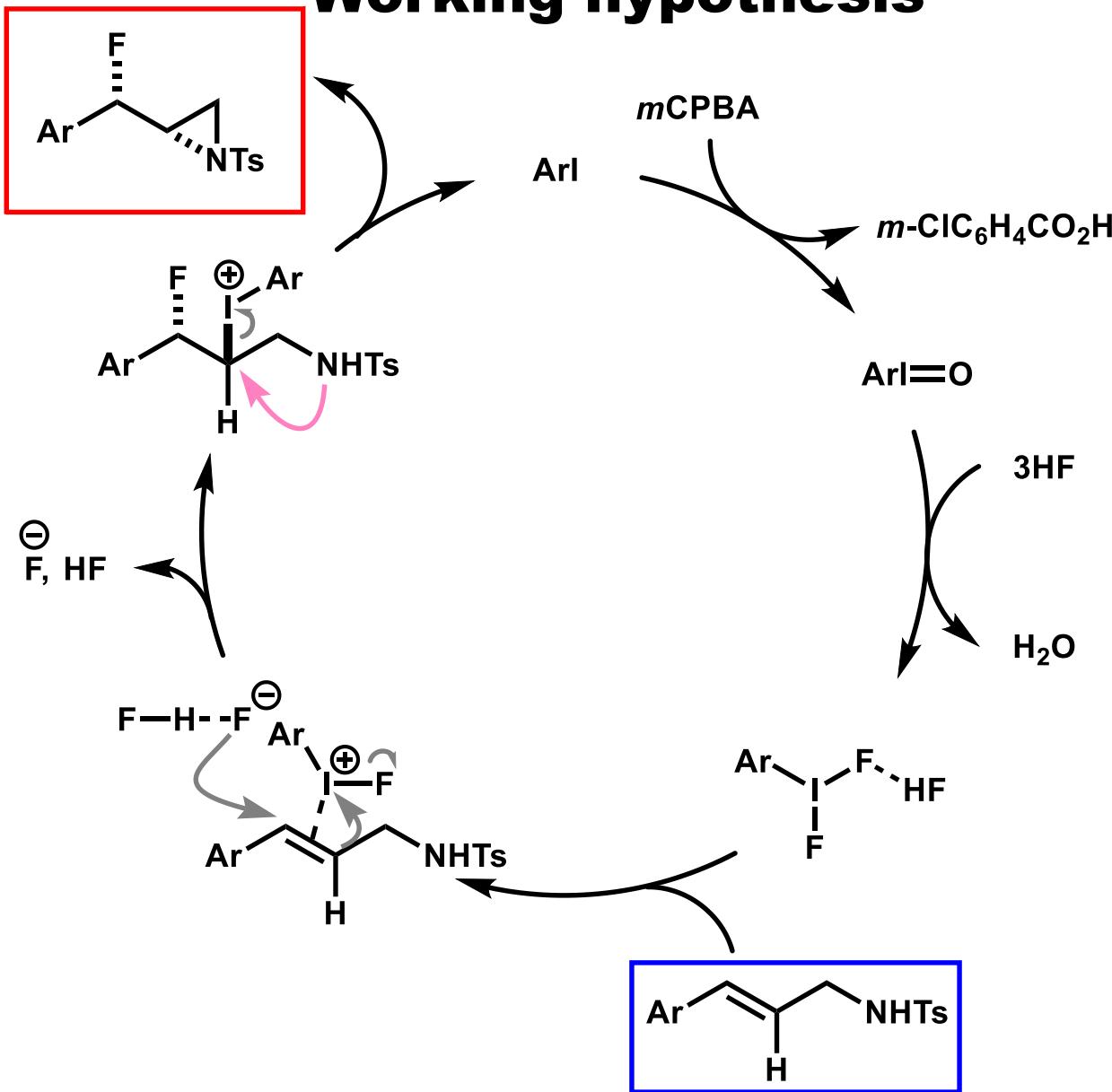
Communication
pubs.acs.org/JACS

Catalytic Diastereo- and Enantioselective Fluoroamination of Alkenes

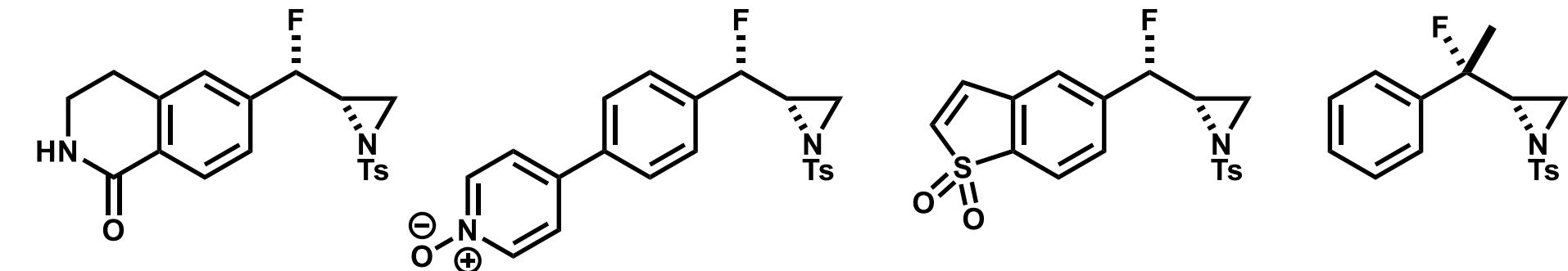
