

Methods for Asymmetric Monofluorination

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May 21st, 2019



Presentation Overview

Introduction

Electrophilic Fluorination

**Nucleophilic Fluorination/Pre-
Fluorinated Elaboration**

Concluding Remarks

Elemental Abundances in Earth's Crust

Rank	Element	Abundance (mg/kg)
1	Oxygen	461000
2	Silicon	282000
10	Hydrogen	1400
11	Phosphorus	1050
13	Fluorine	585
16	Sulfur	350
17	Carbon	200
19	Chlorine	145
34	Nitrogen	19
50	Bromine	2.4
63	Iodine	0.45

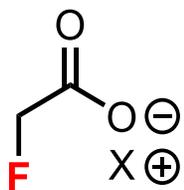
Handbook of Chemistry and Physics 99th Edition

Key Points

- Fluorine is more abundant than many life-forming elements.
- Approximately 5000 natural products containing halogens.
- In 2014, 182 naturally occurring organo-iodide compounds were known.

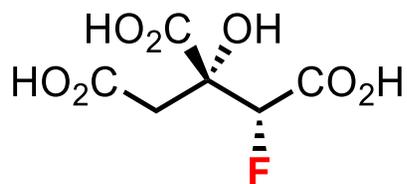
Wang, L.; Zhou, X.; Fredimoses, M.; Liao, S.; Liu, Y. *RSC Adv.* **2014**, *4*, 57350.

Known Fluorine-Containing Natural Products



Fluoroacetate

D. cymosum; Plant



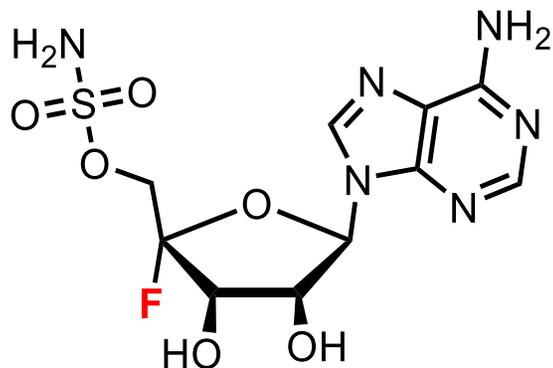
Fluorocitrate

Medicago sativa; Plant
Agropyran cristatum; Plant



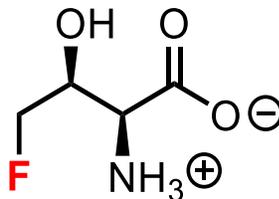
Fluorooleic acid

D. toxicarium; Seeds



Nucleocidin

Streptomyces calvus; Organism



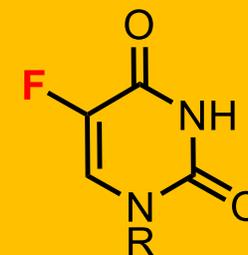
4-Fluorothreonine

S. cattleya; Organism

Putative



Fluoroacetone

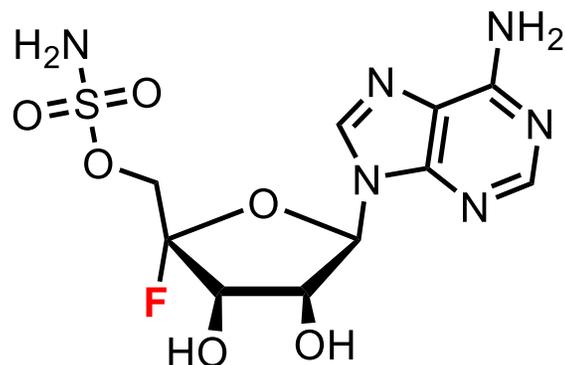


5-Fluorouracils

*Isolation sources are not exhaustive.

O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* 1999, 100, 127-133.

Known Fluorine-Containing Natural Products



Nucleocidin

Streptomyces calvus; Organism

According to Harper and O'Hagan: Recent attempts in several laboratories have failed to reisolate this metabolite from cultures of *S. calvus* grown from freeze dried organisms obtained from several culture collections. This has thwarted attempts to elucidate the mechanism by which fluorination occurs in the bacterium. The gene encoding nucleocidin biosynthesis, or at least as essential part of it, appears to have been lost. Such genetic impairment of an organism can sometimes occur if a metabolic trait is plasmid-encoded due to loss of the plasmid during the freeze drying process used in preservation of micro-organisms in culture collections. Hence unless the native organism is reisolated from soil this fascinating metabolite can probably be classed as extinct!

Reasons for Absence of Fluorometabolites

1. Abundances



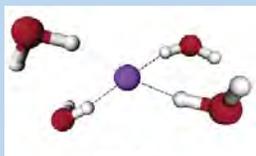
- Fluorite CaF_2 , Fluorapatite $\text{Ca}_5(\text{PO}_4)_3\text{F}$, and Cryolite Na_3AlF_6 have low water solubilities.
- Ocean abundances: Cl^- (20,000 ppm); Br^- (70 ppm); F^- (1.3 ppm); I^- (0.02 ppm).

2. Oxidation Potentials



- $\text{F}^- = -2.87 \text{ eV}$; $\text{Cl}^- = -1.36 \text{ eV}$; $\text{Br}^- = -1.07 \text{ eV}$; $\text{I}^- = -0.54 \text{ eV}$; $\text{H}_2\text{O}_2 = -1.8 \text{ eV}$.
- Haloperoxidases cannot oxidize F^- to the necessary hypohalous intermediates.

3. ΔH Hydration

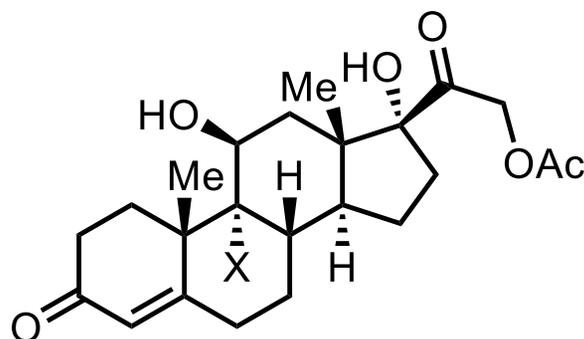


- Highest heat of hydration ($\Delta\text{H}_{\text{Hyd}} \text{F} = 117 \text{ kcal/mol}$).
- Therefore, fluorine is poorly nucleophilic in aqueous systems.
- Enzymes must evolve desolvation protocols.

Consequences:

- Fluorine is essentially xenobiotic.
- Xenobiotic nature and known toxicity led to fluorine being largely underexplored for many years.

Discovery of Fluorine's Bioactivity



Compound	Activity in Rat liver Glycogen Test (Cortisone Acetate=1)
9 α -Fluoro-hydrocortisone acetate	10.7 \pm 2.3
9 α -Chloro-17 α -hydroxycorticosterone acetate	4.0 \pm 0.6
9 α -Chlorocortisone acetate	3.5 \pm 0.6
9 α -Bromo-17 α -hydroxycorticosterone acetate	0.28 \pm 0.04
9 α -Bromocortisone acetate	0.54 \pm 0.08
9 α -Iodo-17 α -hydroxycorticosterone acetate	\sim 0.1

Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1953**, *75*, 2273.

Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 1455.

Influences of Fluorine

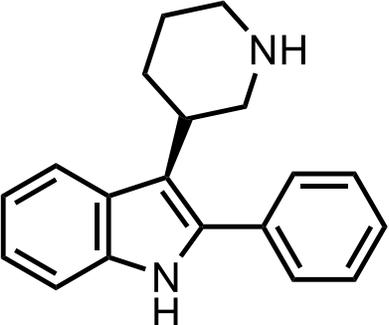
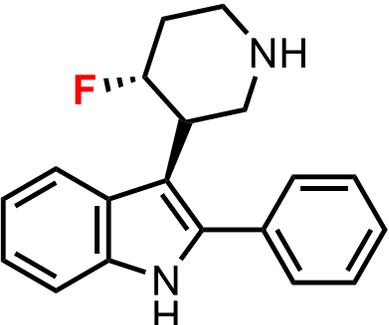
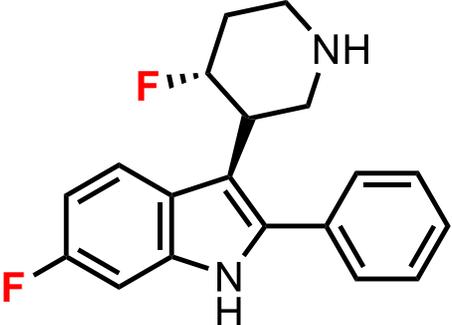
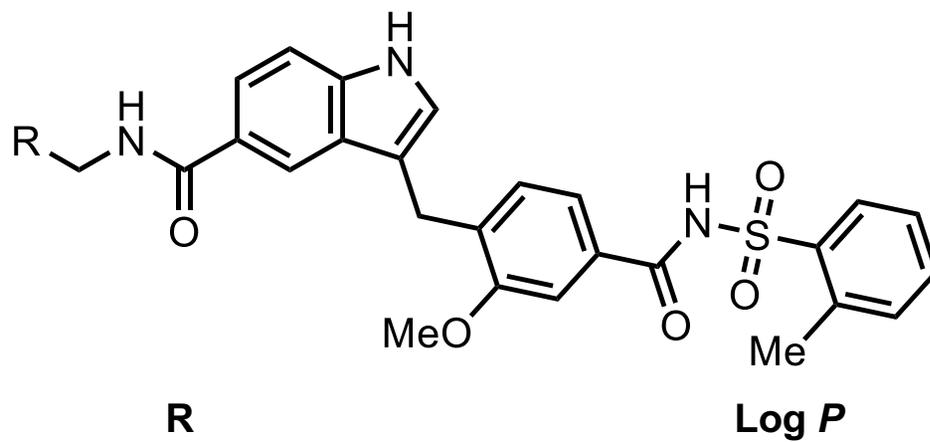
Indole	pK _a	F (%)
	10.4	Poor
	8.5	18
	--	80

Table 1: Modulation of pK_a and bioavailability for 3-piperidinylindole antipsychotics

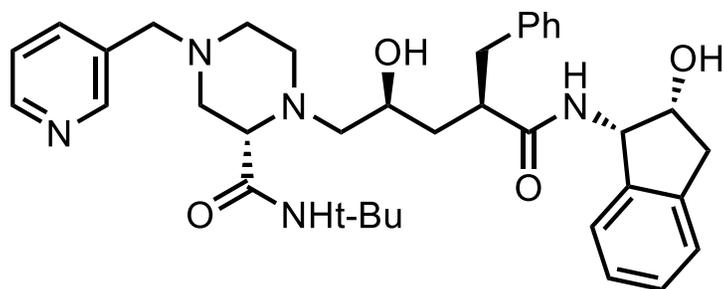


R	Log P
CH ₃ CH ₂ CH(CH ₃)	5.85
CF ₃ CH ₂ CH(CH ₃)	6.18
(CH ₃ CH ₂) ₂ CHCH ₂	6.29
CF ₃ CH ₂ CH(CH ₃ CH ₂)CH ₂	6.45
CF ₃ CH(CH ₃)CH ₂ CH ₂	6.30
CF ₃ CH(CH ₃)CH ₂	5.89

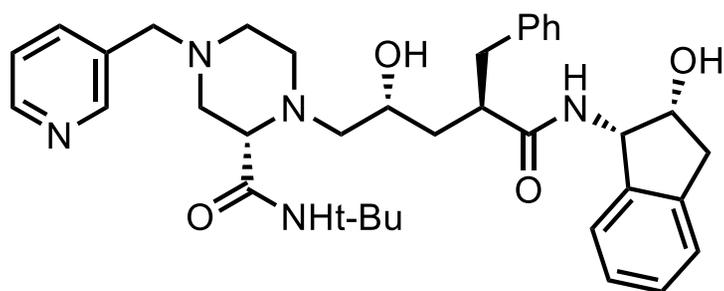
Table 2: Effect of fluorination on lipophilicity Log P

Influences of Fluorine

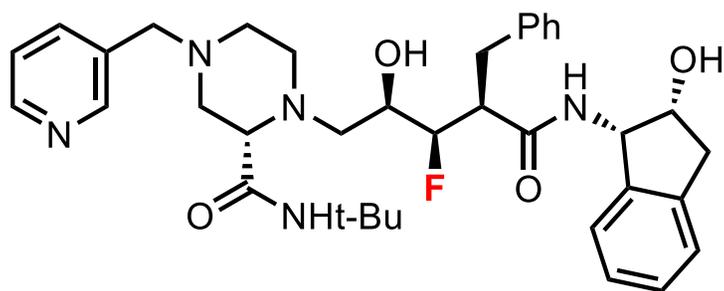
Conformational Effects of Fluorine



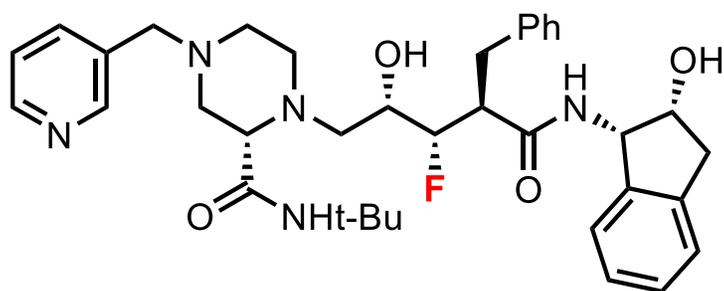
Indinavir $K_i=1.9$ nM
 $\text{Log } P= 3.03$



C₁₇-*epi*-Indinavir
 $K_i=160$ nM
 $\text{Log } P= 3.02$

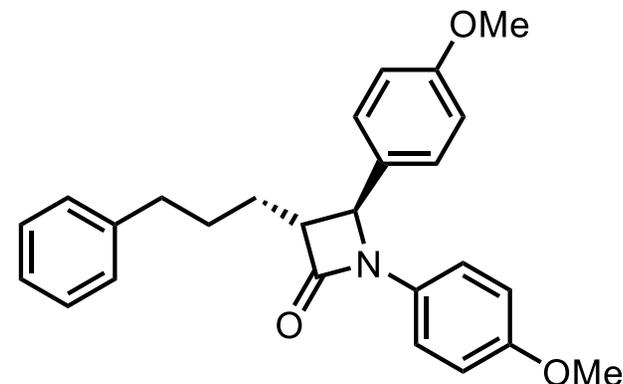


syn,syn fluorinated
 $K_i=160$ nM
 $\text{Log } P= 3.23$

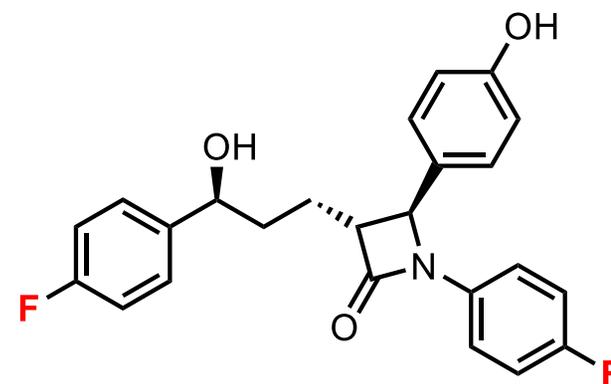


syn,anti fluorinated
 $K_i=20$ nM
 $\text{Log } P= 3.12$

Improved Metabolic Stability by Functionalization



SCH 48461
 ED_{50} 2.2 mg/Kg/day

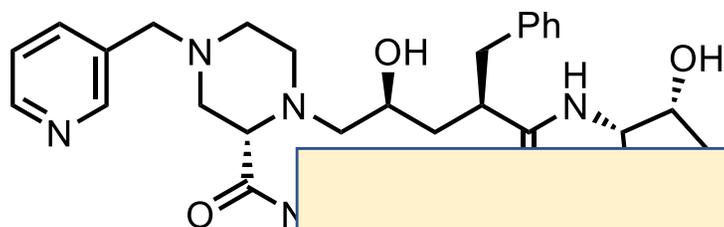


Ezetimib
 ED_{50} 0.04 mg/Kg/day

Influences of Fluorine

Conformational Effects of Fluorine

Improved Metabolic Stability by Functionalization



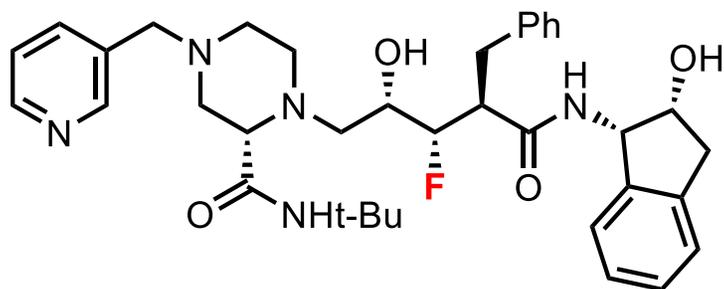
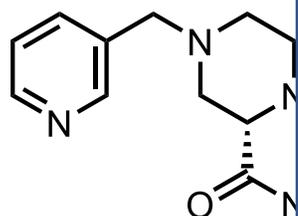
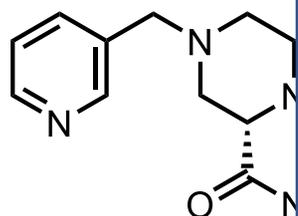
Indinavir $K_i=1.9$ nM

Take-Away Points:

- Fluorine can drastically alter pharmacokinetic properties of drug candidates.
- Survey found that 35% of drug candidates currently in phase II-III clinical trials contain fluorine.
- Fluorine is found in over 50% of the most-prescribed multi-billion dollar pharmaceuticals (3/5 top selling).
- Predicting effects of fluorine is difficult and thus SAR studies are common (fluorine scan).
- Less than 1% of pharmaceuticals containing fluorine in development or on the market contain a C-F stereogenic center.

Toste, F. D. Et al. *Chem. Rev.* **2018**, *118*, 3887.

