Recent Advances in Asymmetric Construction of Carbon–Fluorine Quaternary Stereogenic Center

Dina Boyarskaya

16th of May 2022

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2. Achievements before 2011
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4. Primary Amine Catalysis
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6. Planar-chiral nucleophilic catalysis
7. Transition-metal catalyzed transformations
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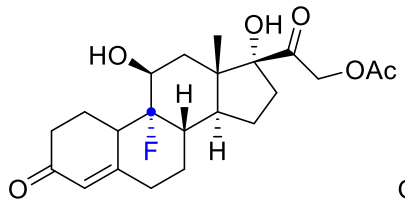
Content - Precisions

1. Only enantioselective transformation
2. Only formation of quaternary carbon atoms
3. Only fluorination methods
4. Only electrophilic N-F fluorinating agents
5. Only achievements during the last 10 years will be discussed

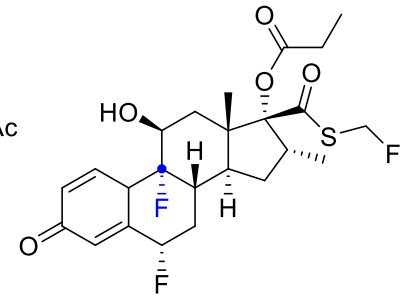
Introduction – fluorine-containing compounds

New methods for preparation of fluorine-containing compounds are in extremely high demand in nearly every sector of chemical industry:

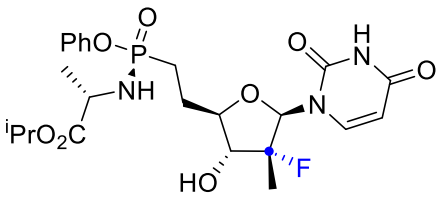
1. Solar cells industry;
2. Fluoro-containing markers for biological studies by NMR;
3. ^{19}F magnetic resonance imaging (MRI), a superior alternative to the current diagnostic procedures using harmful ionizing radiation;
4. Agrochemical industry - about half of newly developed pesticides contain some type of fluorination;
5. Pharmaceutical industry - fluorine is found in more than half of most-prescribed multibillion-dollar pharmaceuticals



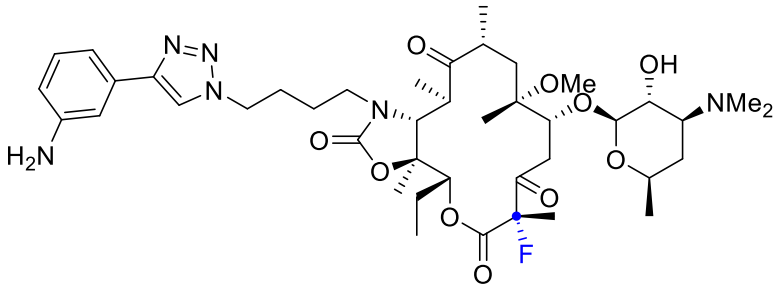
Fludrocortisone



Fluticasone propionate
treatment of asthma



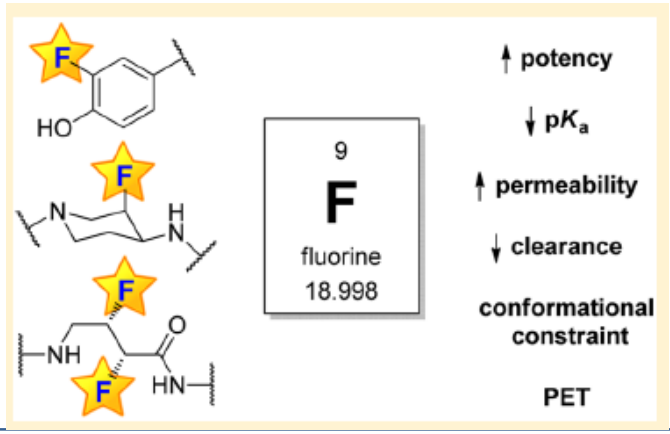
Sofosbuvir
HCV antiviral



Solithromycin
antibacterial

Due to the fact that F is slightly larger and hydrophobic than H, its extreme electronegativity and that F can be H-bond acceptor, introduction of C-F to replace C-H influence the properties of the drug and can lead to modification of :

- Molecular conformation;
- Polarity;
- Acid-base properties;
- Electronic interactions.