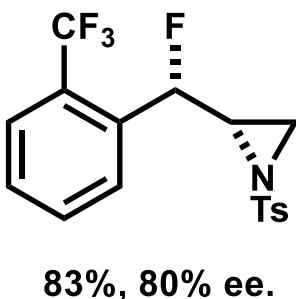
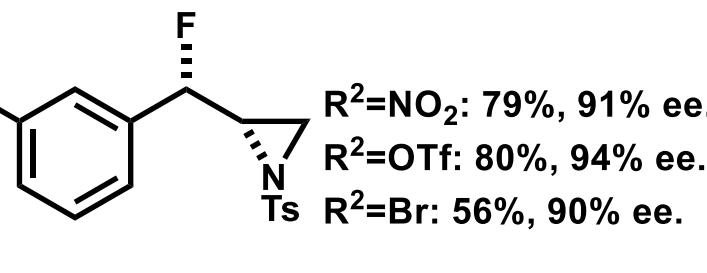
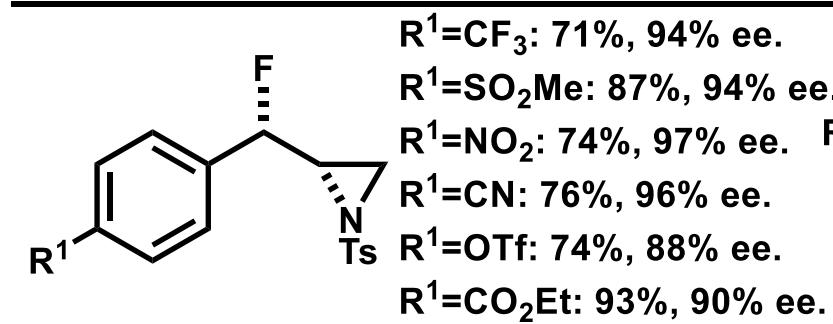
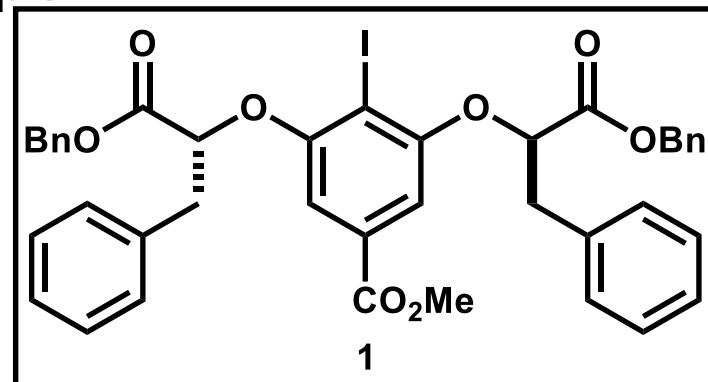