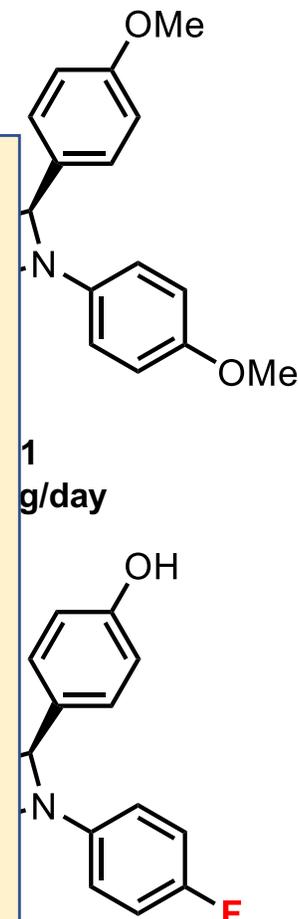
Fustero, S. Et. al. *Chem. Rev.* **2014**, *114*, 2432.



syn,anti fluorinated

$K_i=20$ nM

Log $P=3.12$

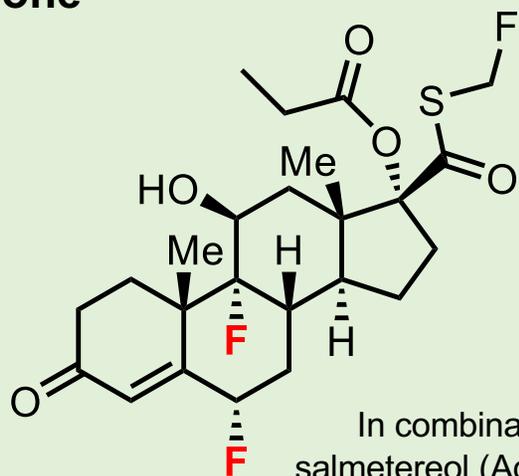


1 g/day

Ezetimib
ED₅₀ 0.04 mg/Kg/day

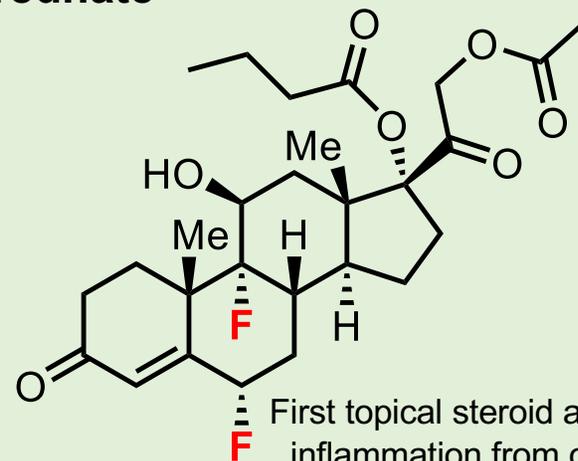
Stereogenic C-F Bearing Pharmaceuticals

Fluticasone



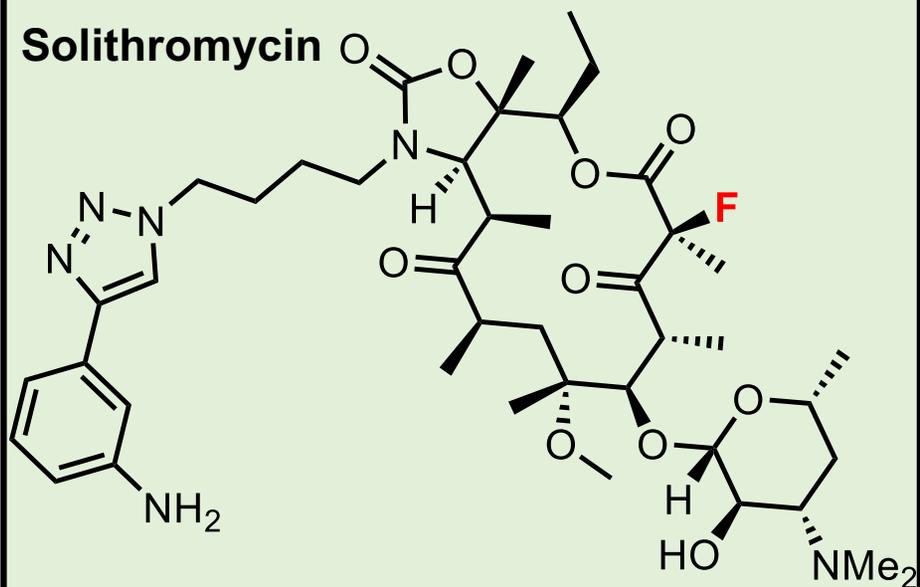
In combination with salmeterol (Advair Diskus) sales >\$5.0 billion

Difluprednate

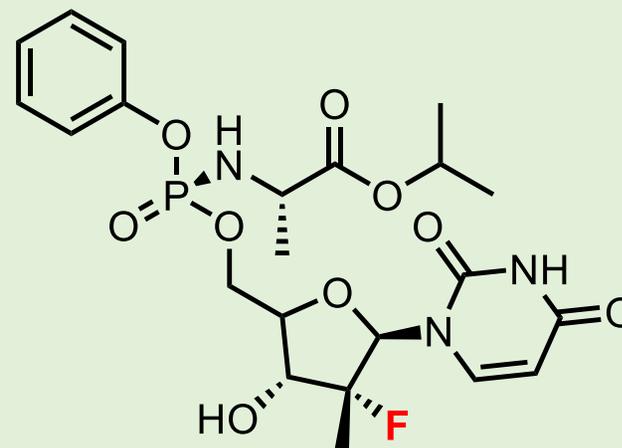


First topical steroid approved for inflammation from ophthalmic procedures.

Solithromycin



Sofosbuvir



*Representative examples, list not exhaustive.

Toste, F. D. Et al. *Chem. Rev.* **2018**, *118*, 3887.

Presentation Overview

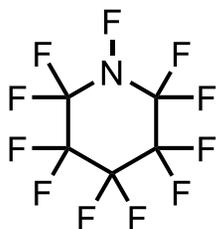
Introduction

Electrophilic Fluorination

**Nucleophilic Fluorination/Pre-
Fluorinated Elaboration**

Concluding Remarks

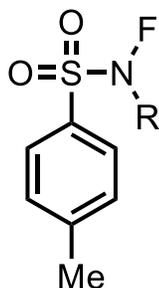
Select Electrophilic N-F Reagents



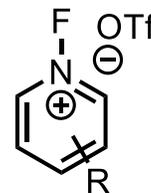
Banks
1964



Purrington
1983



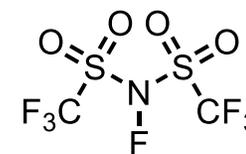
Barnette
1984



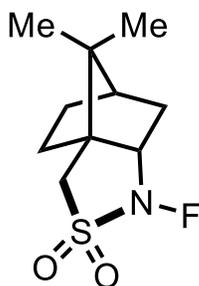
Umemoto
1986 -1991



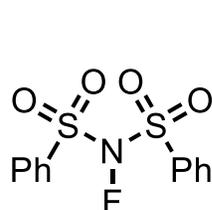
Banks
1986 -1991



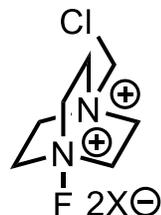
DesMarteau
1987



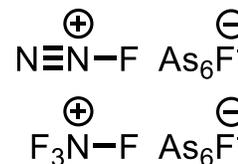
Differding/Lang
1988



Differding
1991



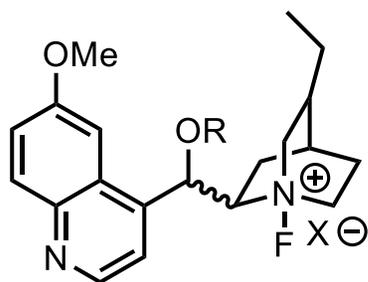
Banks
1992



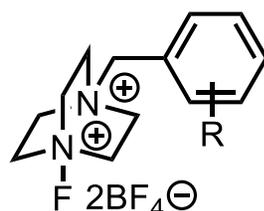
Olah, Prakash, Christie
1994



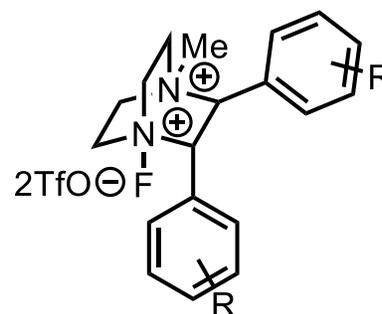
Shibata/Takeuchi
2000



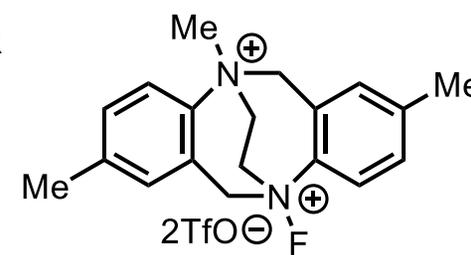
Shibata
2000



Toste
2013

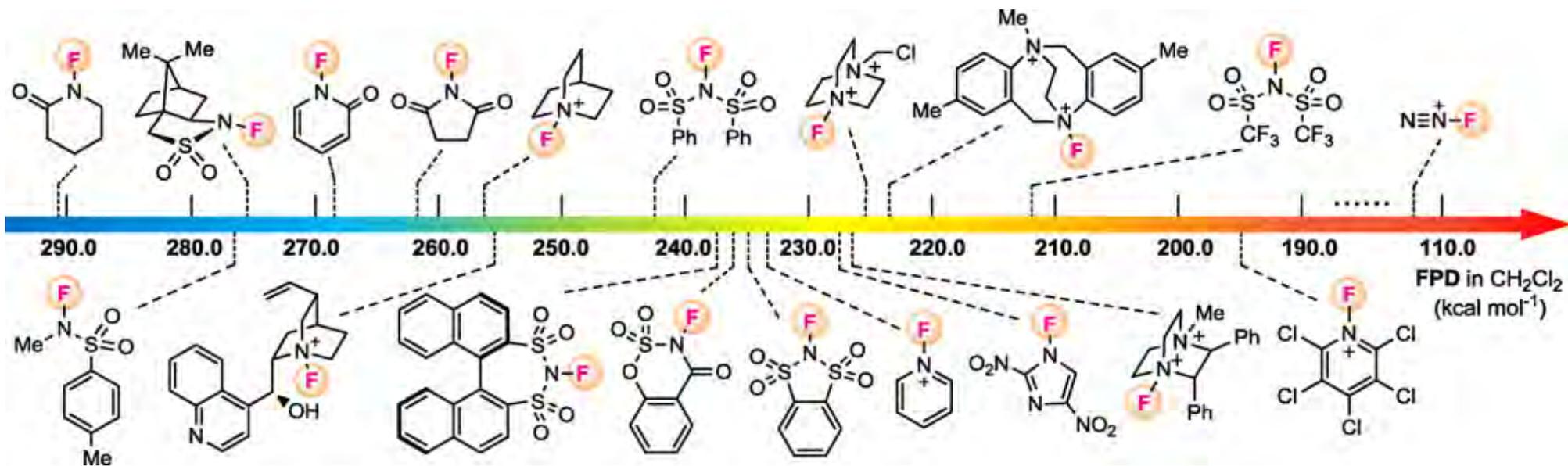


Gouverneur
2013



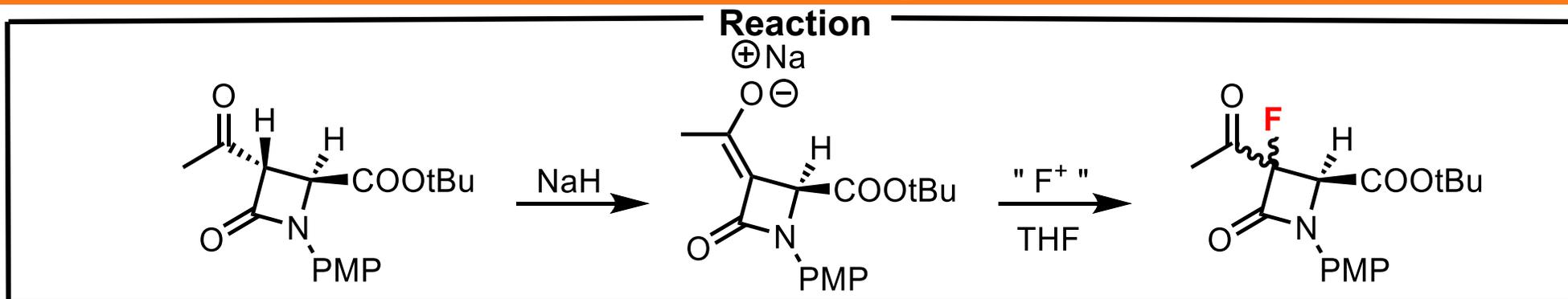
Gouverneur
2015

Select Electrophilic N-F Reagents

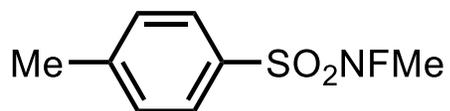
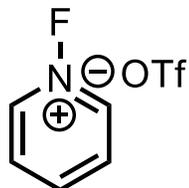
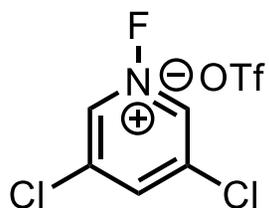


Fluorine Plus Detachment (FPD) values calculated for 130 electrophilic N-F reagents.

Diastereoselective Electrophilic Fluorination



Fluorinating Agent



Conditions

12h, -20°C
3 days, r.t.
12h, reflux

3 days, r.t.

12 h, r.t.
5h, r.t. toluene

1 h, 20°C

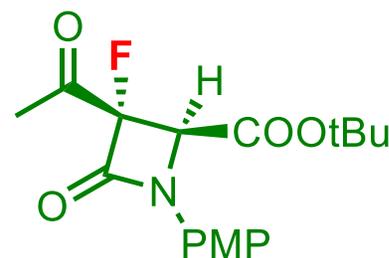
1 h, -15°C

Results

S.M.

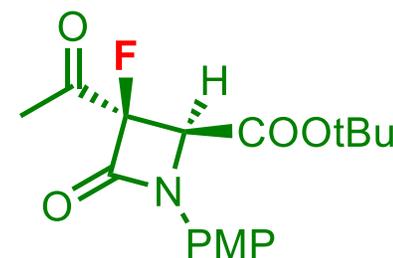
S.M./Degradation

Complex Mix.



85

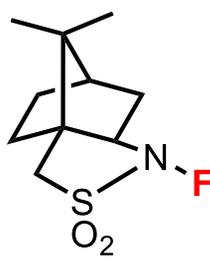
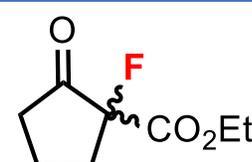
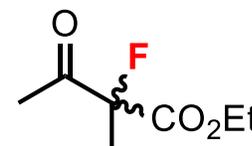
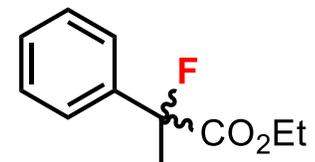
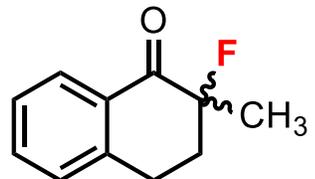
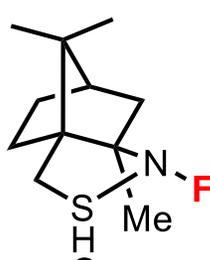
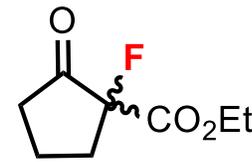
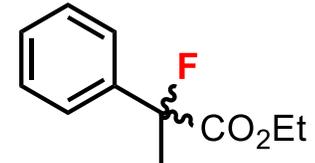
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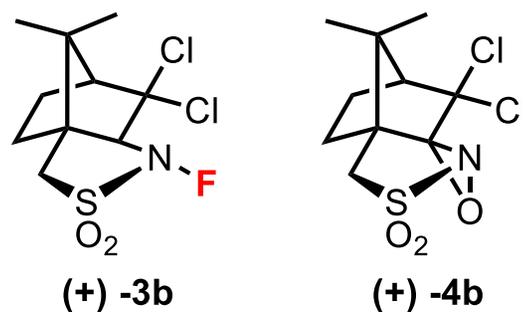
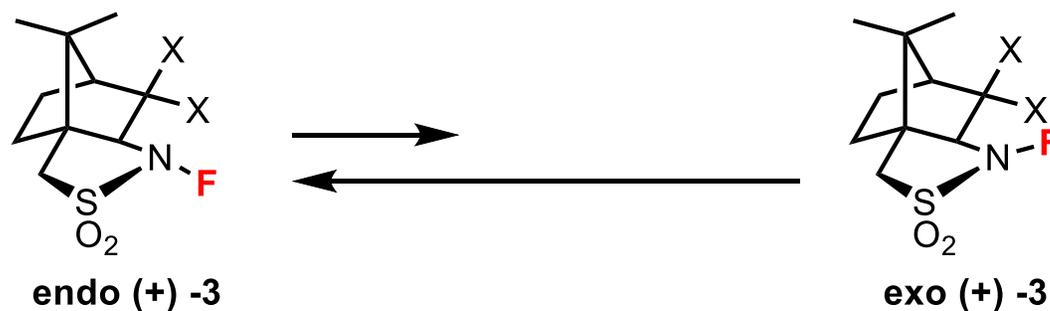
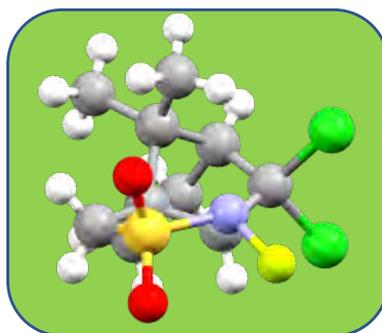
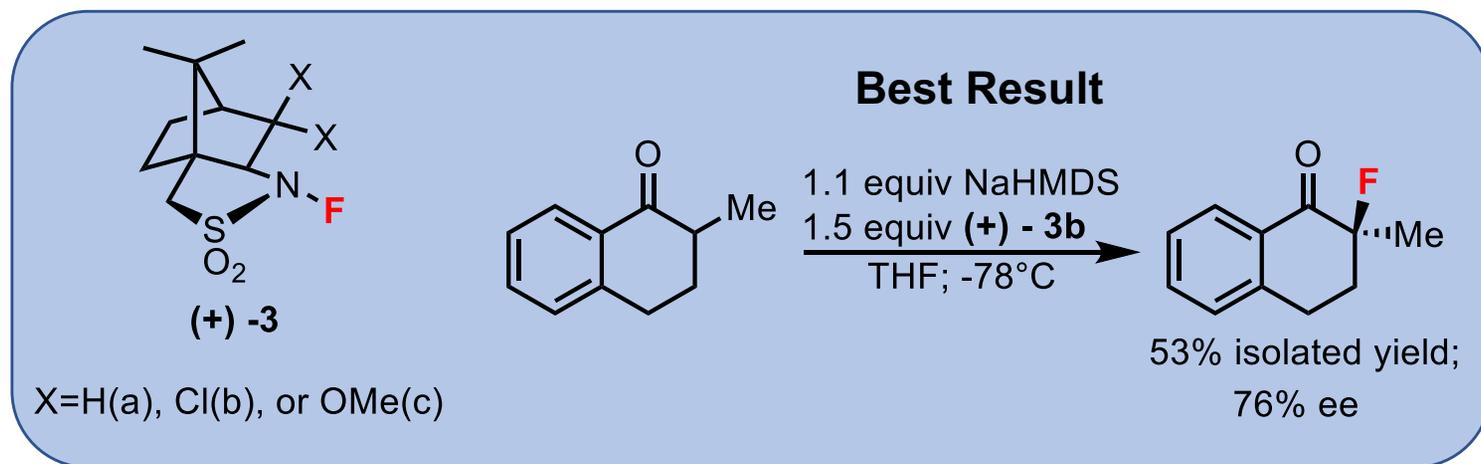
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First Report of Enantioselective Fluorination