Meanwell, N.A. *J. Med. Chem*. **2015**, *58*, 8315−8359

Introduction – fluorine-containing compounds

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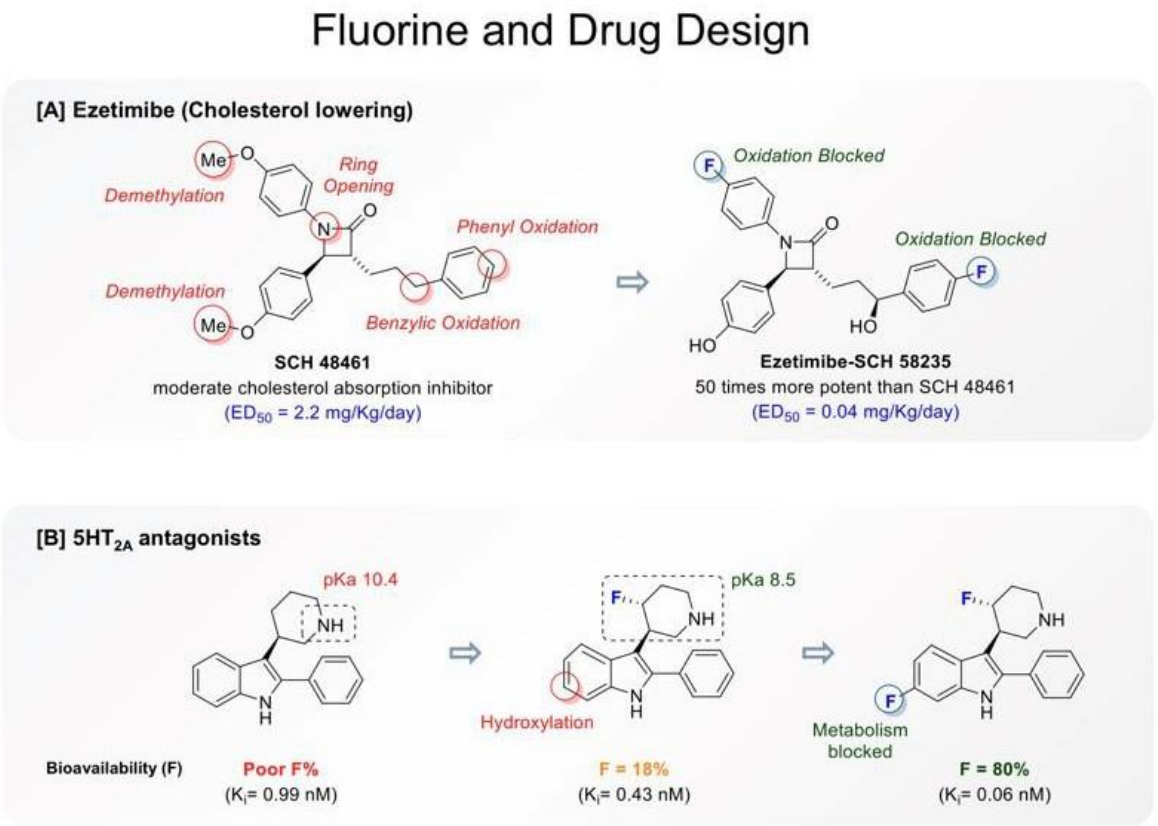
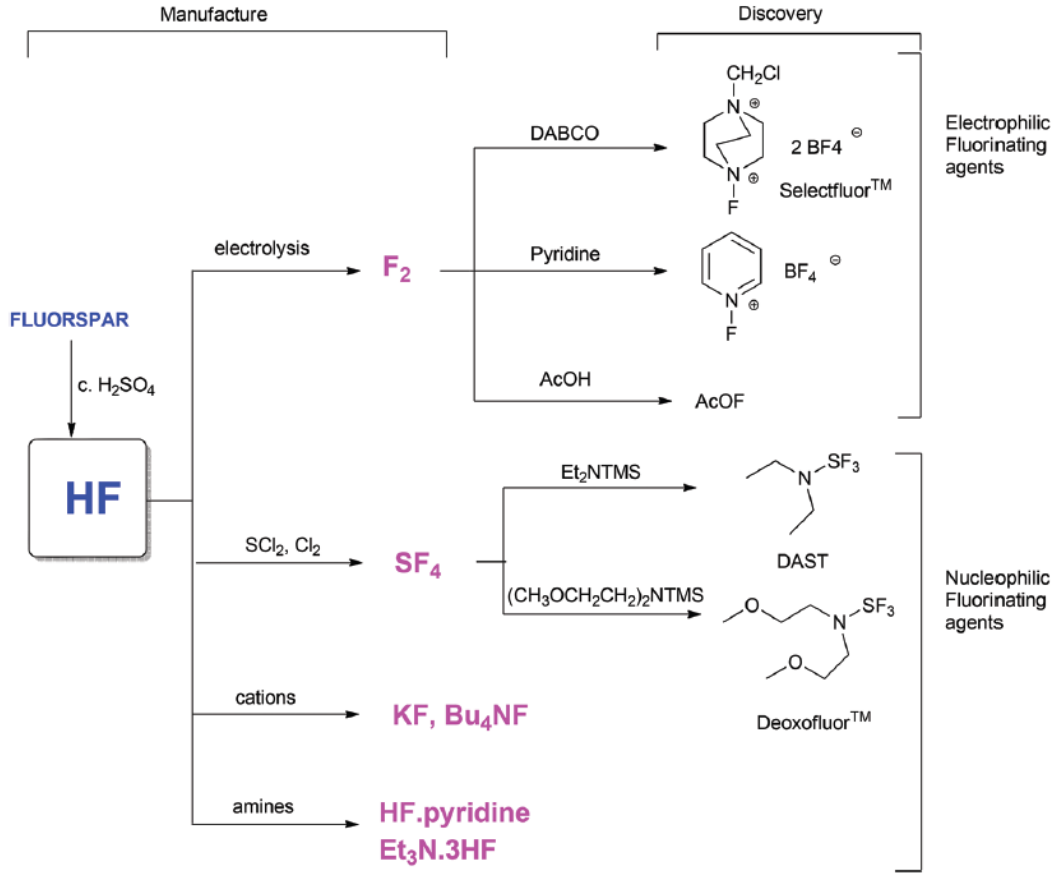


Meanwell, N.A. *J. Med. Chem*. **2015**, *58*, 8315−8359

Introduction – fluorinating reagents

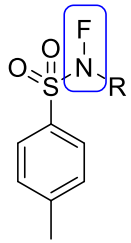
Three major factors prohibit chemical and biological evolution of fluorine:

1. the three richest natural sources of fluorine, the minerals fluorospar (CaF_2), fluorapatite ($Ca_5(PO_4)_3F$), and cryolite (Na_3AlF_6) are water-insoluble;
2. high oxidation potential of fluorine (−3.06 V);
3. high hydration energy of fluorine (117 kcal/mol) renders fluoride a very poor nucleophile in an aqueous/biological environment.