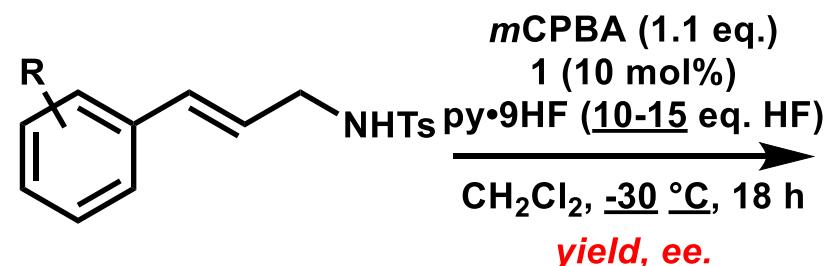
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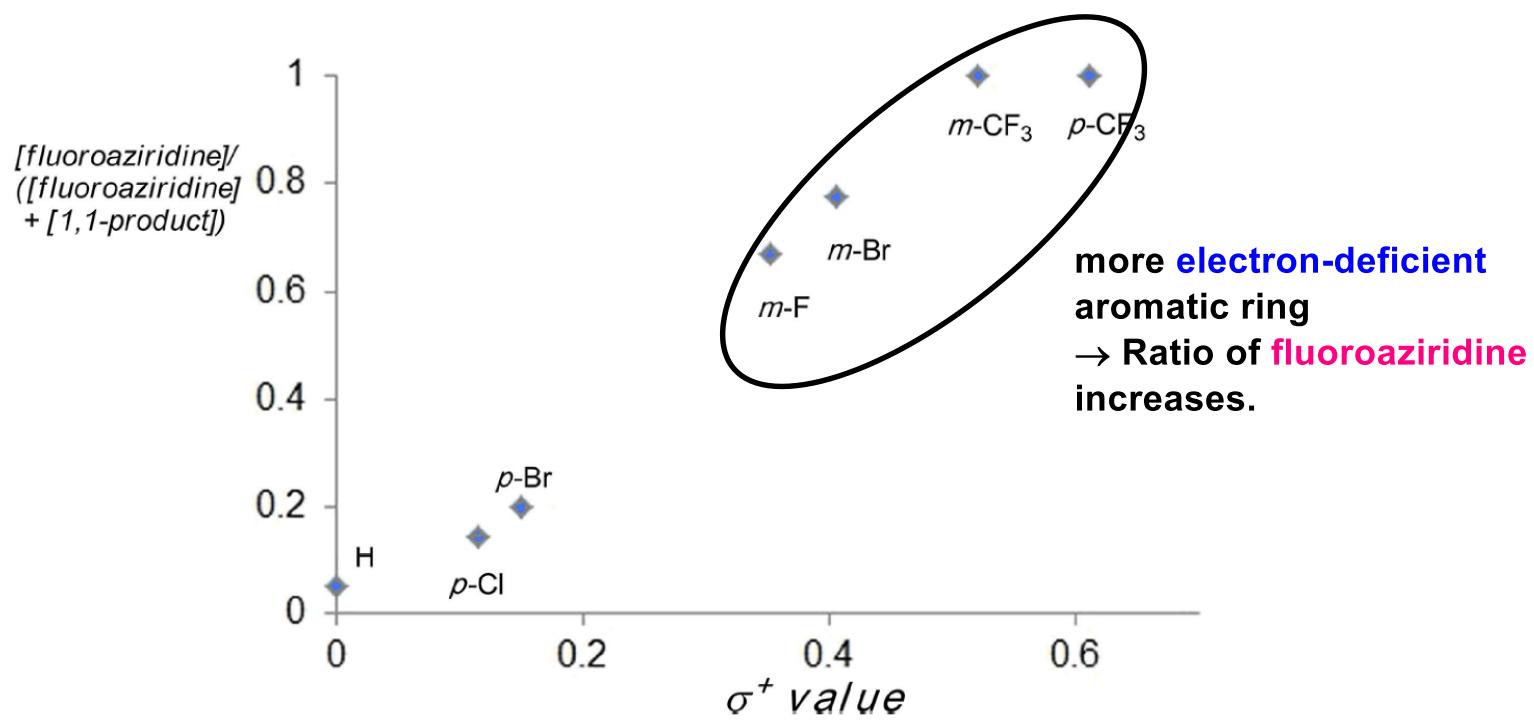
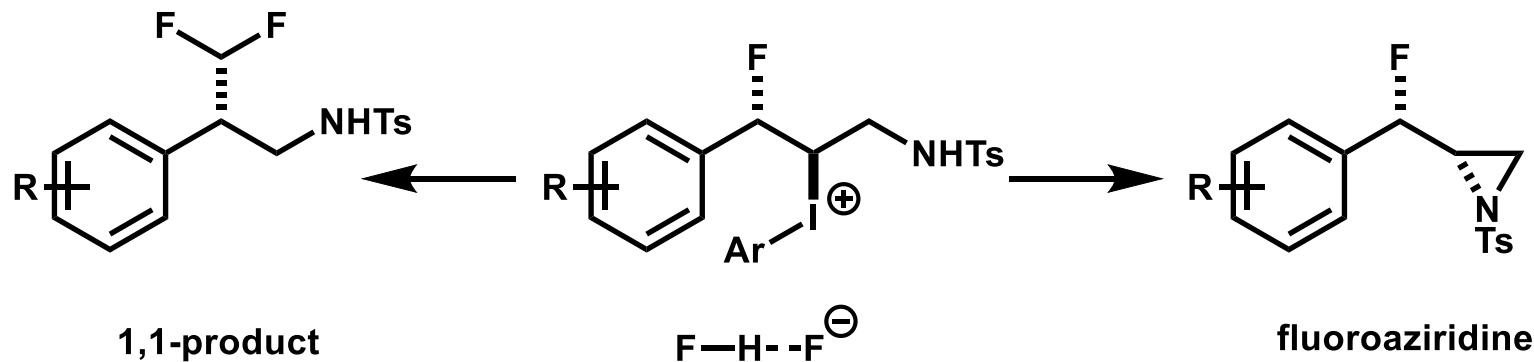
Working hypothesis