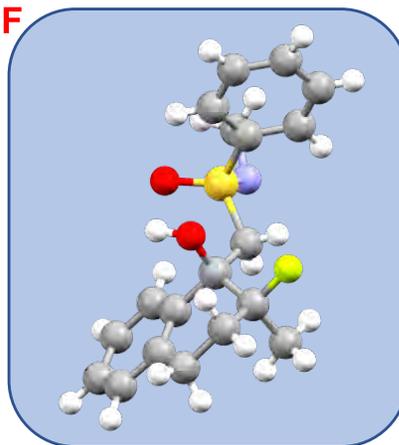
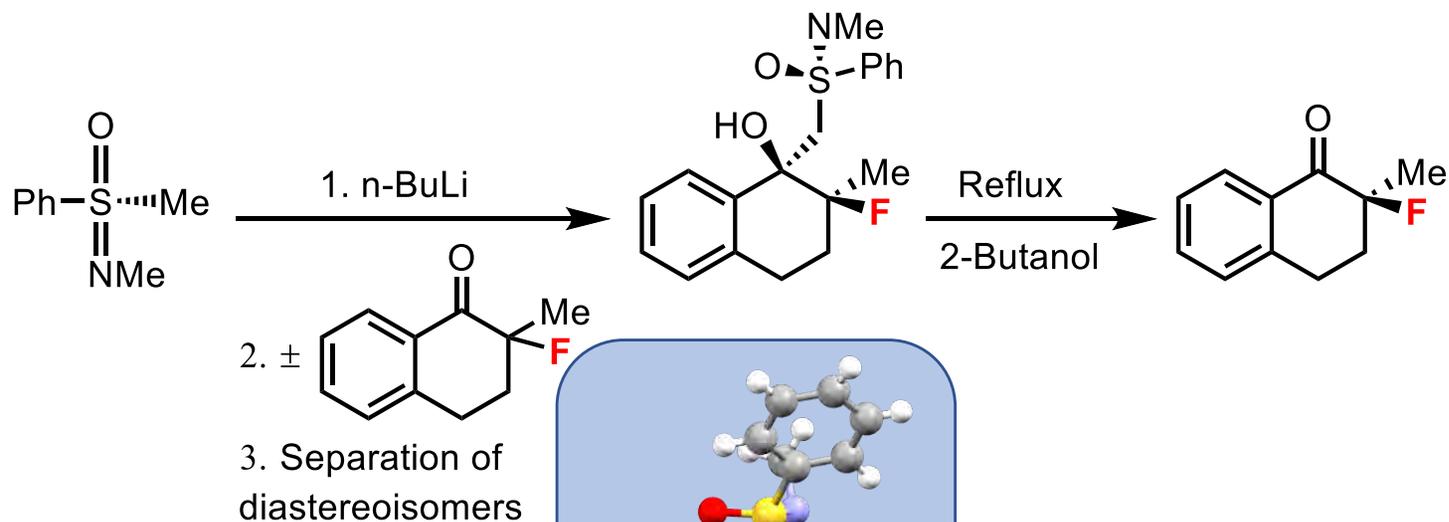
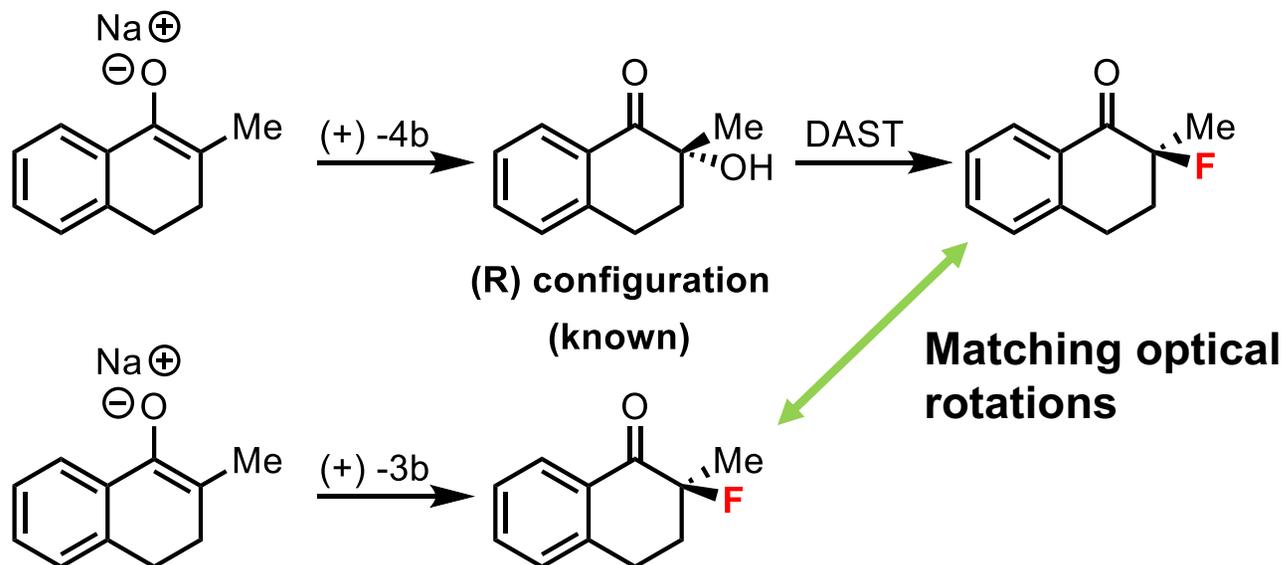
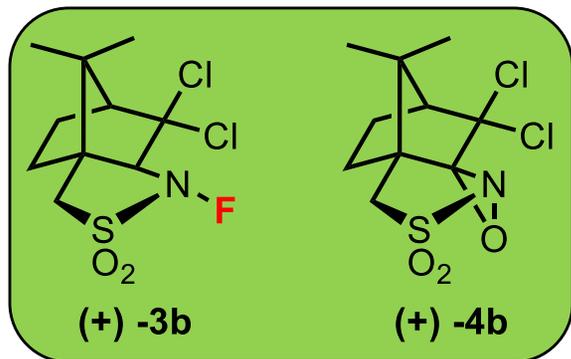
N-Fluoro Sultam	Product	Conditions	Results
 (-)-3		NaH; Et ₂ O; 0°C - r.t. 1.5 equiv (-)-3	63% yield; 70% ee
		LiH; Et ₂ O; 0°C 1.3 equiv (-)-3	31% yield; < 10% ee
		LDA; THF; -78°C - r.t. 1.2 equiv (-)-3	27% yield; 35% ee
		LDA; THF; -78°C - r.t. 1.3 equiv (-)-3	35% yield, < 5% ee
 (+)-5		KH; Tol./THF; 0°C - r.t. 1.3 equiv (+)-5	< 5% yield, < 10% ee
		LDA; THF; -78°C - r.t. 1.3 equiv (-)-3	34% yield, < 10% ee

3,3-Disubstituted N-Fluoro Camphorsultams



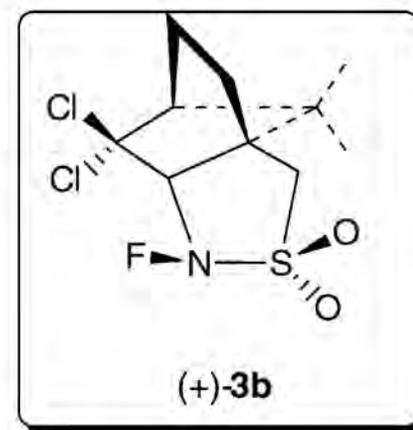
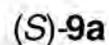
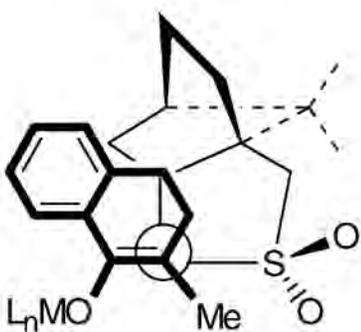
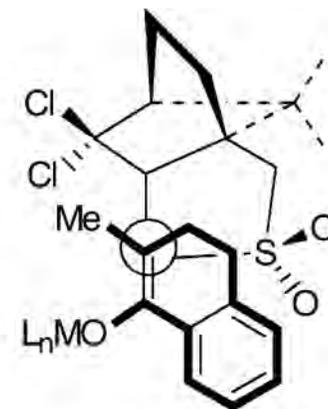
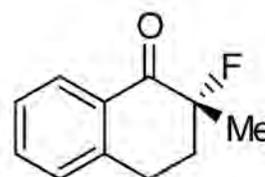
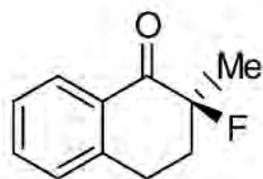
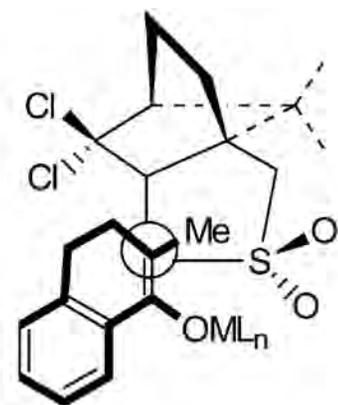
**Same
asymmetric
induction?**

3,3-Disubstituted N-Fluoro Camphorsultams

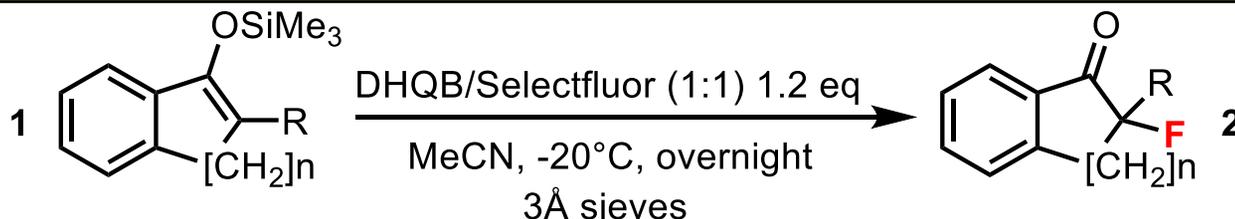
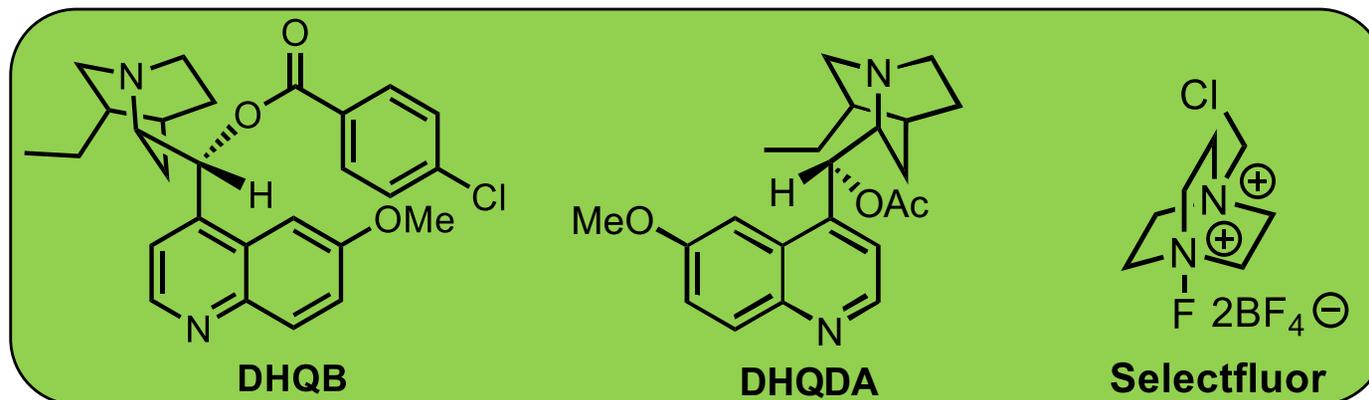


3,3-Disubstituted N-Fluoro Camphorsultams

Transition State Analysis



Cinchona Alkaloid-Derived N-F Reagents

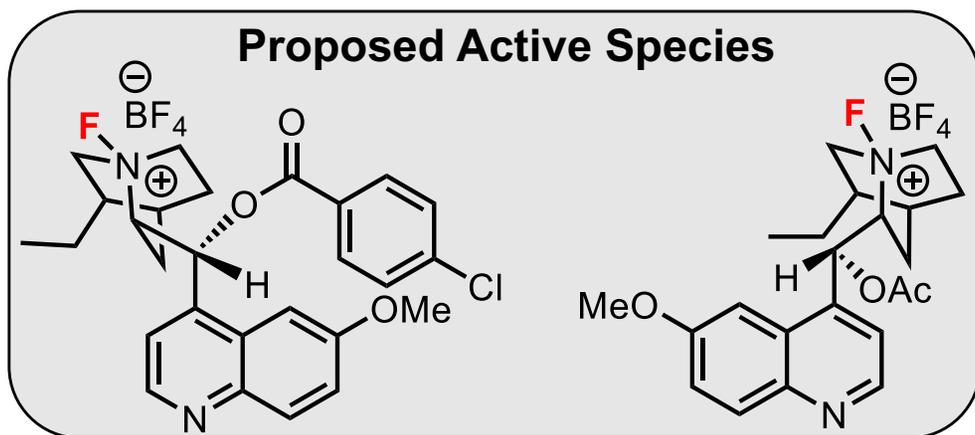
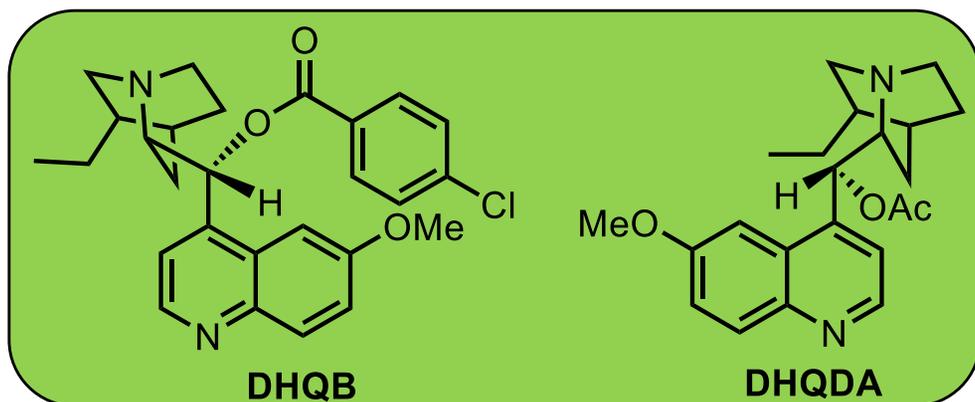


entry	1	<i>n</i>	R	2	yield %	ee (%)	Config.
1	1a	1	Bn	2a	99	89	<i>R</i>
2^a	1a	1	Bn	2a	86	91	<i>R</i>
3	1b	1	Me	2b	93	54	<i>R</i>
4	1c	1	Et	2c	99	73	<i>R</i>
5	1d	2	Me	2d	94	42	<i>R</i>
6^b	1e	2	Et	2e	71	67	<i>R</i>
7	1f	2	Bn	2f	95	71	<i>S</i>

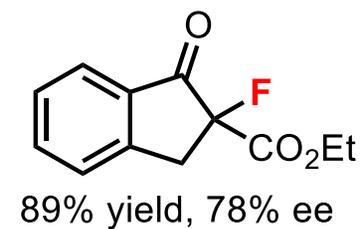
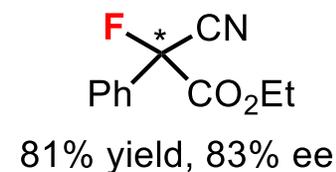
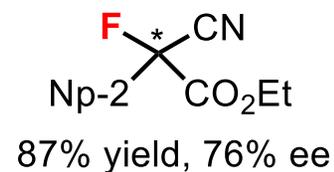
a: -80°C
 MeCN/CH₂Cl₂ (3:4)
 48 h

b: -50°C
 MeCN/CH₂Cl₂ (3:4)
 12 h

Application to Acyclic Esters



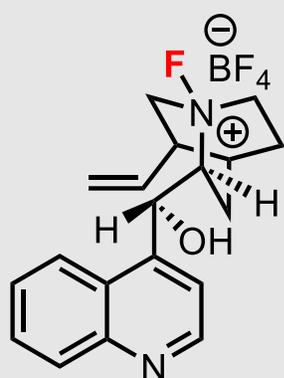
- Pre-stirring alkaloid and enolate followed by addition of Selectfluor yielded racemate



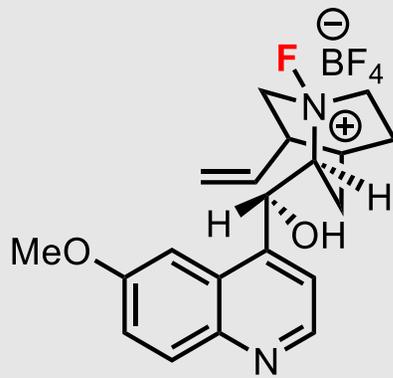
DHQDA/Selectfluor (1:1) 1.2 eq,
MeCN/CH₂Cl₂ (3:4); -80°C, 2 h, 3Å sieves

Cinchona Alkaloid-Derived N-F Reagents

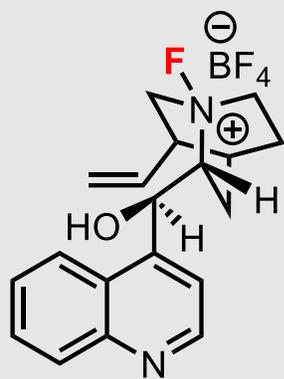
Proposed Active Species



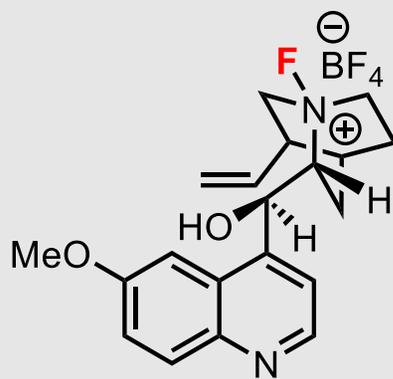
N-fluorocinchonium-BF₄
F-CN-BF₄



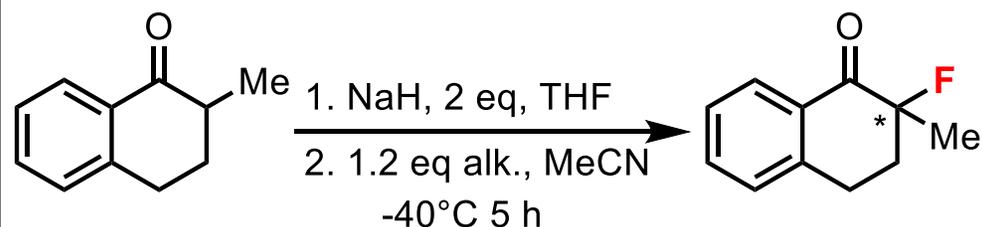
N-fluoroquinidinium-BF₄
F-QD-BF₄



N-fluorocinchonium-BF₄
F-CD-BF₄



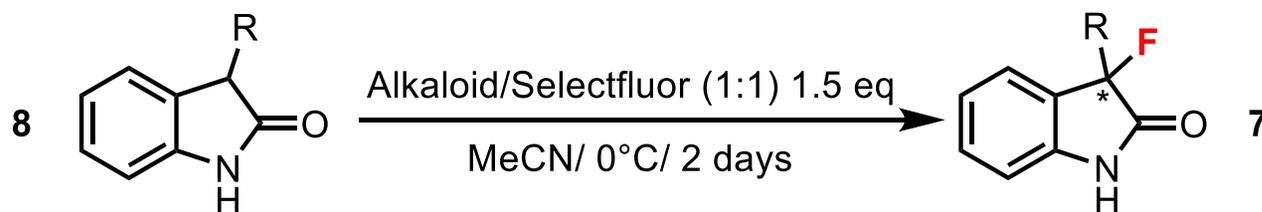
N-fluoroquinidinium-BF₄
F-QN-BF₄



entry	[N-F] ⁺ reagent	ee (%)	config	yield (%)
1	F-CD-BF ₄	50	S	98
2	F-CN-BF ₄	40	R	70
3	F-QD-BF ₄	27	R	87
4	F-QN-BF ₄	20	S	98