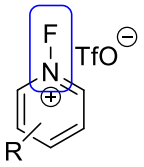


Introduction – Electrophilic N-F fluorinating reagents

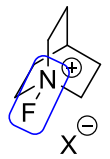
Shelf-stable electrophilic fluorinating reagents



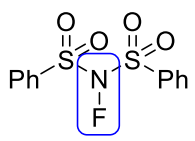
Barnette
1984



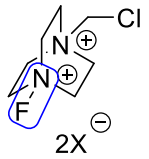
Umemoto
1986-1991



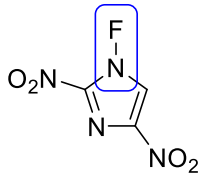
Banks
1986-1991



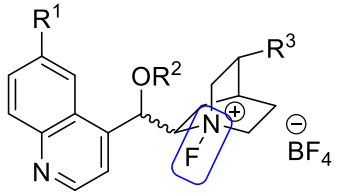
Differding
1991



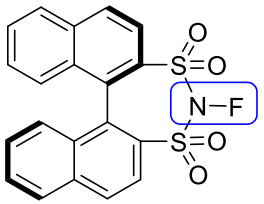
Banks
1992



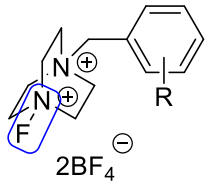
Laali
1998



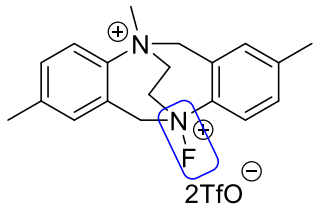
Shibata, Cahard
2000



Shibata, Ma, Cahard
2013

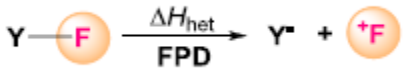


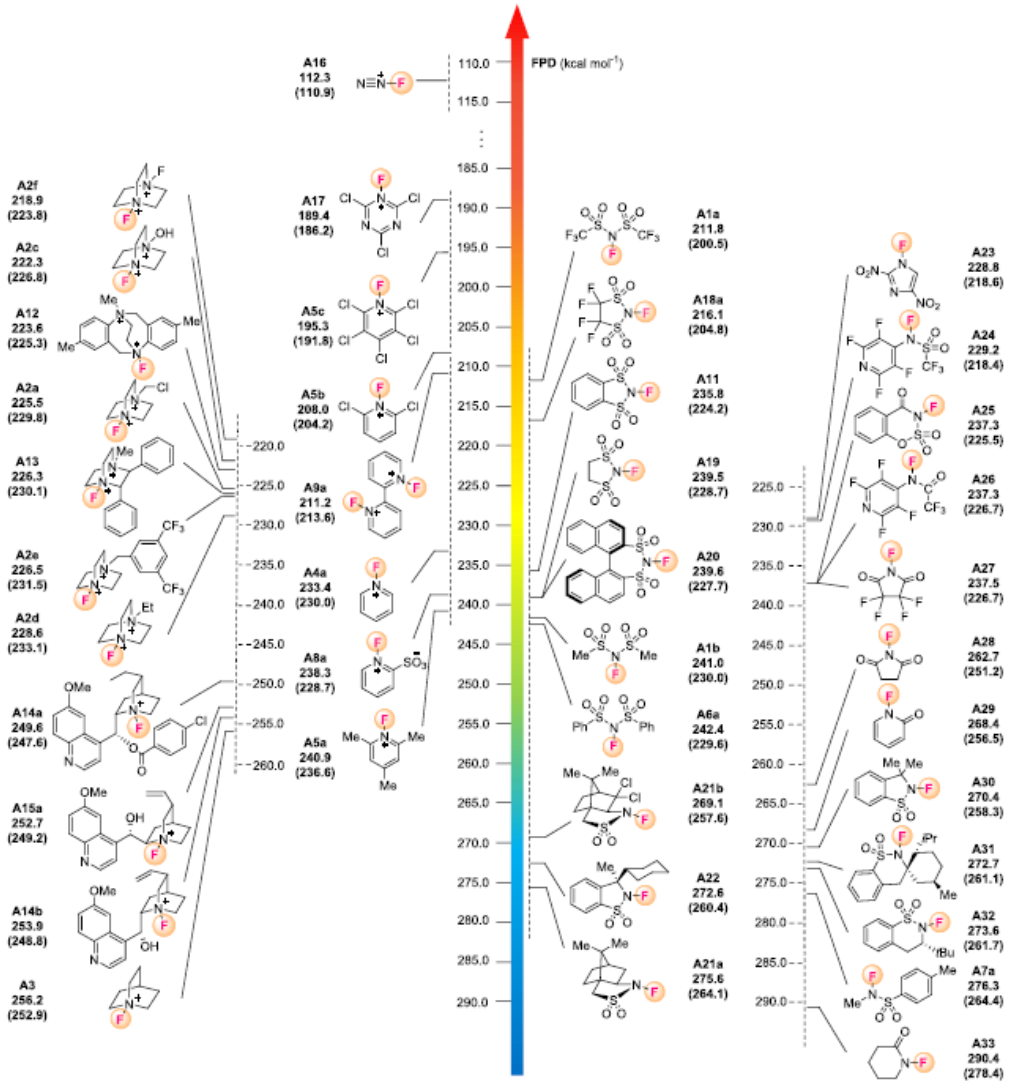
Toste
2013



Gouverneur
2015

In 2016, the first systematic quantum mechanical calculation of fluorinating strength of 130 electrophilic N−F reagents values was performed in two commonly used solvents (CH_2Cl_2 and CH3CN) based on FPD (**F**luorine **P**lus **D**etachment) energy.