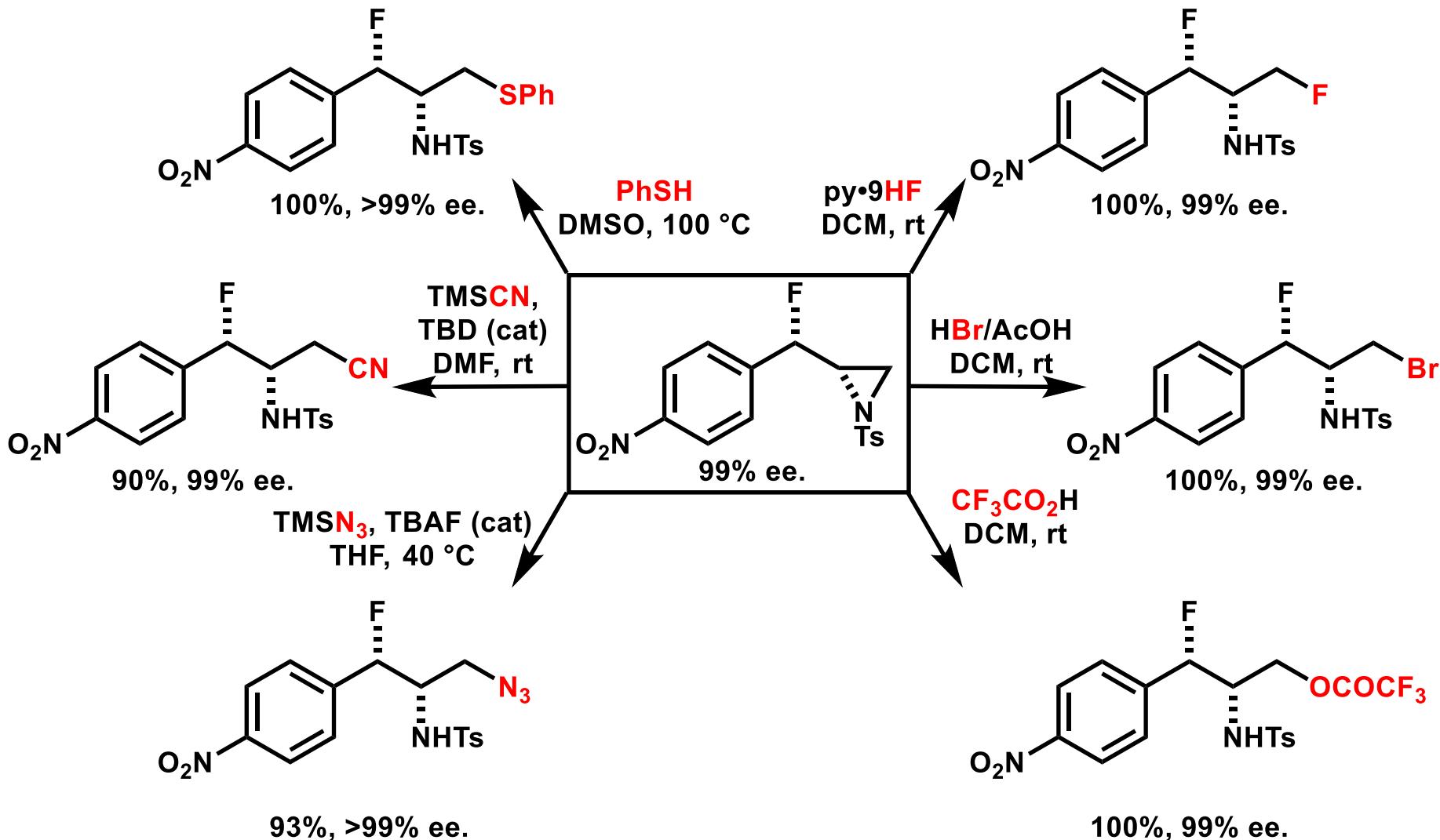
Substrate scope



Competition between 1,1-product and fluoroaziridine



Reactions of fluoroaziridine

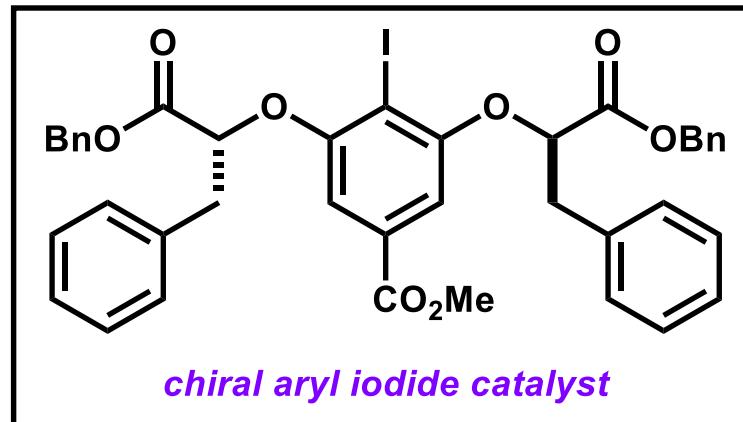
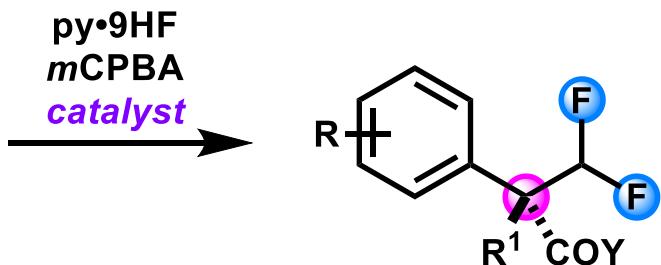
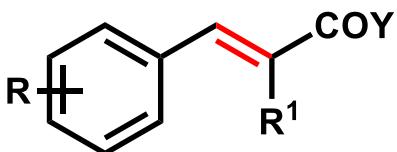