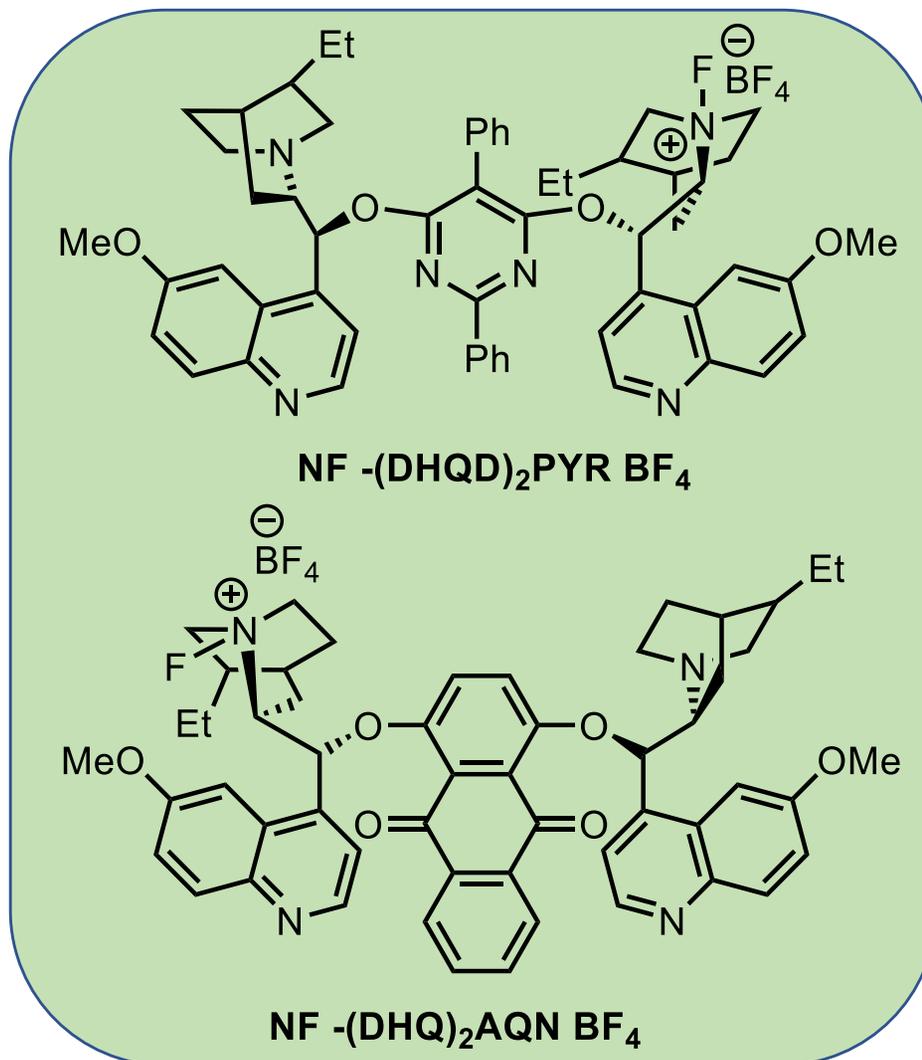
- 1:1 alkaloid:Selectfluor in MeCN; 20 min, recrystallized in acetone to yield white crystalline solids

Extension to Oxindoles

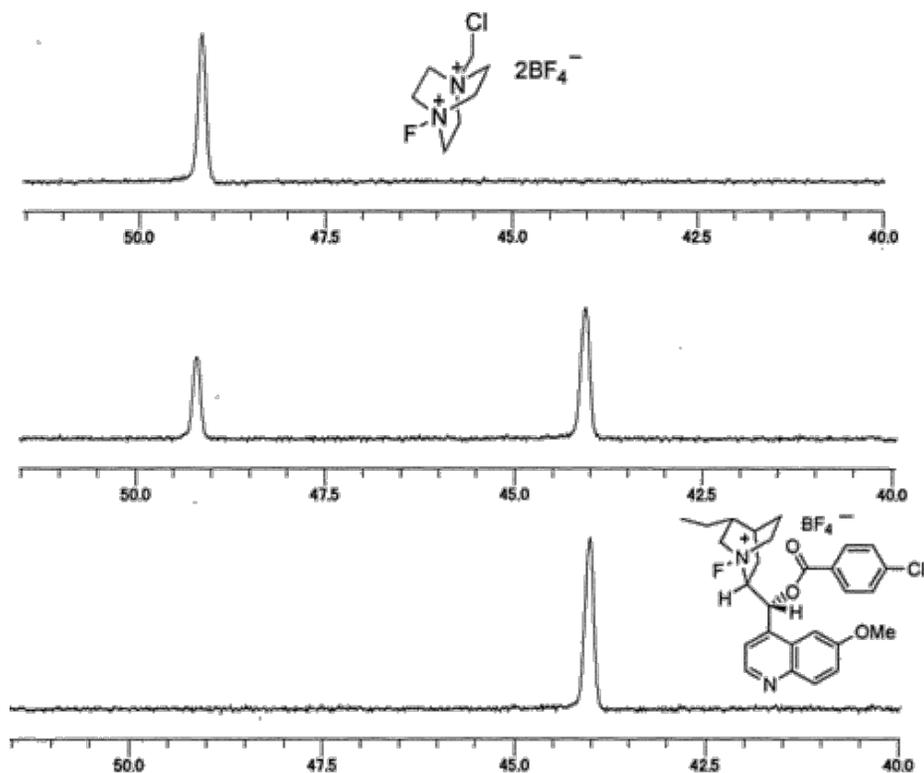


*No prior existing asymmetric preparations.

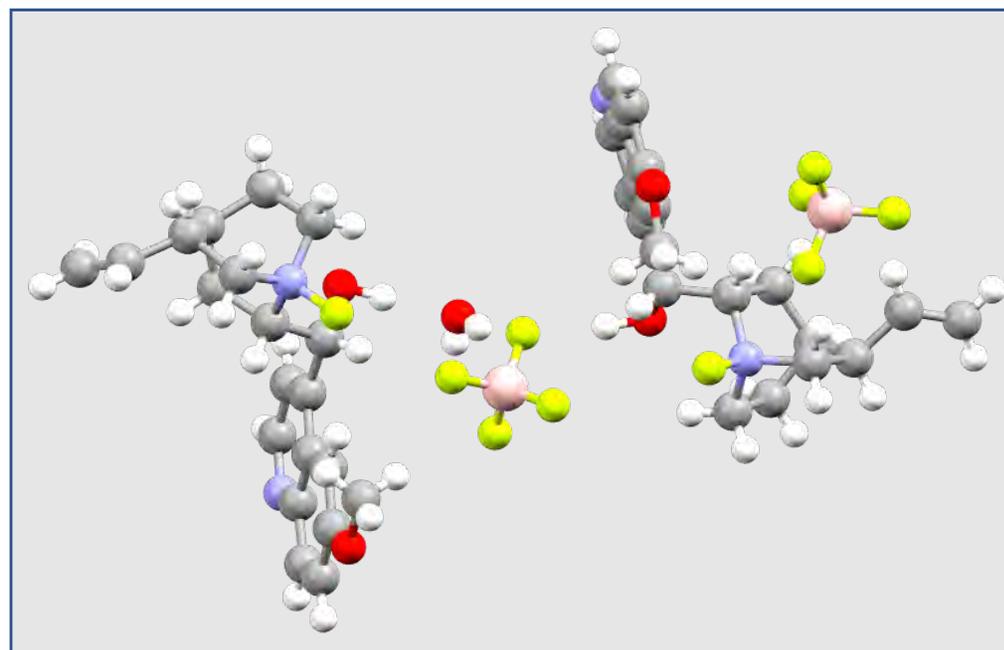
entry	8	R	7	alkaloid	yield (%)	ee (%)	major isomer
1	8a	Bn	7a	(DHQD) ₂ PYR	91	72	F
2	8a		7a	(DHQ) ₂ AQN	100	78	F
3	8b	<i>p</i> -MeOBn	7b	(DHQD) ₂ PYR	79	82	F
4	8c	Me	7c	(DHQD) ₂ PYR	94	67	S
5	8c		7c	(DHQ) ₂ AQN	56	52	S
6	8d	Et	7d	(DHQD) ₂ PYR	79	76	S
7	8d		7d	(DHQ) ₂ AQN	90	58	S
8	8e	<i>i</i> Pr	7e	(DHQ) ₂ PHAL	12	40	F
9	8f	COOEt	7f	(DHQD) ₂ PYR	93	37	S
10	8f		7f	(DHQ) ₂ AQN	91	23	S



Confirmation of Suspected Cinchona N-F Species

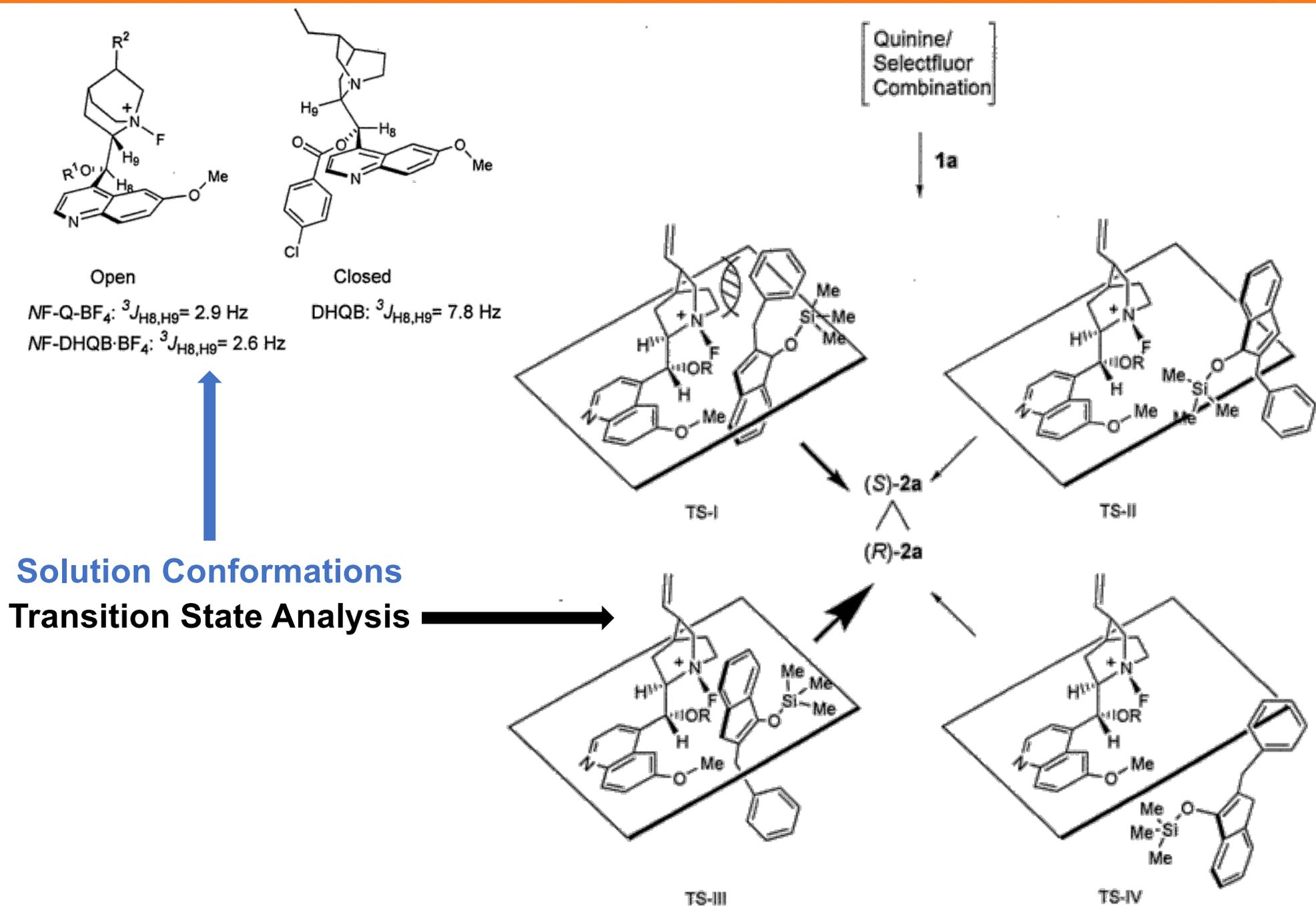


Fluorine transfer observed by ^{19}F NMR.



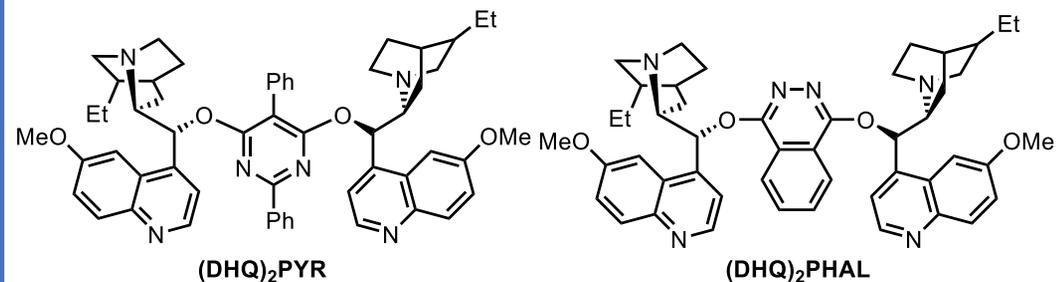
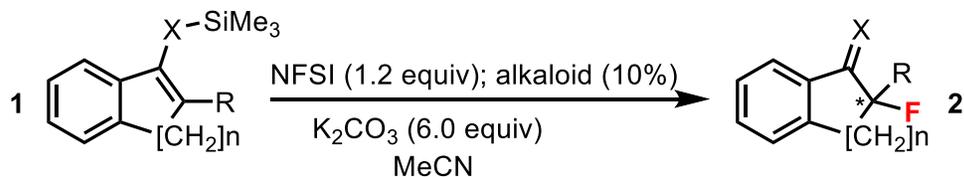
X-ray crystallographic structure for NF-Q BF_4^- .
(open conformation III)

Rationalization of Stereoinduction



Solution Conformations
Transition State Analysis

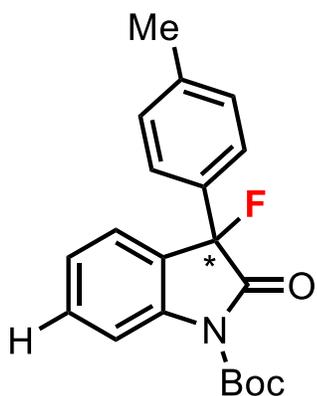
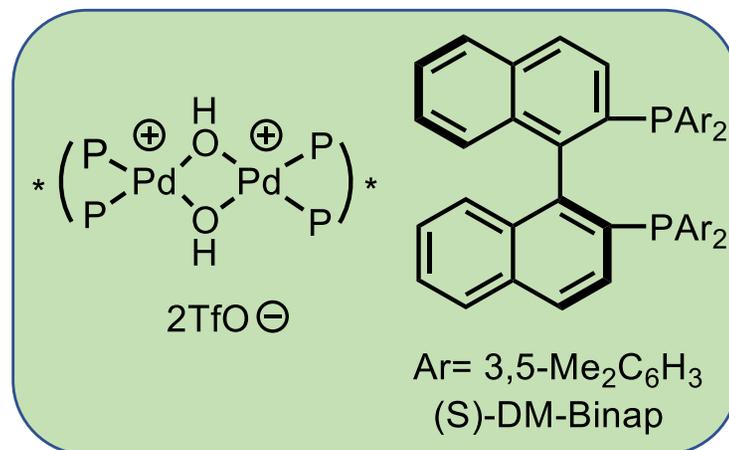
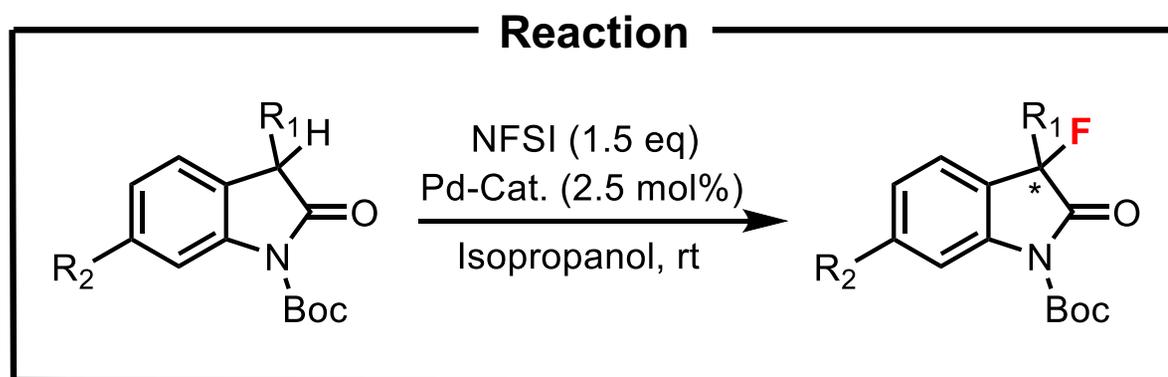
Catalytic Cinchona Alkaloids



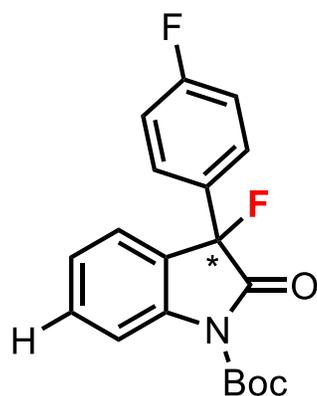
Entry	1	X	R	n	Bis-cinchona alkaloid	2	T [°C]	t	Yield [%]	ee [%]
1	1 b	CH ₂	CH ₂ C ₆ H ₄ - <i>p</i> -Me	1	(DHQ) ₂ PYR	2 b	-20	12 h	75	95
2	1 d	CH ₂	CH ₂ C ₆ H ₄ - <i>p</i> -OMe	1	(DHQ) ₂ PYR	2 d	-20	34 h	65	90
3	1 g	CH ₂	Me	1	(DHQ) ₂ PYR	2 g	-40	24 h	73	72
4	1 l	O	CH ₂ C ₆ H ₄ - <i>p</i> -Me	2	(DHQ) ₂ PHAL ^[a]	2 l	-40	8 days	79	86
5	1 n	O	CH ₂ C ₆ H ₄ - <i>p</i> -OMe	2	(DHQ) ₂ PHAL ^[a]	2 n	-40	6 days	84	85

[a]: 20 mol% alkaloid used.