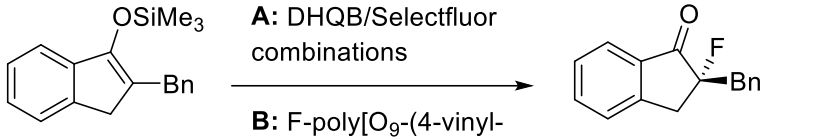




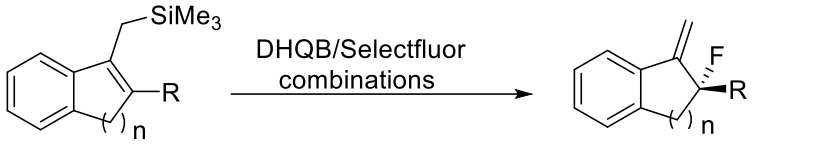
Achievements before 2011

Stochiometric reactions

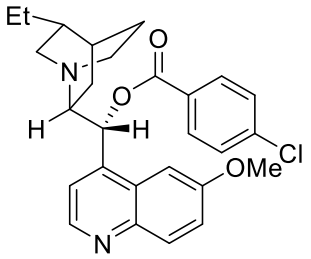
Cinchona alkaloids



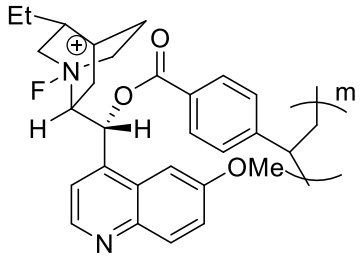
A: 86%, 91% ee
B: 98%, 85% ee



n = 1: >95%, 96% ee
n = 2: >95%, 83% ee



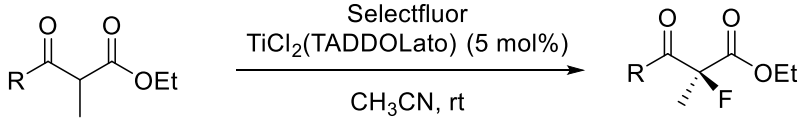
DHQB



F-poly[O_9-(4-vinyl-benzoate)-DHQN]

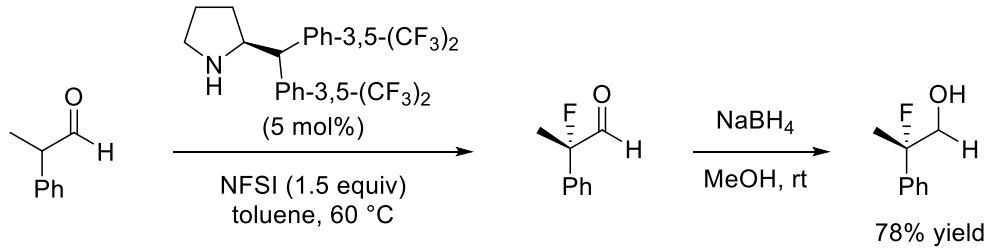
Catalytic reactions (first approaches)

Metal Catalysed, Togni, 2000



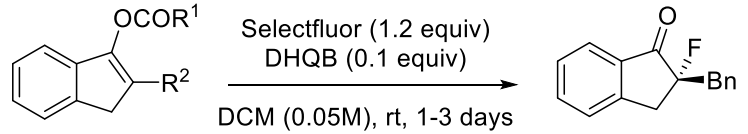
6 examples
ee 66-90%

Enamine catalysis, Jorgensen, 2005



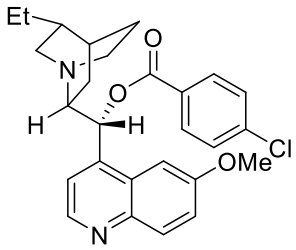
78% yield
48% ee

Tertiary amine catalysts, Shibata, 2006



17% to 96% yield
3% to 54% ee

R^1 = Me, Et, *i*-Pr, *n*-pent, Ph, CH_2Cl, OEt, CF_3
R^2 = Bn, Me, Et, *p*-$MeOC_6H_2CH_2$, *p*-$ClC_6H_2CH_2$