Summary

Catalytic, enantioselective fluorination of alkene by Jacobsen's group

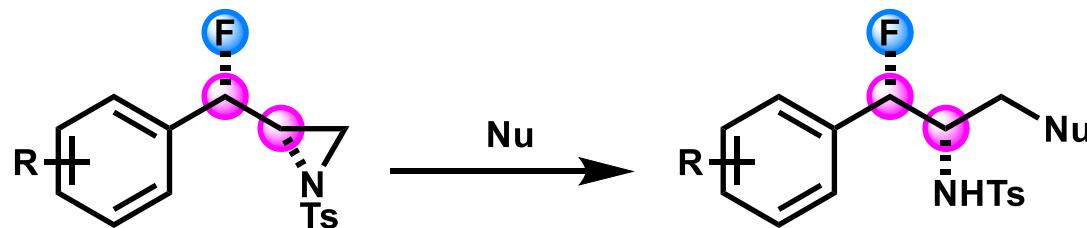
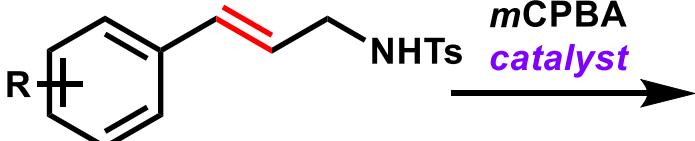
→ py•9HF, *m*CPBA, and chiral aryl iodide catalyst were used.

Difluoromethylation



chiral aryl iodide catalyst

Fluoroamination



Appendix

Parameters of C-X bond/X atom

X	BDE (kcal/mol) CH ₃ -X	Bond length (Å) C-X	Dipole moment (Debye unit), CH ₃ X	Electronegativity (Pauling scale)
F	110	1.39	1.82	4.0
Cl	85	1.78	1.94	3.0
Br	71	1.93	1.97	2.8
I	57	2.14	1.64	2.5
H	99	1.09	0	2.2

Harper, D. B.; O' Hagan, D. *Nat. Prod. Rep.* **1994**, 11, 123.