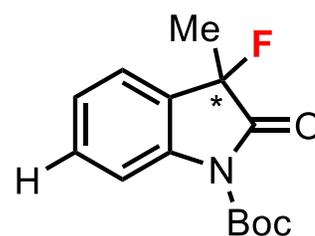
Transition Metal-Catalyzed Asymmetric Fluorination



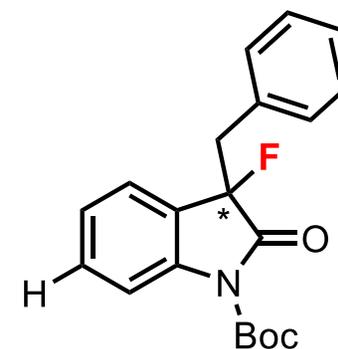
3 h
97% yield; 86% ee



3 h
94% yield; 84% ee



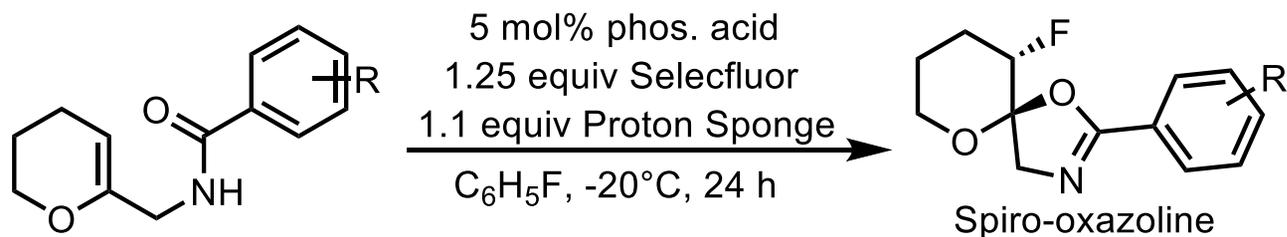
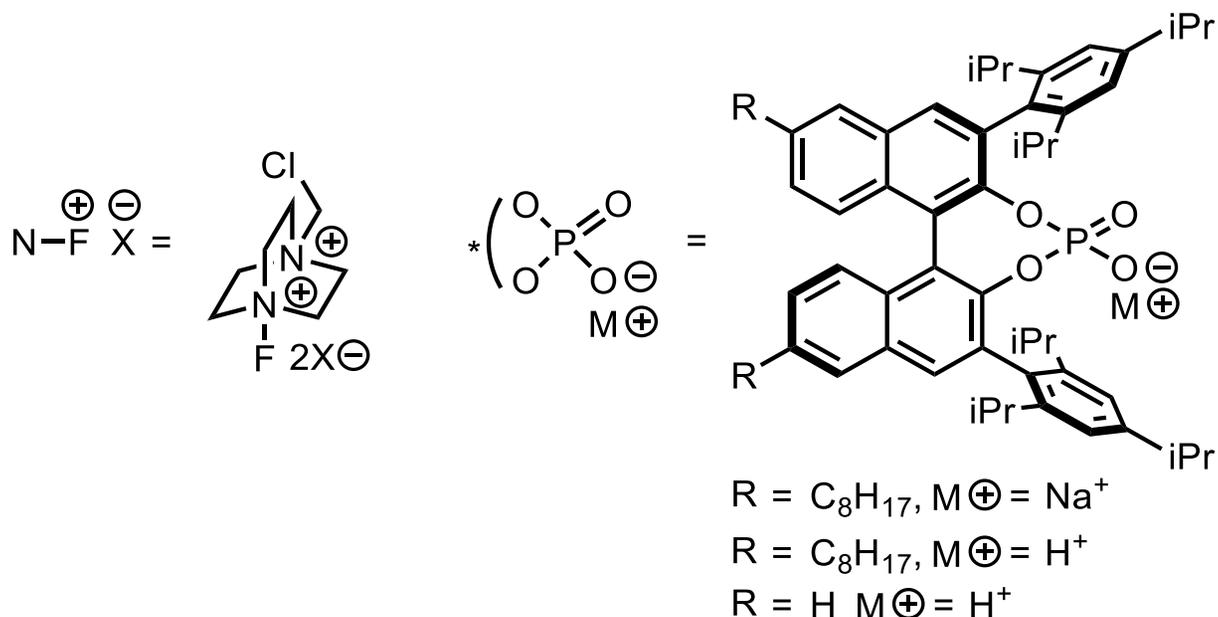
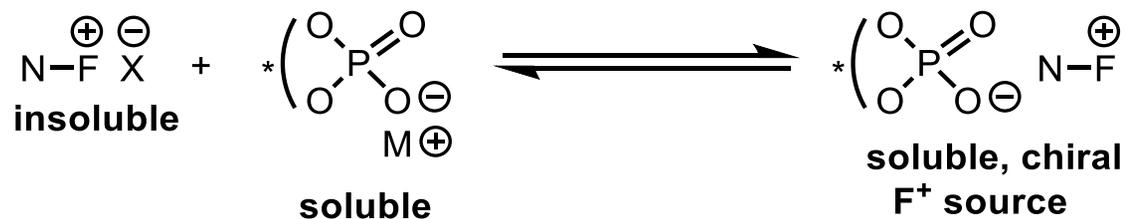
5 h
86% yield; 95% ee



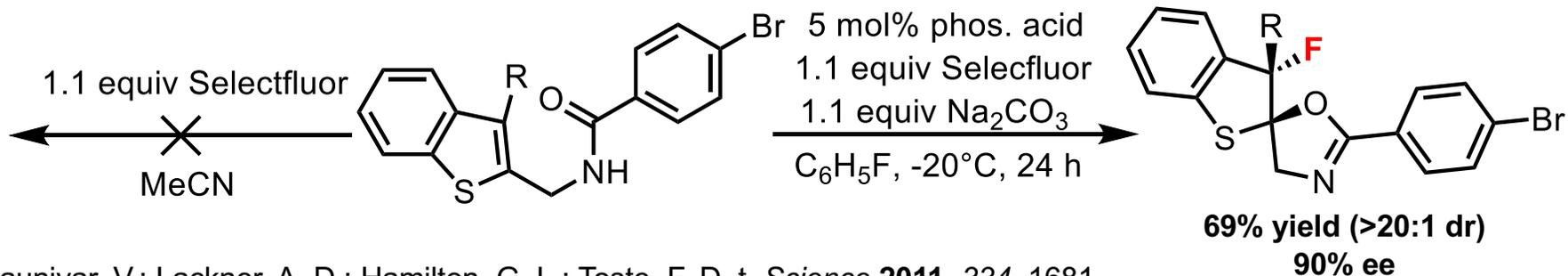
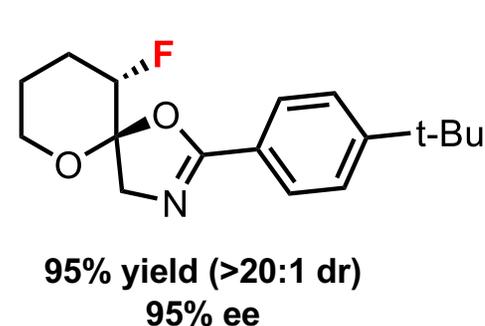
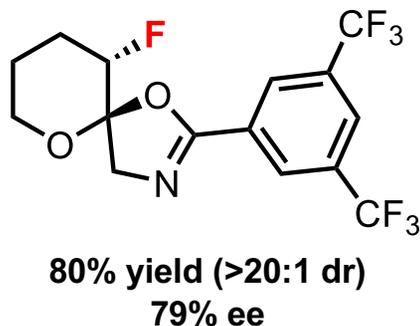
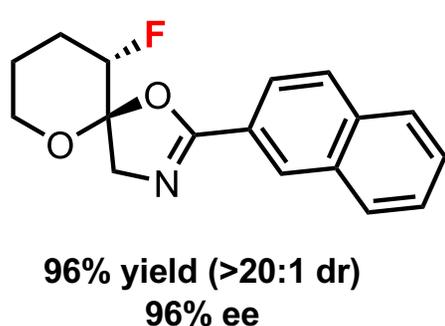
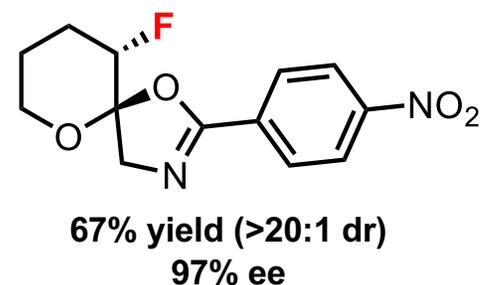
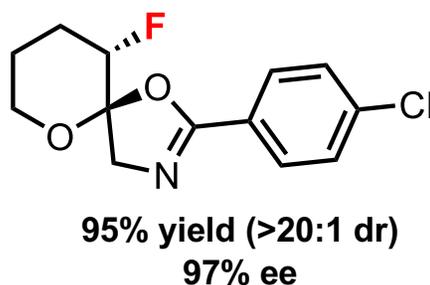
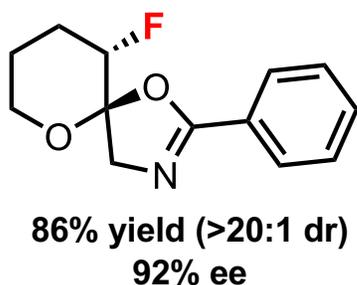
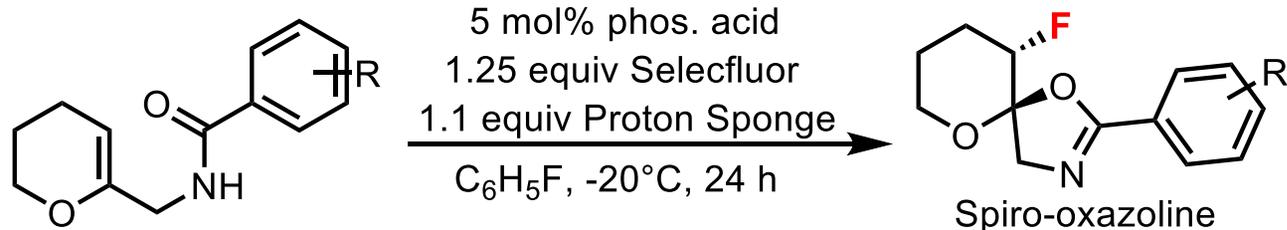
4 h
72% yield; 80% ee

*Representative products

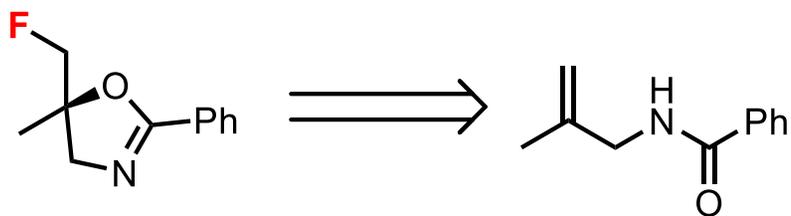
Anionic Chiral Phase-Transfer Catalysis



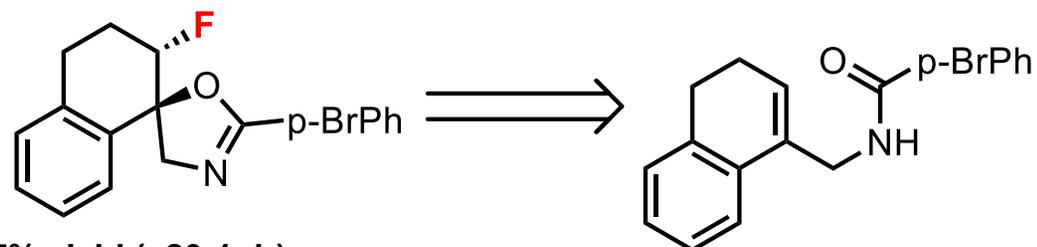
Anionic Chiral Phase-Transfer Catalysis



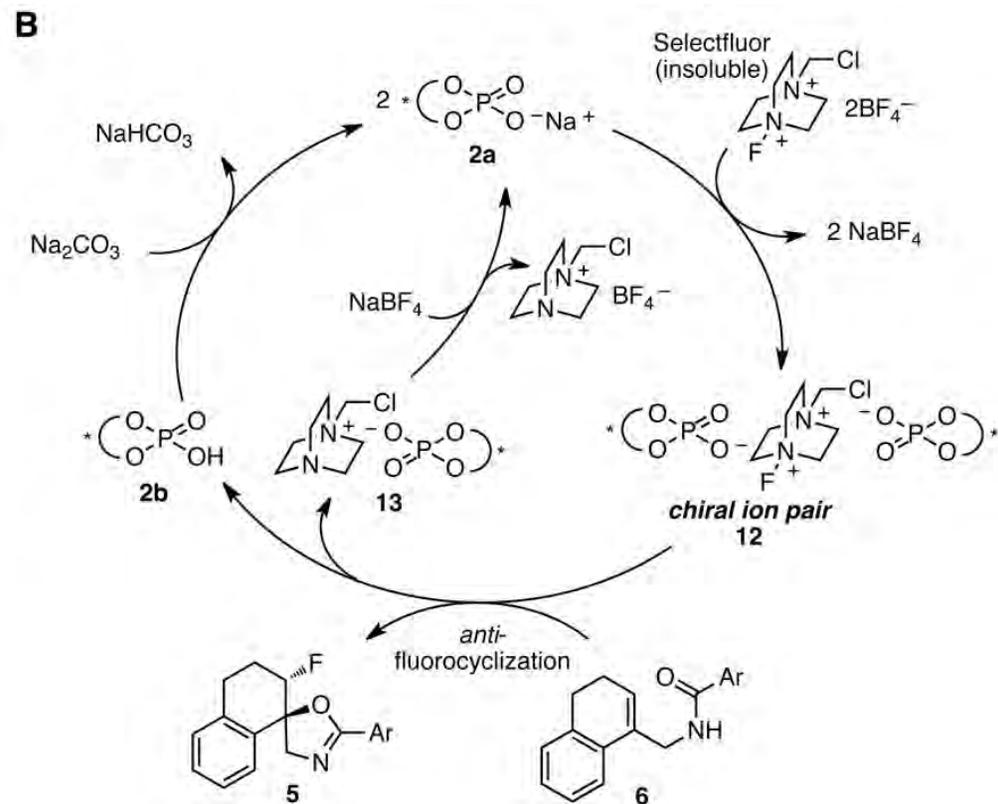
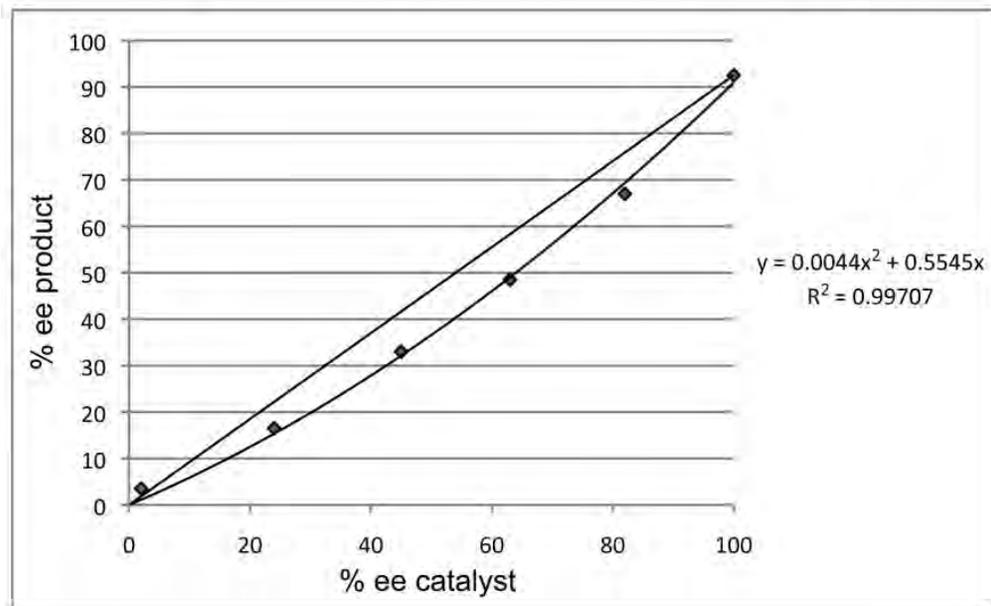
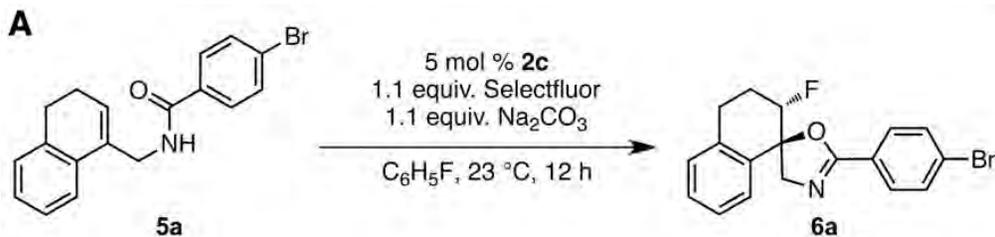
Anionic Chiral Phase-Transfer Catalysis



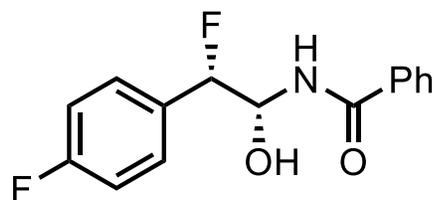
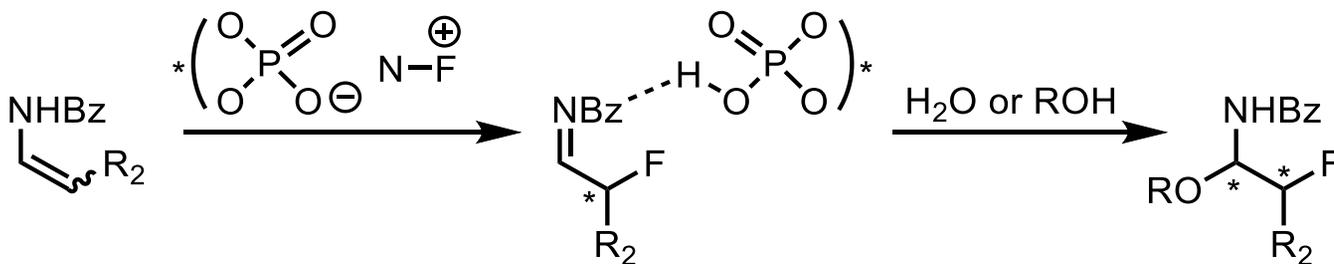
75% yield
70% ee



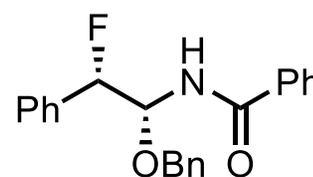
87% yield (>20:1 dr)
93% ee



Oxyfluorination of Enamides

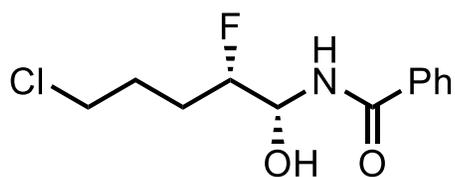


63% Yield, 97% ee

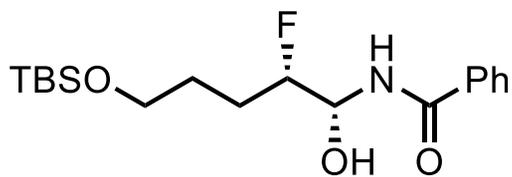


66% Yield, 94% ee

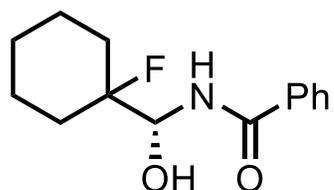
6:1 d.r.