DHQB

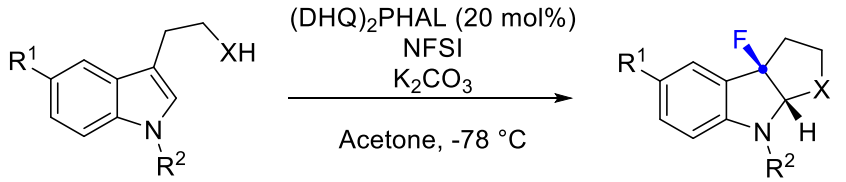
Many of the most effective published enantioselective fluorination protocols require formation of a **nucleophilic chiral enolate equivalent/activated starting materials**.
The **catalytic** generation of a chiral electrophile has proven quite challenging; usually a stoichiometric amount of chiral promoter is necessary to suppress the **racemic background reaction**

Shibata, N. *JACS* **2000**, *122*, 10728−10729; Cahard, D. *Synlett* **2004**, 0856−0860; Gouverneur, V. *ACIE* **2003**, *42*, 3291−3294; Togni, A. *ACIE* **2000**, *39*, 4359-4362; Jorgensen, K.A. *ACIE*, **2005**, *44*, 3703-3706; Shibata, N. *J. Fluorine Chem.* **2006**, *127*, 548−551

Content

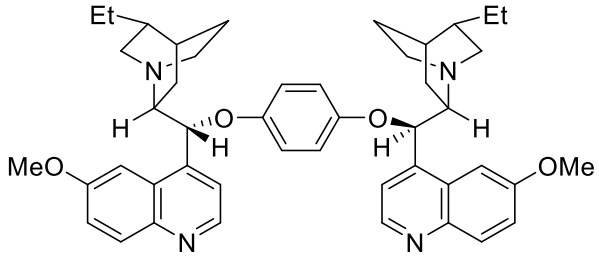
Cinchona alkaloids

1. Fluorocyclization of indoles – 1st example of enantioselective fluorocyclization

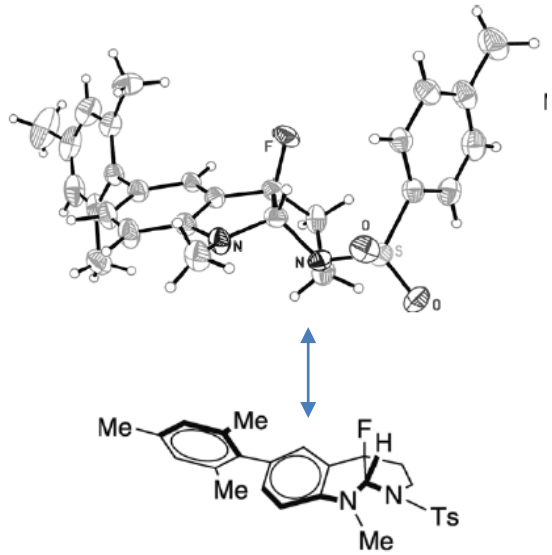


X = O, NHTs, NHCOOMe

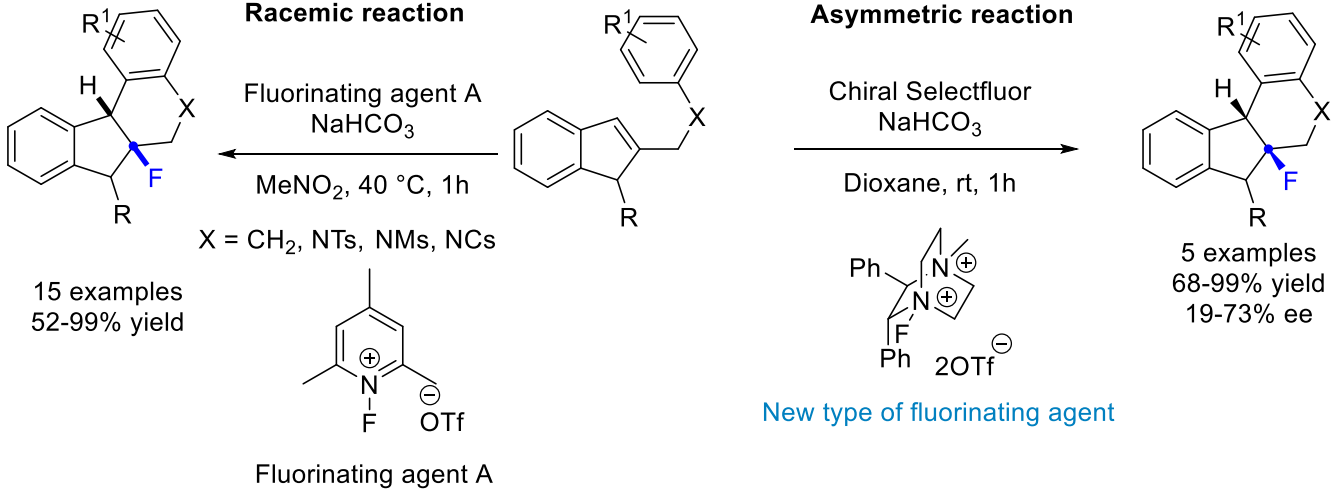
23 examples
33-95% yield
52-84% ee
X-ray structure