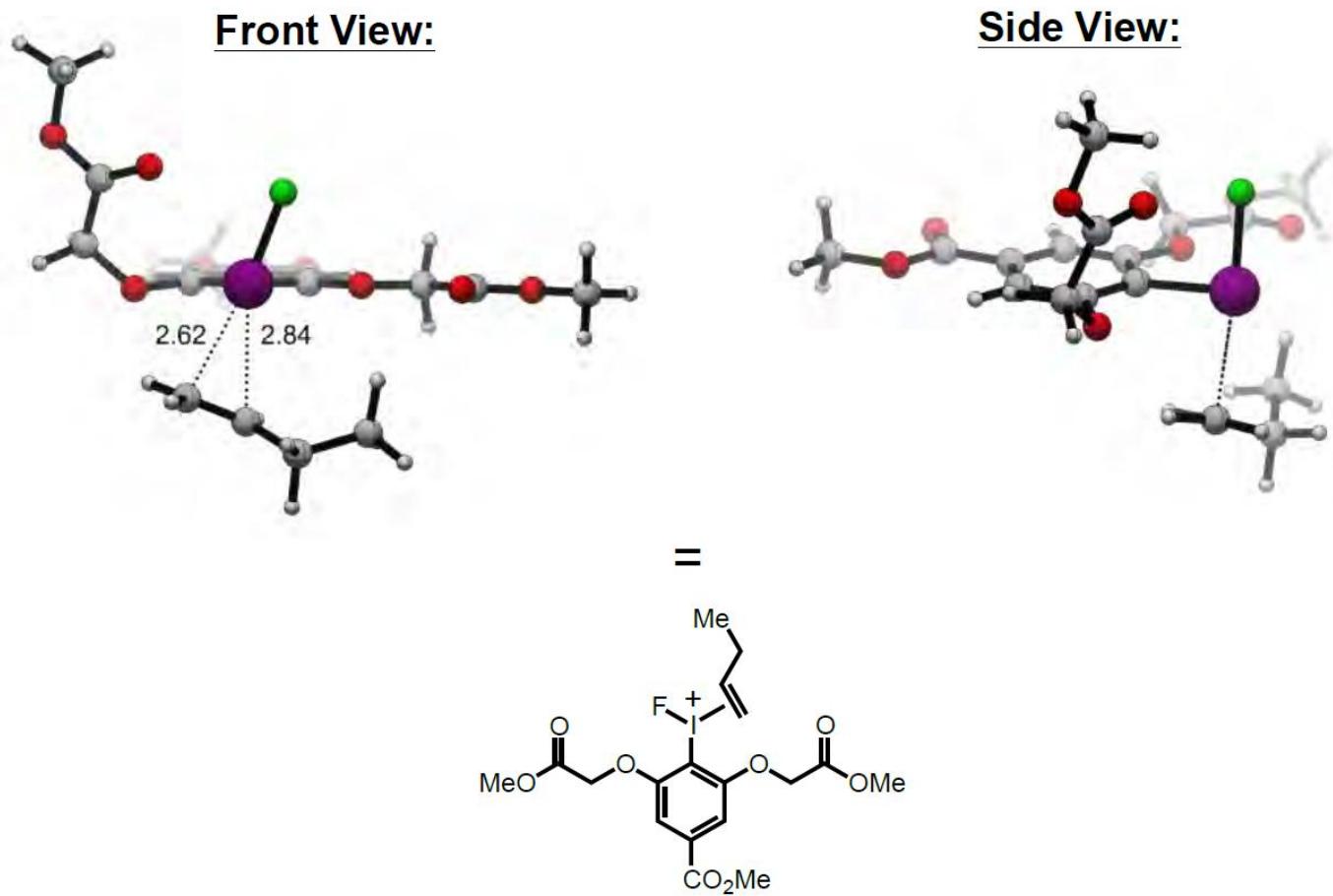