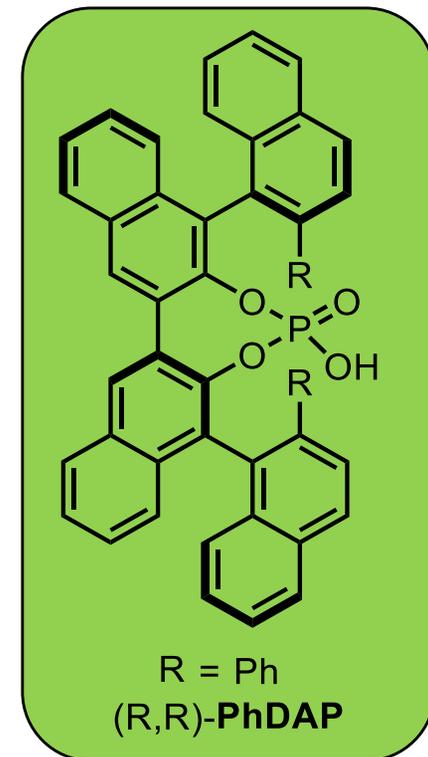
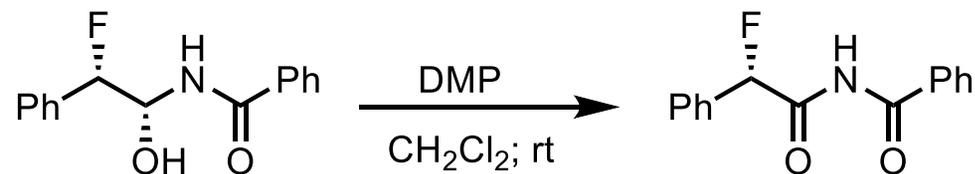
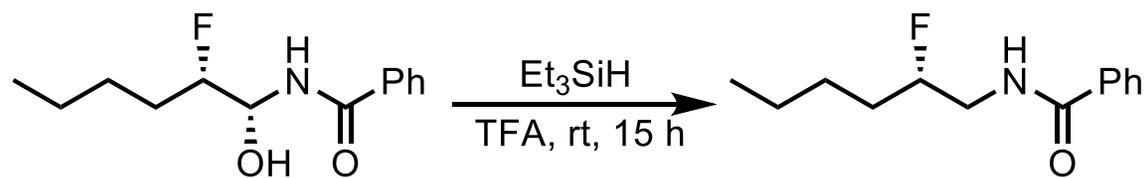
60% Yield, 92% ee



61% Yield, 87% ee



80% Yield, 90% ee



Presentation Overview

Introduction

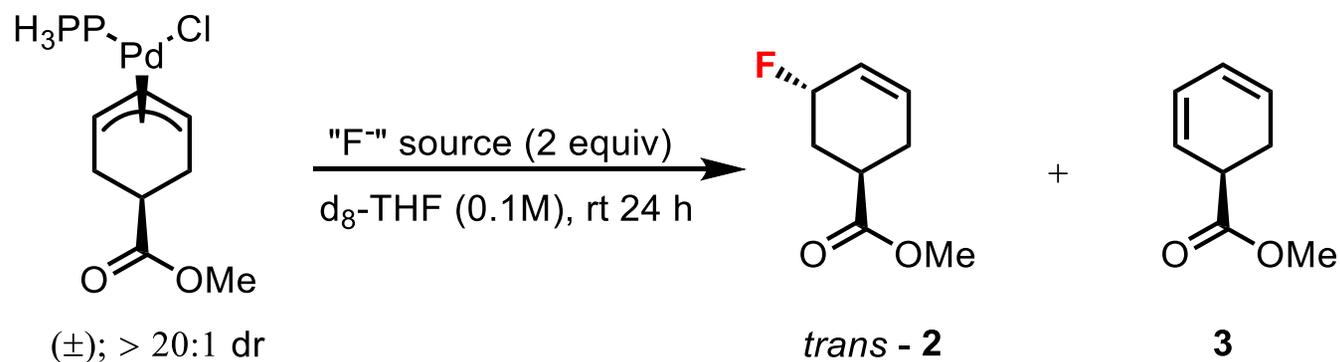
Electrophilic Fluorination

**Nucleophilic Fluorination/Pre-
Fluorinated Elaboration**

Concluding Remarks

Palladium-Catalyzed Fluorination of Allylic Halides

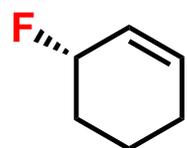
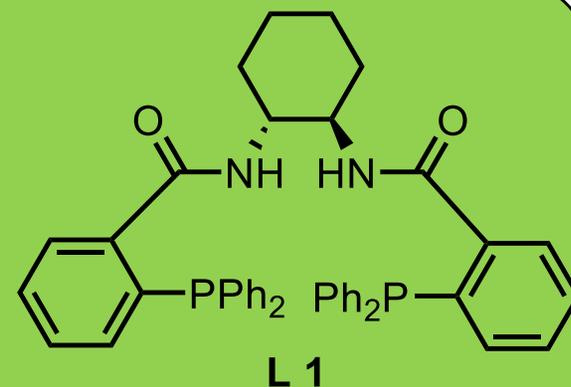
“Our lab has initiated a program aimed at the development of asymmetric catalytic methods for nucleophilic fluorination.”



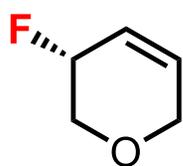
entry	"F-" source	conv. (%)	yield 2 (%)	yield 3 (%)
1	KF	77	0	14
2	CsF	96	0	24
3	TBAT	72	10 ^a	19
4	AgF	100	49 ^a	4
5	CuF ₂	36	0	1

a: >20:1 dr

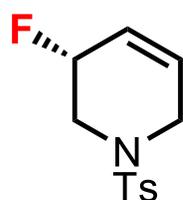
Palladium-Catalyzed Fluorination of Allylic Halides



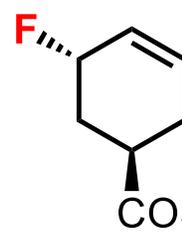
85%; 88% ee



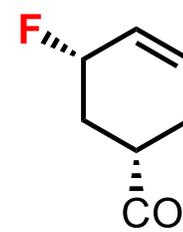
62%; 90% ee



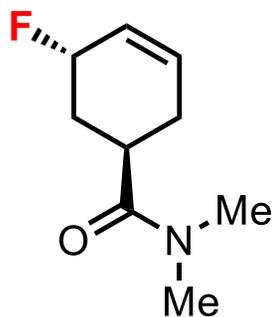
74%; 96% ee



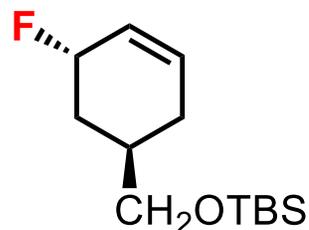
68%; 90% ee
14:1 dr



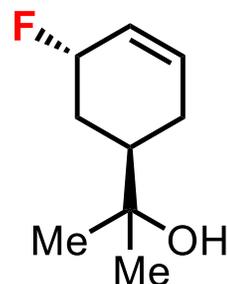
70%; 91% ee
3:1 dr



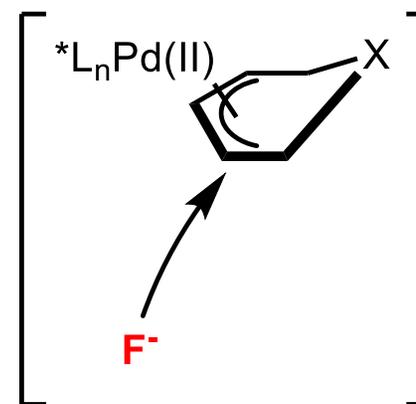
85%; 85% ee
> 20:1 dr



56%; 93% ee
7:1 dr

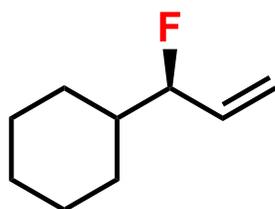
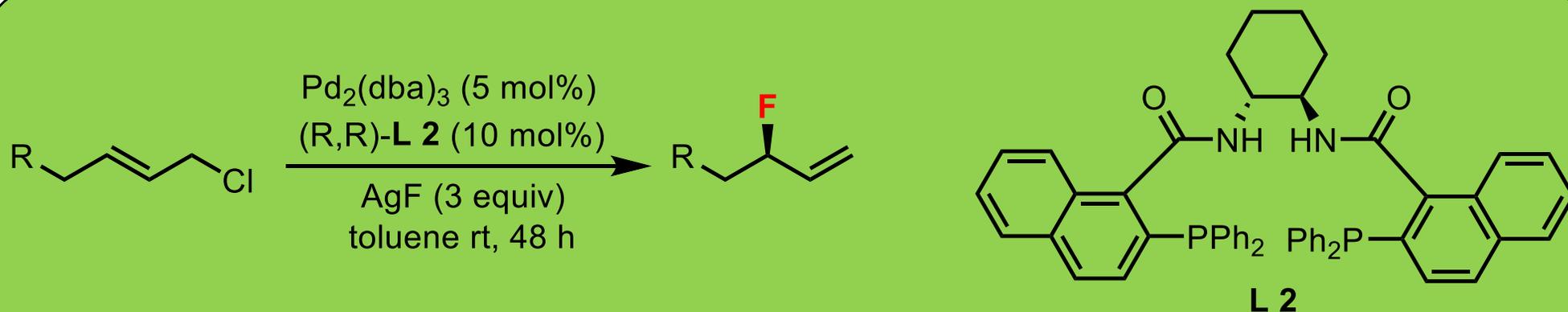


59%; 87% ee
20:1 dr

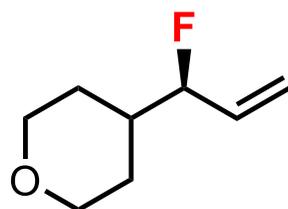


Outer-sphere fluoride attack

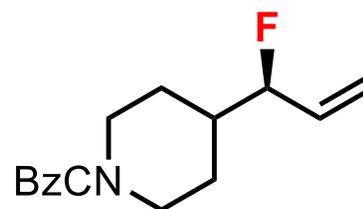
Branch-Selective Fluorination of Allylic Halides



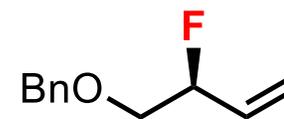
84%; 90% ee
> 20:1 b:l



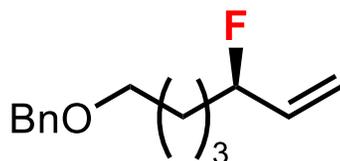
62%; 97% ee
> 20:1 b:l



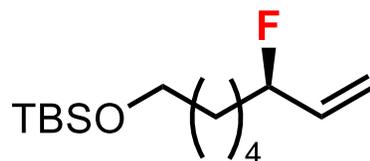
88%; 93% ee
10:1 b:l



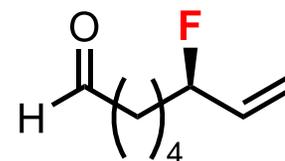
50%; 90% ee
16:1 b:l



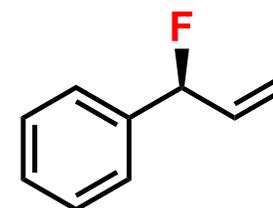
78%; 58% ee
> 20:1 b:l



84%; 58% ee
> 20:1 b:l

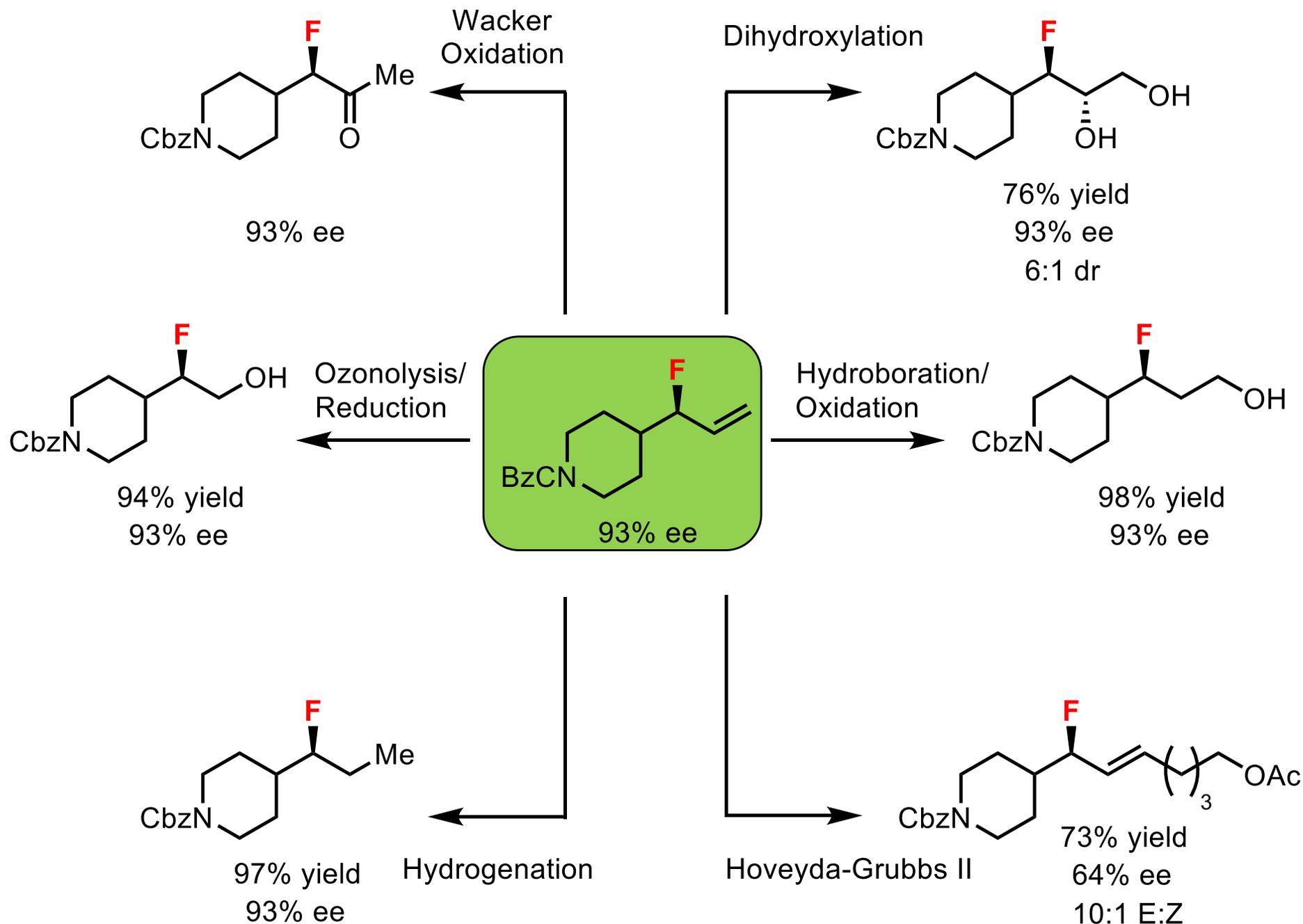


67%; 71% ee
> 20:1 b:l

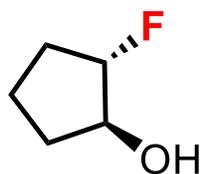
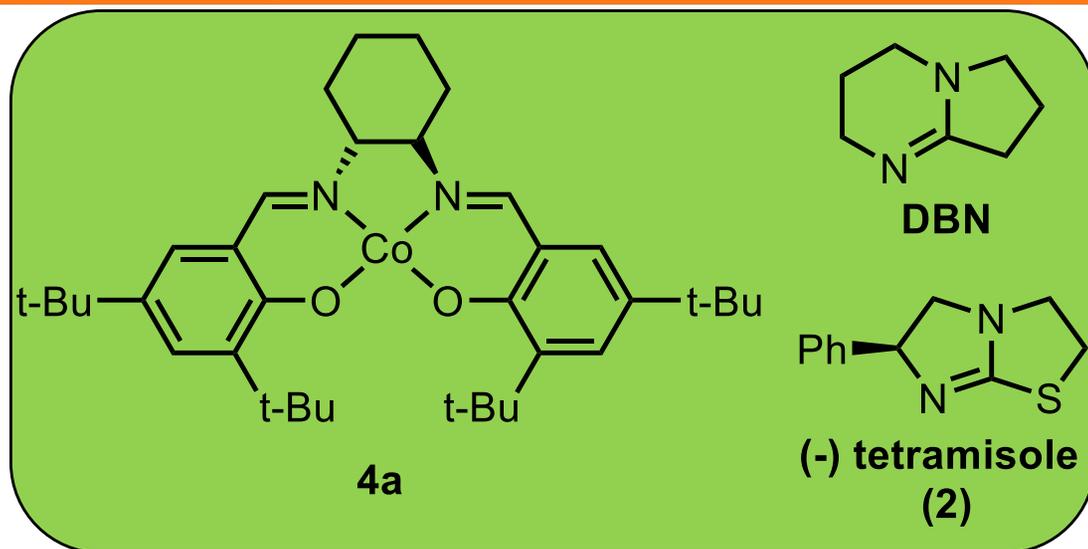
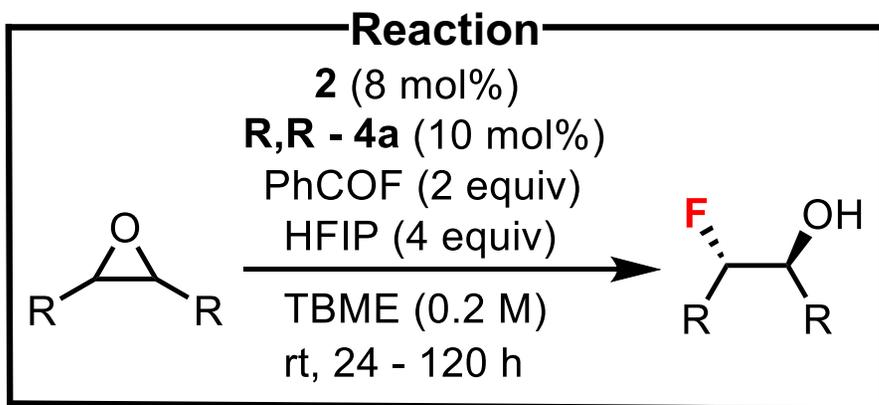