$(DHQ)_2PHAL$



2. Fluorocyclization of prochiral polyenes



15 examples
52-99% yield

Fluorinating agent A

New type of fluorinating agent

5 examples
68-99% yield
19-73% ee

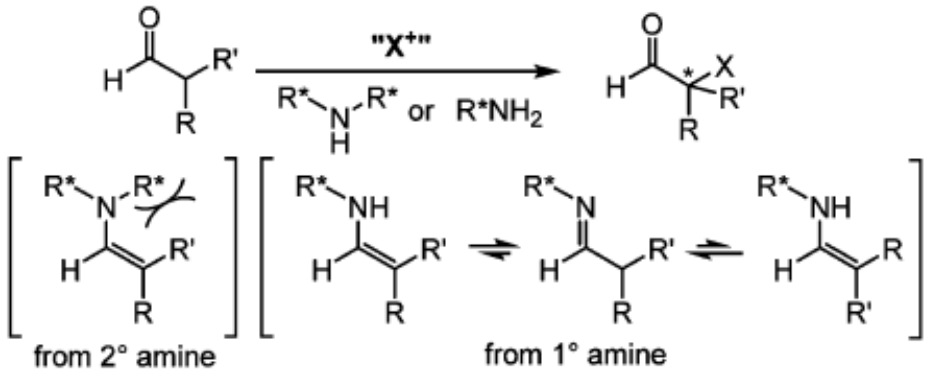
Syn – diastereoisomers – confirmed by NMR

Gouverneur, V. *ACIE.* **2011**, *50*, 8105-8109; *ACIE.* **2013**, *52*, 9796-9800

Primary Amine Catalysis

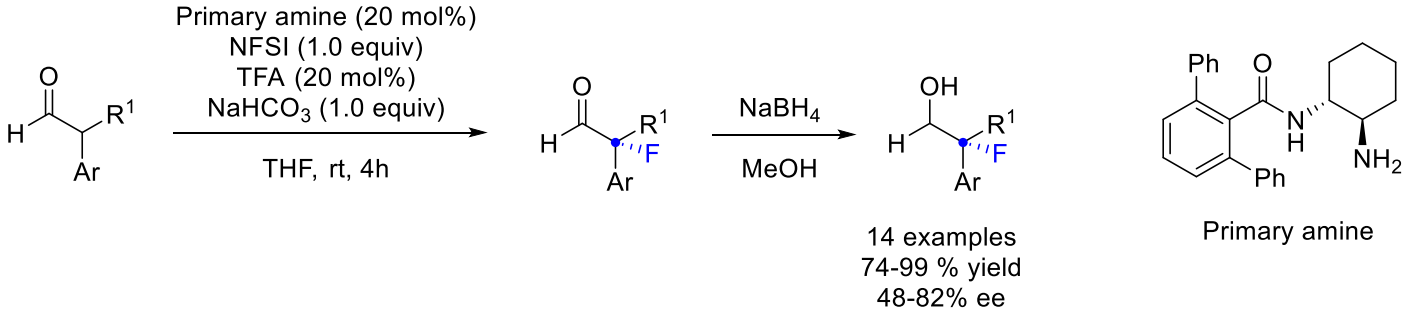
1. α-Fluorinations of Branched Aldehydes

Before 2015 – 2 examples with moderate yields and ee

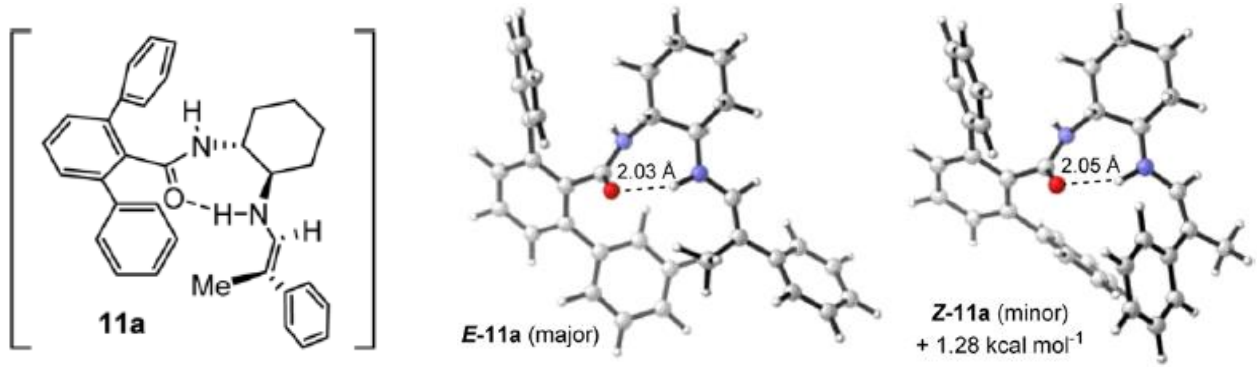


Secondary amines are ineffective catalysts due to the steric hindrance and primary amines suffers from the formation of E and Z isomers.

Jacobsen, 2015



Substituted arylpropionaldehyde derivatives undergo α-fluorination with consistent results. α,α- dialkyl branched aldehydes afforded products with significantly lower ee.