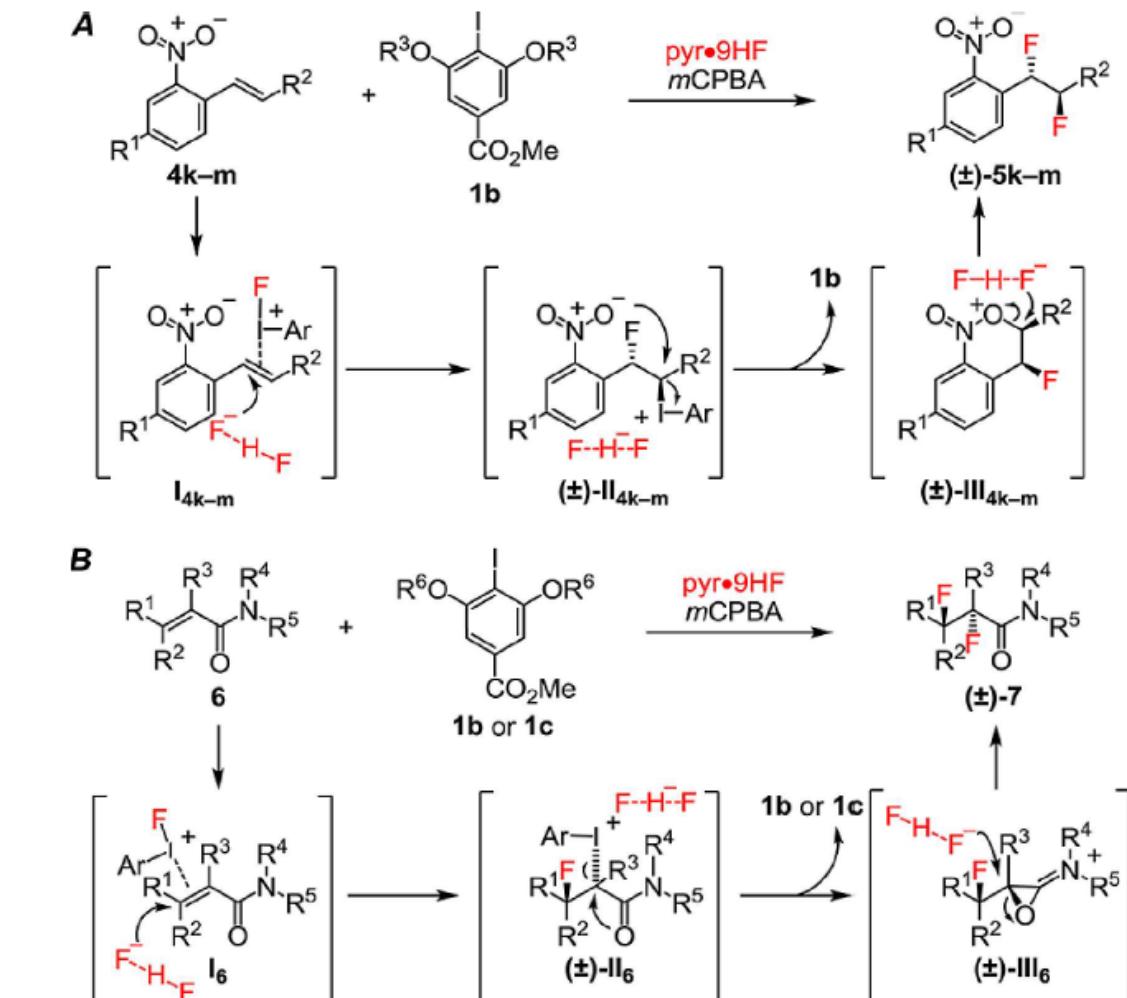