77%; 0% ee
1:4 b:l

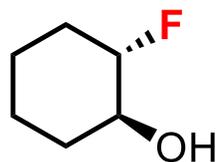
Derivatization of Allylic Fluorides



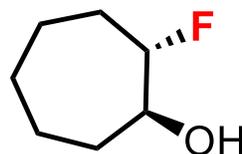
Enantioselective Fluorohydrin Formation



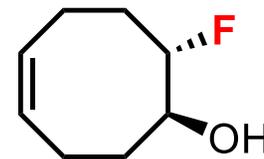
77% yield; 85% ee



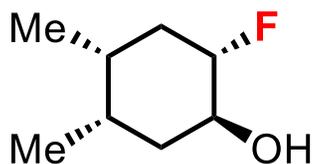
65% yield; 93% ee



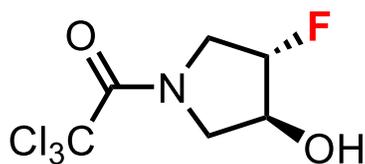
82% yield; 90% ee



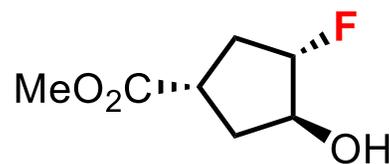
87% yield; 95% ee



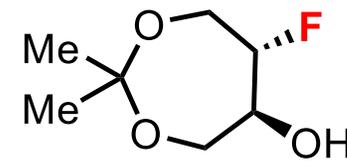
75% yield; 90% ee



84% yield; 80% ee

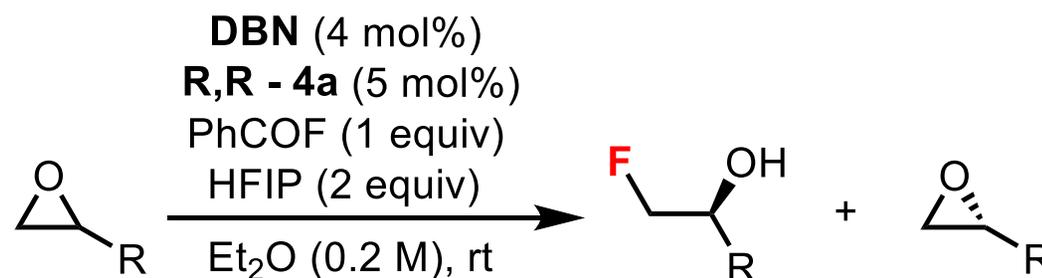
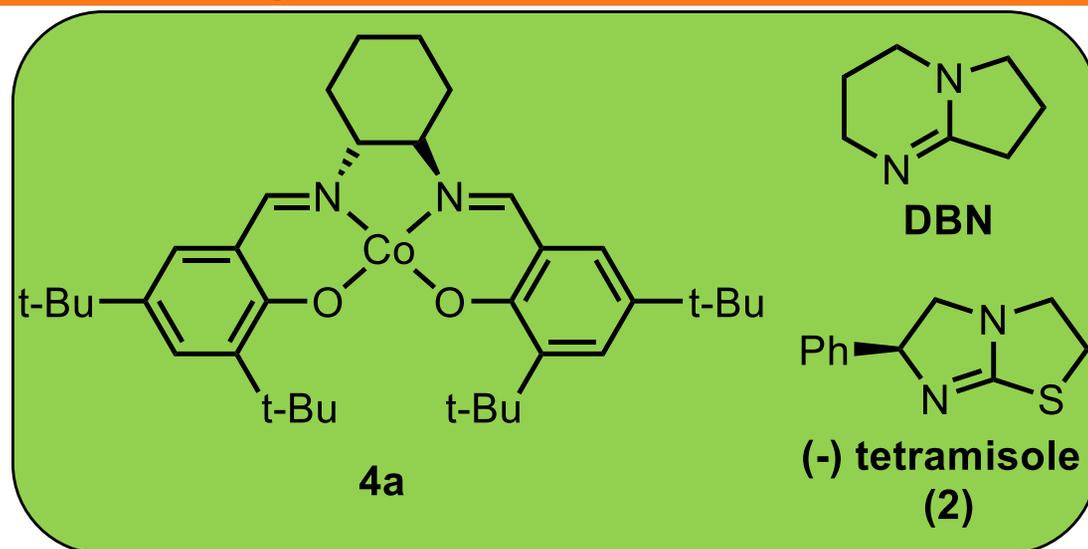
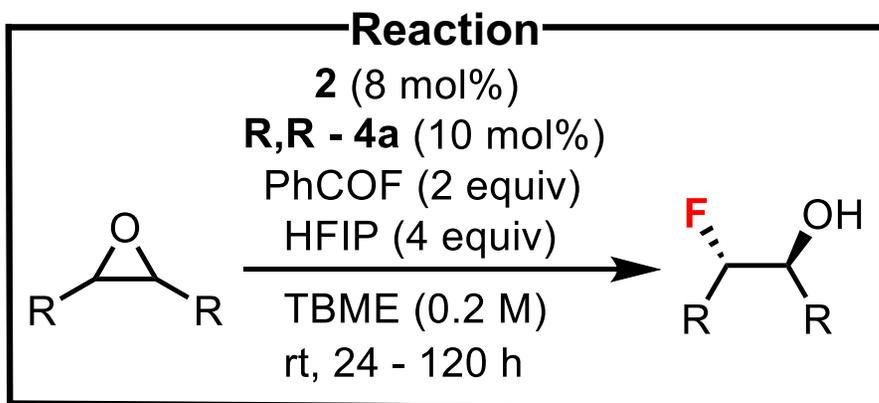


88% yield; 86% ee



55% yield; 58% ee

Enantioselective Fluorohydrin Formation



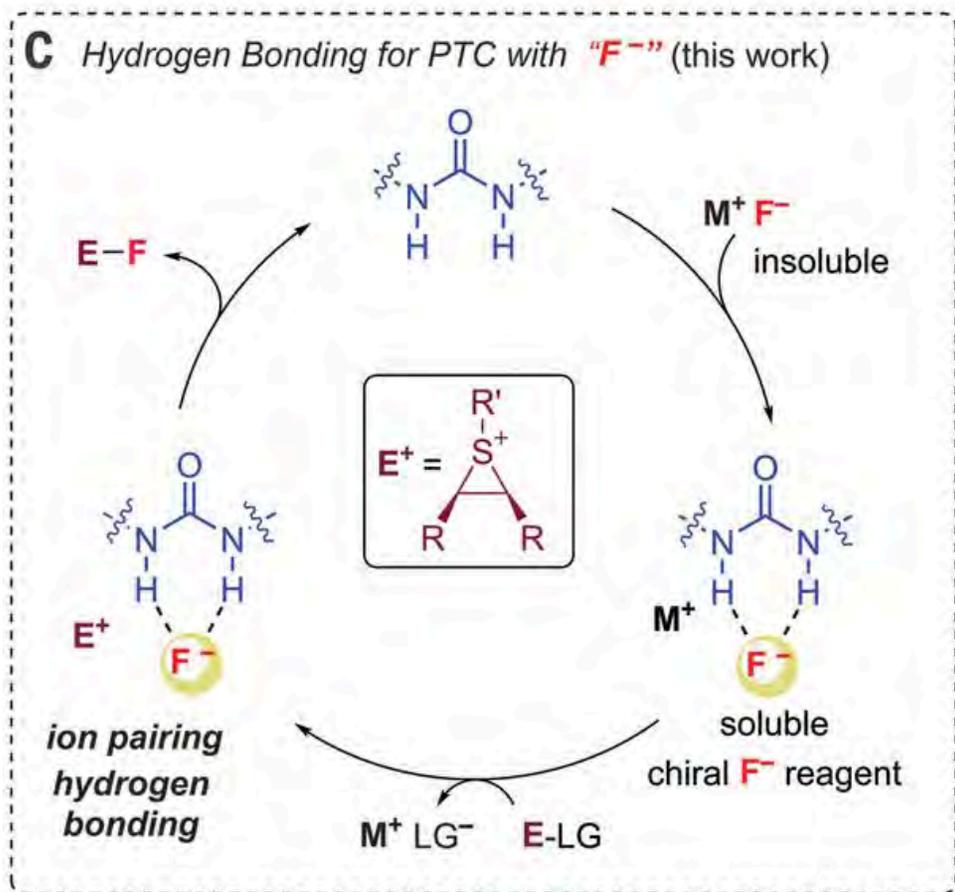
entry	R	time (h)	yield (%)	ee (%)	<i>k</i> _{rel}
1 ^a	<i>n</i> -Bu	30	36 (47)	99	>300
2	Ph	10	44	99	>300
3	TBSOCH ₂	24	44	88	32

a: 1.6 mol% **1**; 2 mol% **4a**.

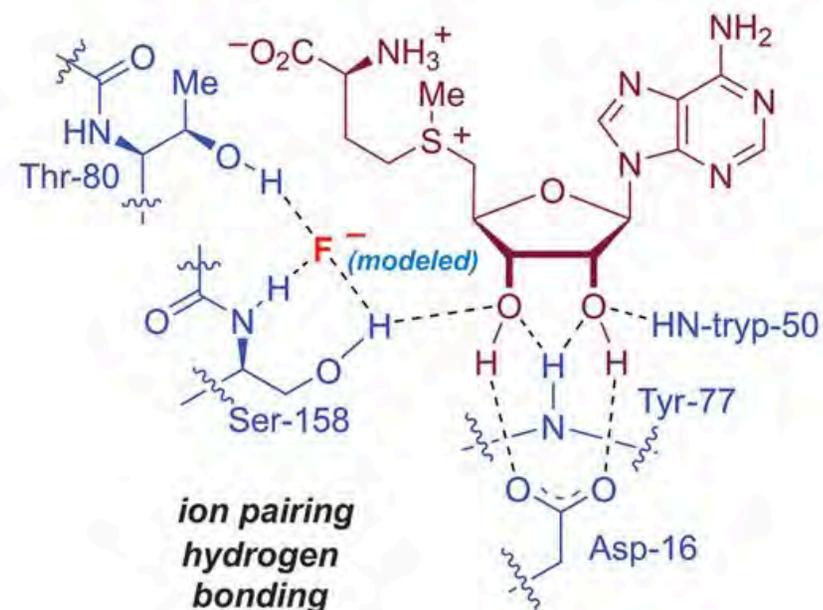
*All reactions conducted on 5 mmol scale.

Hydrogen Bonding Phase-Transfer Catalysis

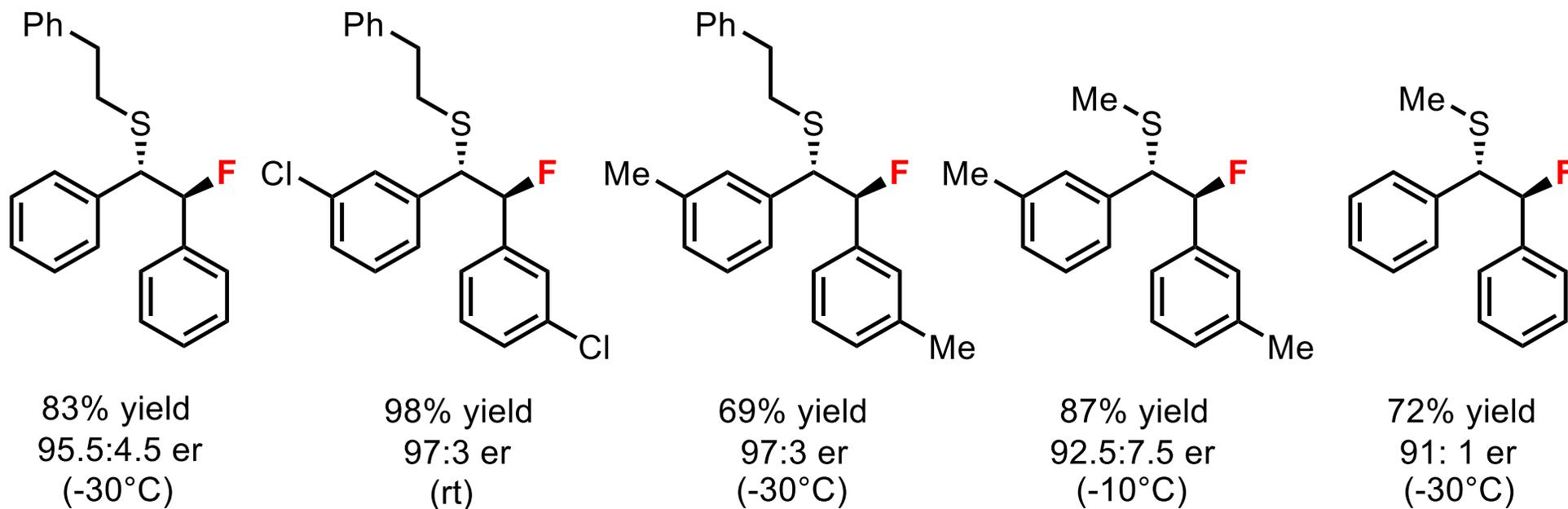
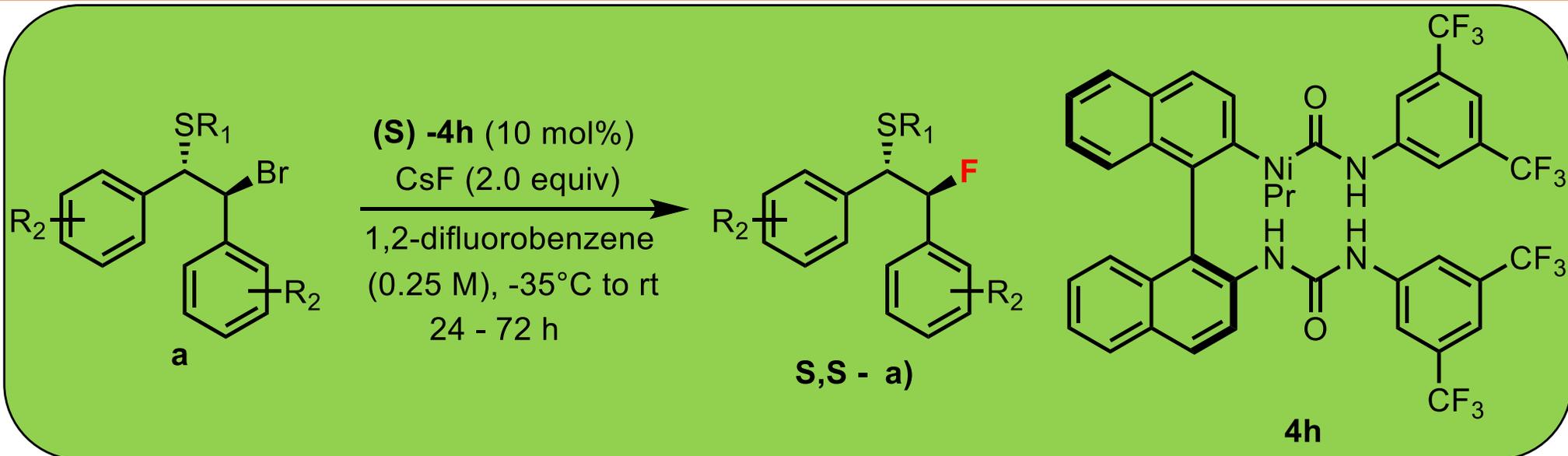
C Hydrogen Bonding for PTC with "F⁻" (this work)



D Enzymatic Fluorination with "F⁻" (O'Hagan)

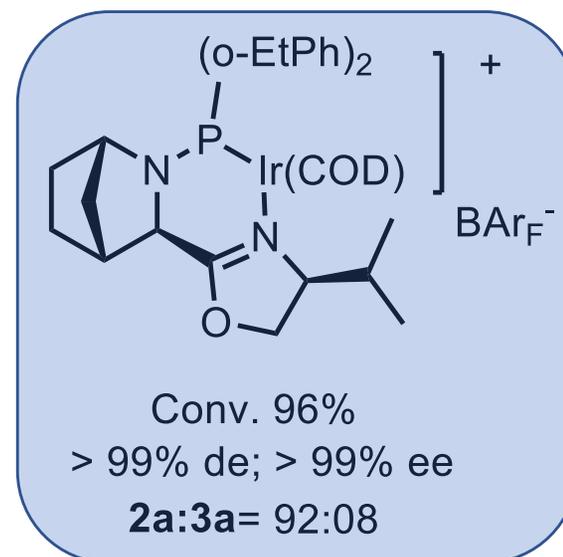
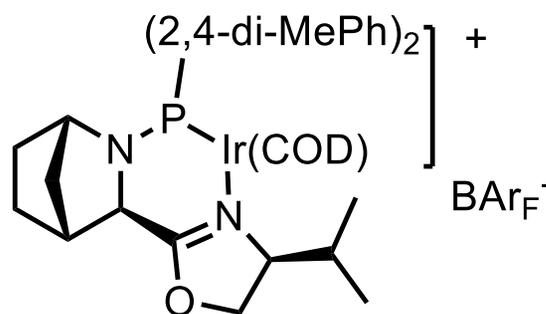
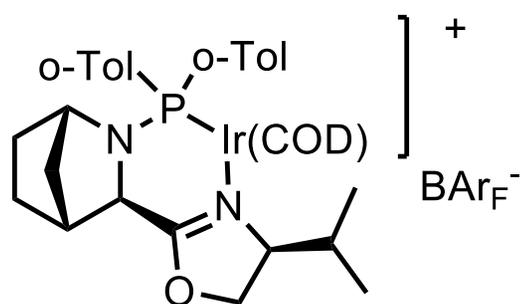
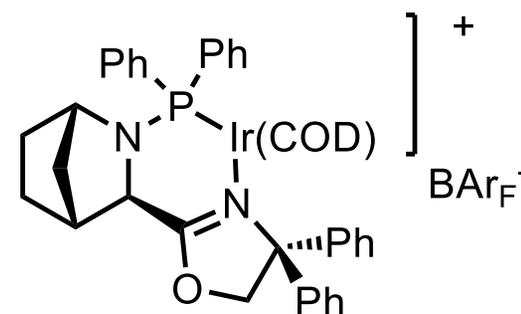
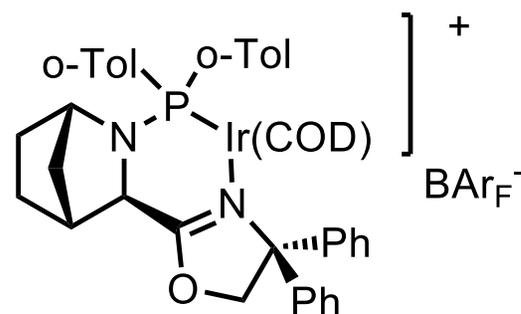
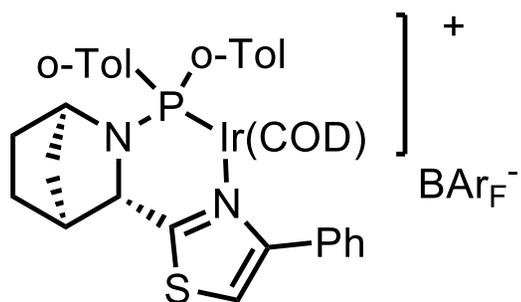
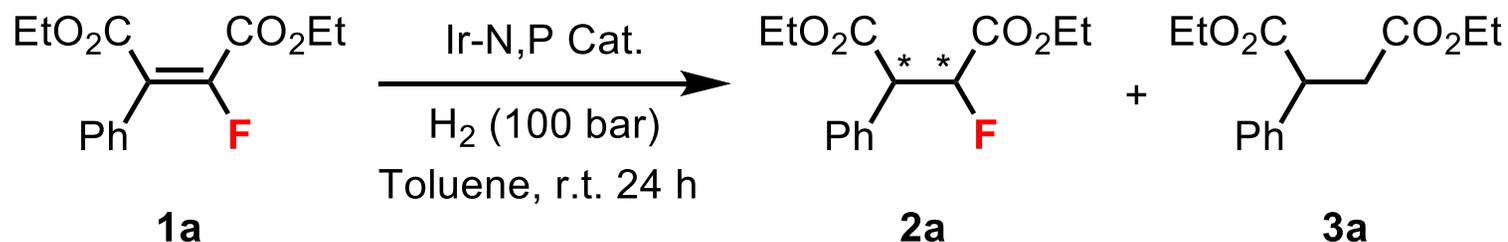