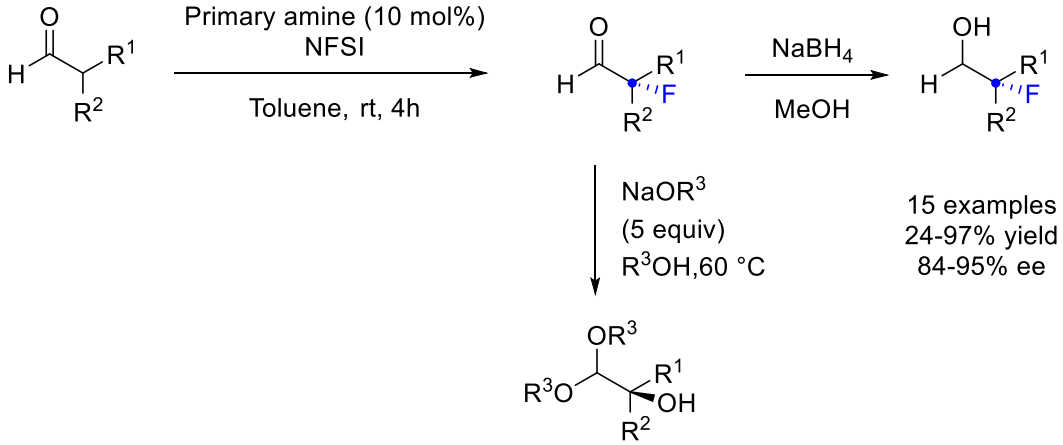
The stereochemical analysis raises the possibility that enantioselectivity is dictated primarily by the E/Z ratio of the enamine intermediates.

Jacobsen, E.N. *Org.Lett* **2015**, *17*, 2772-2775

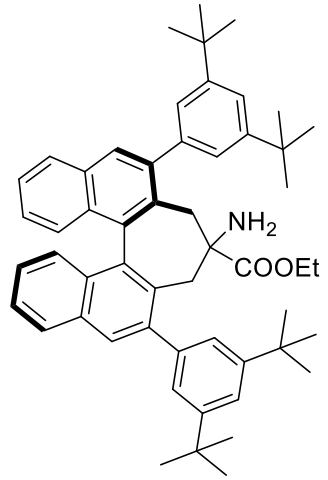
Primary Amine Catalysis

2. α-Fluorinations of Branched Aldehydes

Iwasa

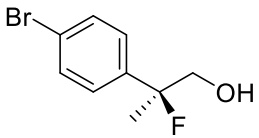


Stereospecific process

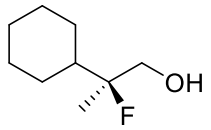


Primary amine

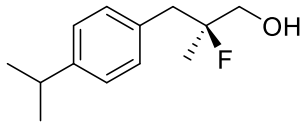
Various α-alkyl-α-aryl aldehydes were successfully fluorinated to afford the corresponding α-fluoroaldehydes in high yields with high ee. The reaction with α,α-dialkyl aldehydes yielded the products with worse results.