Figure S1: Computed binding mode of butene to aryl iodonium derived from catalyst **1b**. Structures calculated at the M06-2X/6-31+G(d,p)[SDD, for I] level of theory in DCM.

Scheme 3. Anti Difluorination via Proposed Anchimeric Assistance



Interpretation for the result of Eyring analysis (1)

$$k = \frac{k_B T}{h} \exp\left(-\frac{\Delta H^\ddagger}{RT} + \frac{\Delta S^\ddagger}{R}\right) \quad (1)$$

$$\ln \frac{k_{major}}{T} = -\frac{\Delta H^\ddagger}{RT} + \frac{\Delta S^\ddagger}{R} + \ln \frac{k_B}{h} \quad (2)$$

$$\ln \frac{k_{minor}}{T} = -\frac{\Delta H^\ddagger}{RT} + \frac{\Delta S^\ddagger}{R} + \ln \frac{k_B}{h} \quad (3)$$

$$(2) - (3)$$

$$\ln \frac{k_{major}}{k_{minor}} = -\frac{\Delta \Delta H^\ddagger}{RT} + \frac{\Delta \Delta S^\ddagger}{R} \quad (4)$$

$$\ln(e.r.) = -\frac{\Delta \Delta H^\ddagger}{RT} + \frac{\Delta \Delta S^\ddagger}{R} \quad (5)$$

k: second-order rate constant

k_B : Boltzmann's constant

h: Planck's constant ; **T:** absolute temp.

R: gas constant

$\Delta \Delta H^\ddagger$: enthalpy of activation

$\Delta \Delta S^\ddagger$: entropy of activation

(1): Eyring equation

When **k** of major enantiomer (k_{major}) and minor enantiomer (k_{minor}) follow (1), (2) and (3) can be derived.

Enantiomer ratio (e.r.) is expressed as k_{major} / k_{minor} , so (5) can be derived.

→ $\ln(e.r.)$ is plotted vs. $1/T$, $\Delta \Delta H^\ddagger$ is obtained from the slope and $\Delta \Delta S^\ddagger$ from the intercept.