Hydrogen Bonding Phase-Transfer Catalysis



Asymmetric Hydrogenation of Vinyl Fluorides

Development of an N,P-Iridium Catalyst

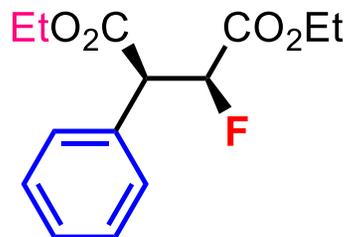
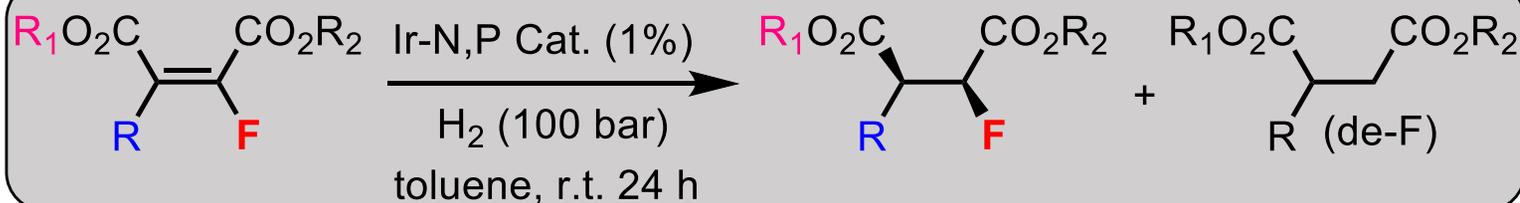


2a:3a= 88:12

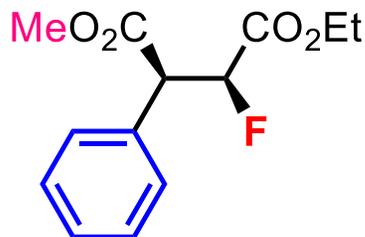
2a:3a= 90:10

2a:3a= 92:08

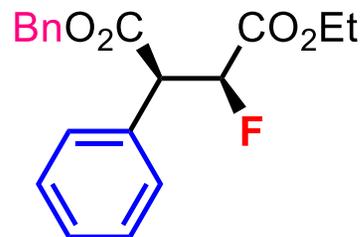
Hydrogenation of Various Fluoromaleates



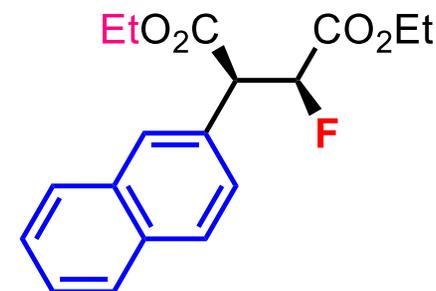
92% yield, 8% de-F
> 99% de; > 99% ee



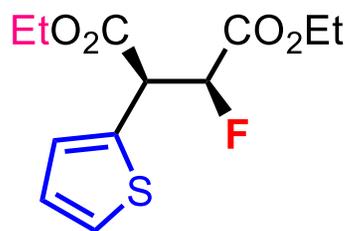
86% yield, 9% de-F
> 99% de; > 99% ee



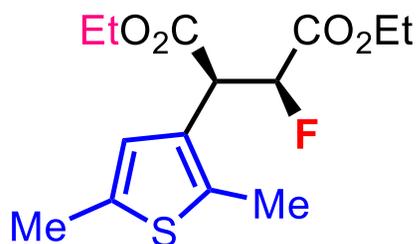
97% yield, 13% de-F
> 99% de; > 99% ee



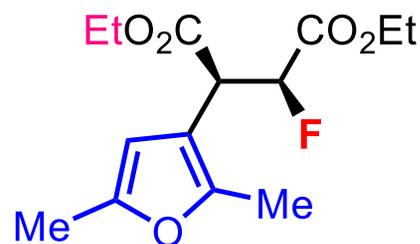
98% yield, 7% de-F
> 99% de; > 99% ee



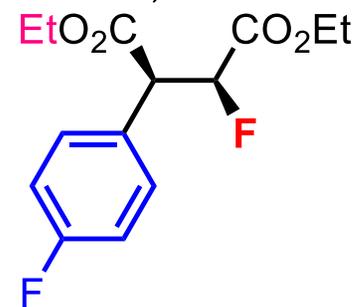
97% yield, 9% de-F
> 99% de; > 99% ee



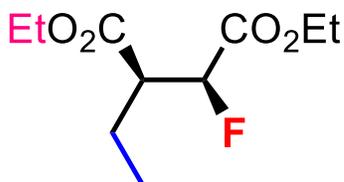
97% yield, 10% de-F
> 99% de; > 99% ee



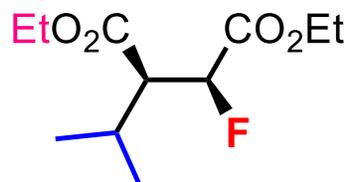
98% yield, 6% de-F
> 99% de; > 99% ee



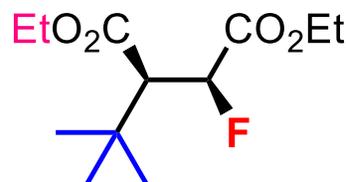
98% yield, 9% de-F
> 99% de; > 99% ee



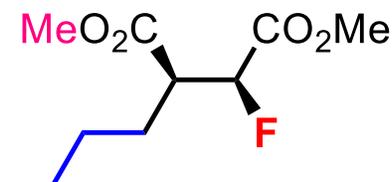
30% yield, 0% de-F
> 99% de; 97% ee



20% yield, 0% de-F
> 99% de; > 99% ee

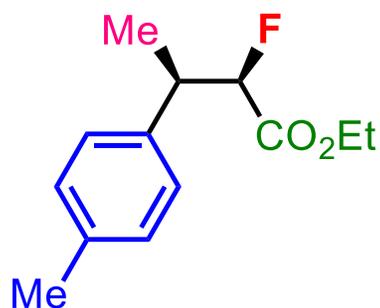
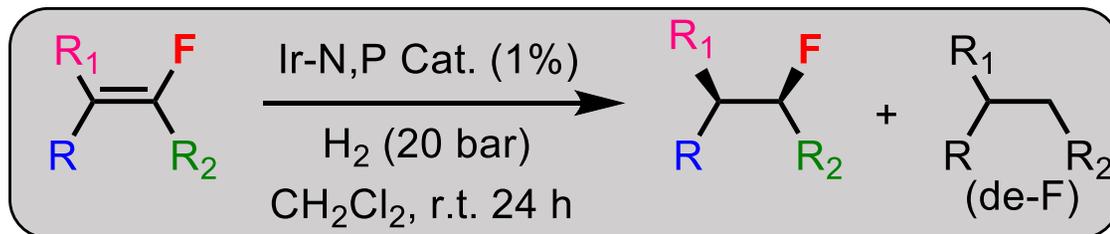


48% yield, 2% de-F
> 99% de; > 99% ee

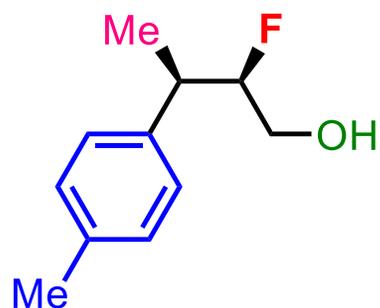


38% yield, 16% de-F
> 99% de; 91% ee

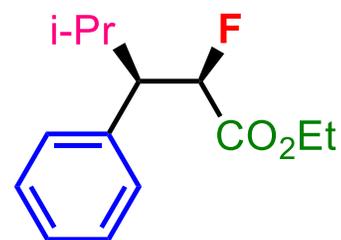
Hydrogenation of Functionalized Vinyl Fluorides



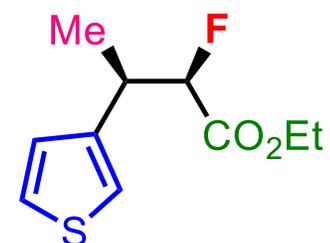
90% yield
> 99% de; 98% ee



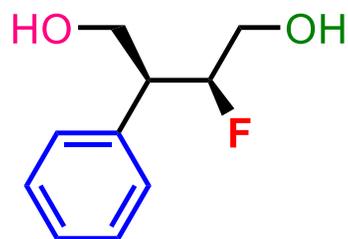
99% yield
> 99% de; 97% ee



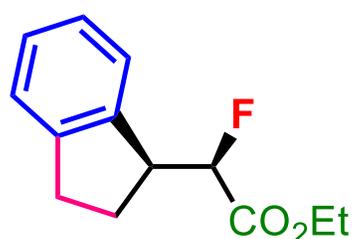
42% yield
> 99% de; 98% ee



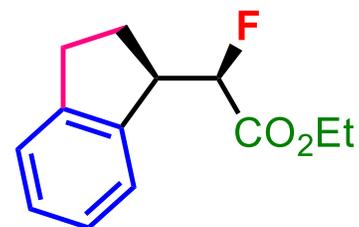
94% yield
> 99% de; 98% ee



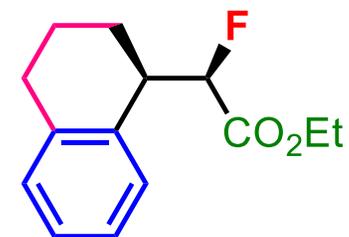
99% yield
> 99% de; 91% ee



99% yield
> 99% de; 90% ee

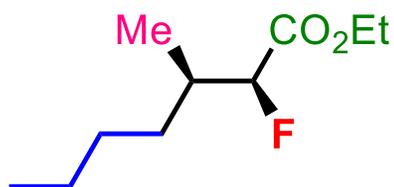


99% yield
> 99% de; 97% ee

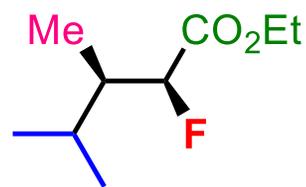


99% yield
> 99% de; > 99% ee

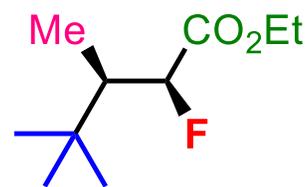
Hydrogenation of Aliphatic Vinyl Fluorides



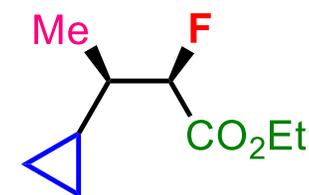
99% yield
> 99% de; 93% ee



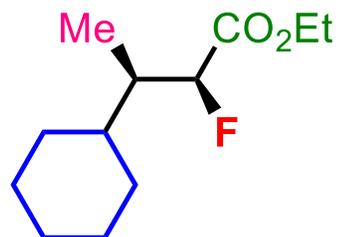
80% yield
> 99% de; 92% ee



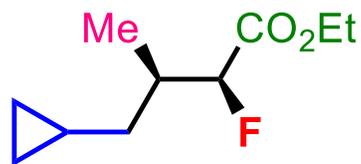
98% yield, 12% de-F
> 99% de; 99% ee



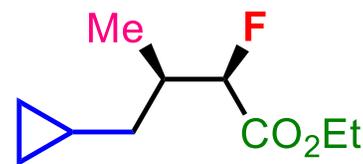
74% yield
> 99% de; 97% ee



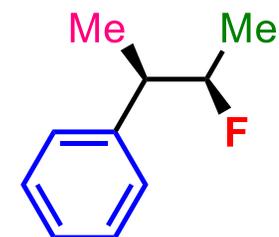
80% yield
> 99% de; 96% ee



99% yield
> 99% de; 92% ee

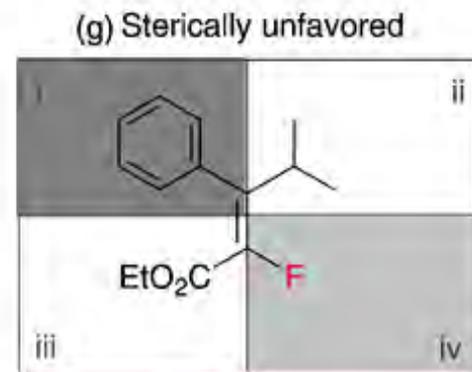
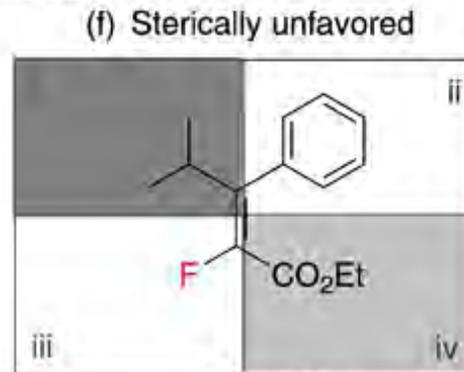
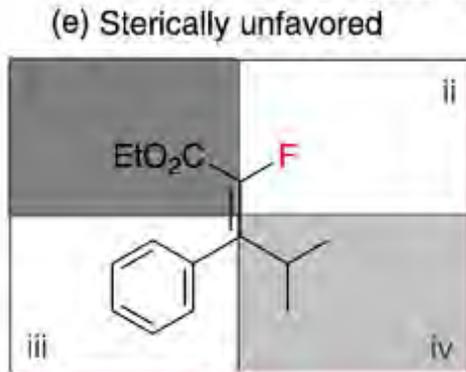
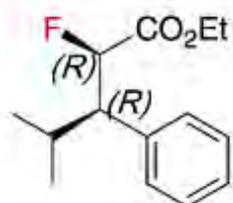
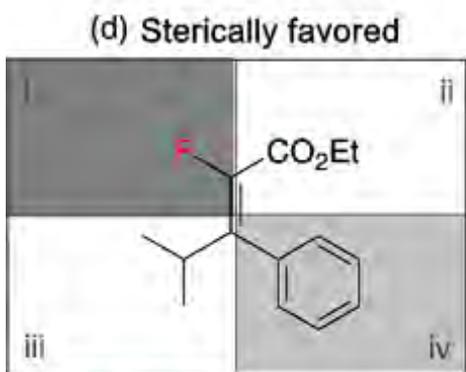
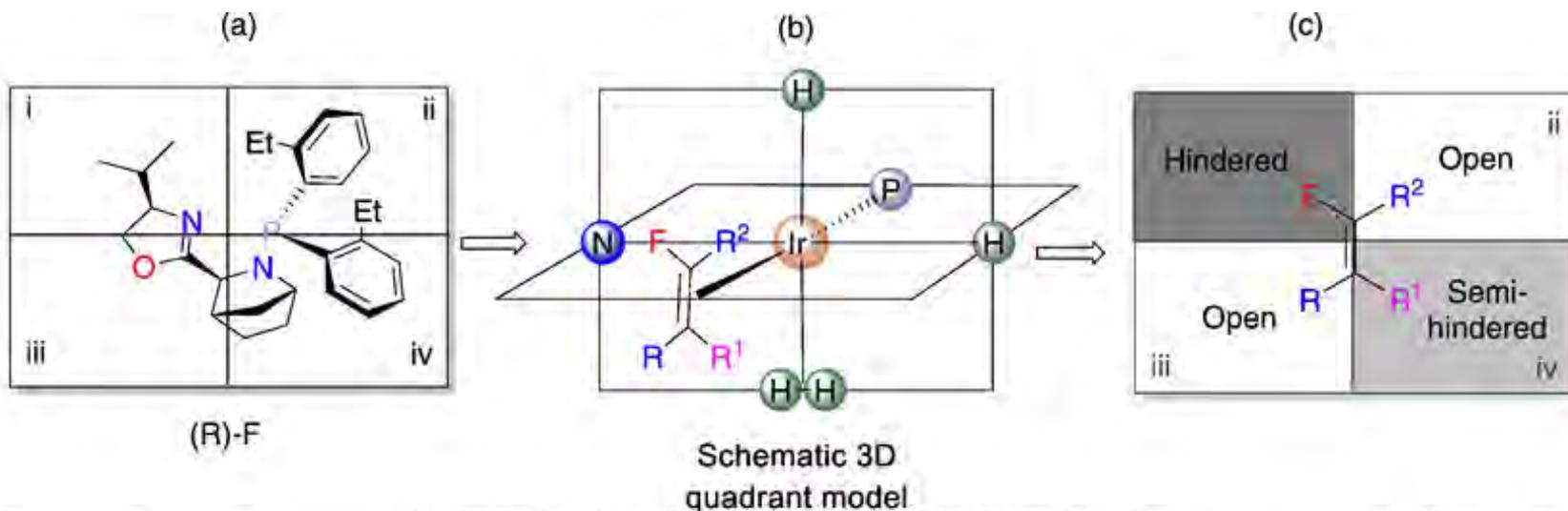


90% yield
> 99% de; 92% ee



55% yield
> 99% de; 96% ee

Quadrant Model for Stereoselectivity



Presentation Overview

Introduction

Electrophilic Fluorination

**Nucleophilic Fluorination/Pre-
Fluorinated Elaboration**

Concluding Remarks

Future Directions

- **C-F stereogenic motifs are richly under-explored (chemistry and chemical biology).**
- **Over representation of α -carbonyl functionalization.**
 - **These motifs are biologically relevant but we need methods to introduce novel stereogenic C-F functionality.**
- **Computational methods to predict beneficial SAR reactivity could streamline discovery.**