97% yield
92% ee



24% yield
83% ee



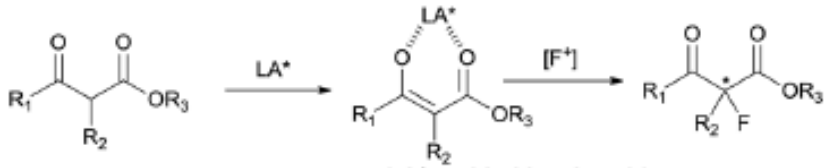
59% yield
14% ee

Iwasa, S. *Chem.Sci.* **2016**, *7*, 1388-1392

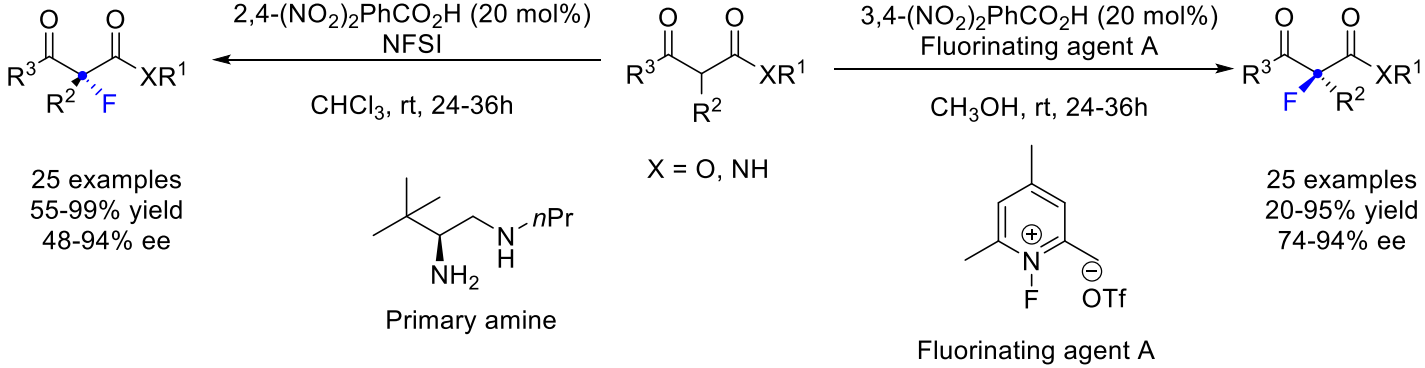
Primary Amine Catalysis

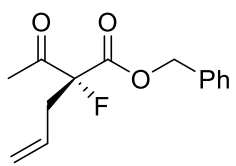
3. α-Fluorinations of acyclic ketones

I. Lewis-acid-catalyzed asymmetric fluorination of acyclic β-ketoesters [5]

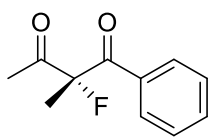


• Only when R_3 = *t*-Bu, with high *ee*

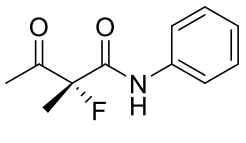




88% yield
92% ee



99% yield
53% ee

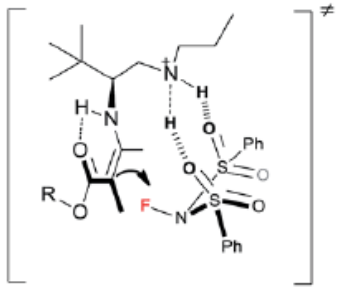


95% yield
62% ee

β-ketoesters – 18 examples, high yields and ee
1,3-dicarbonyls – 1 example, good reactivity, moderate ee
β-ketoamides – 7 examples, good yields and good to moderate ee

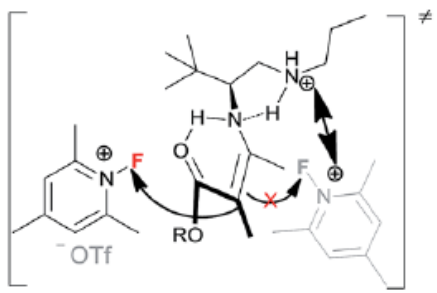
(a) Proposed transition states

I: H-bonding Mode



***R*-selective**
H-bonding guided *Re*-facial attack

II: Electrostatic repulsion Mode

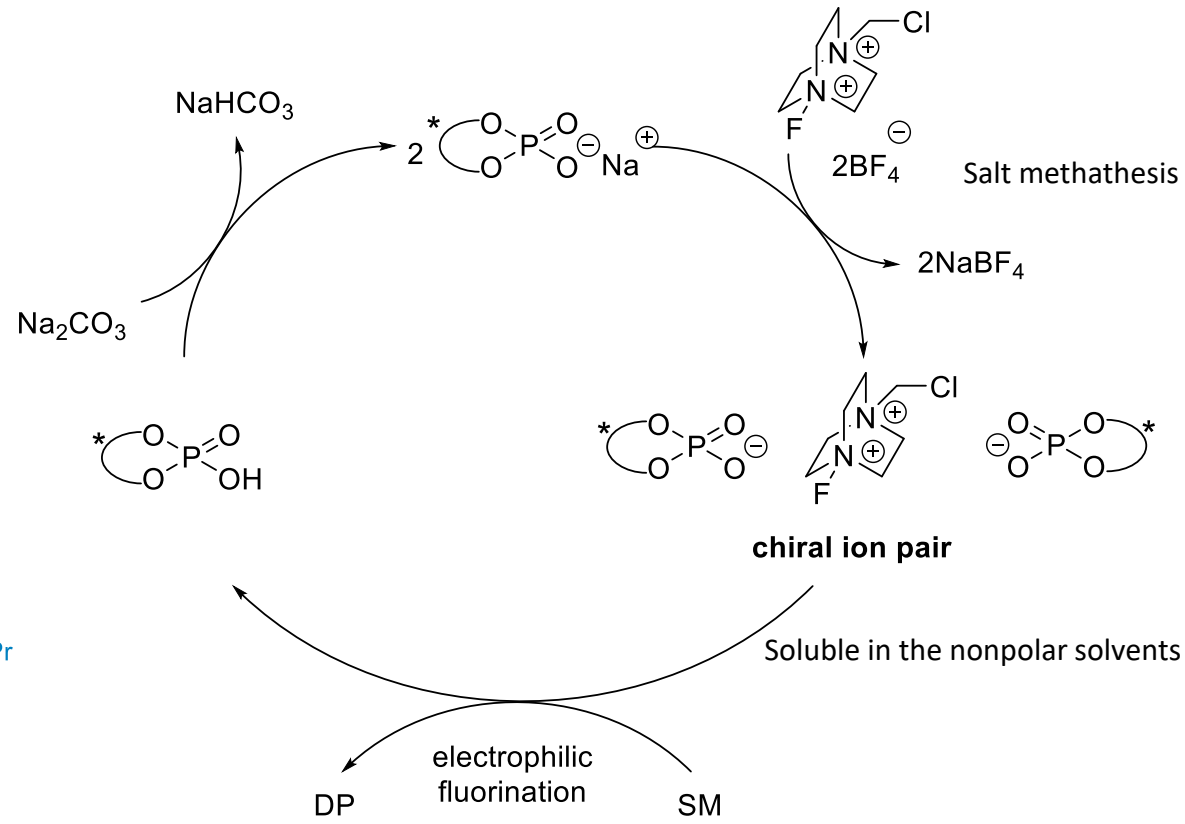


***S*-selective**
Electrostatic repulsion pushed *Si*-facial attack

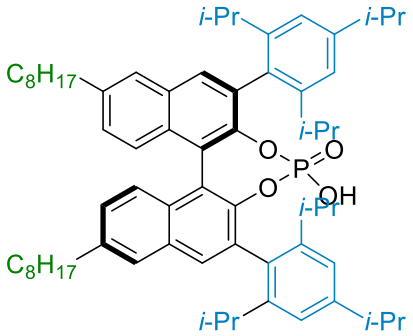
Anionic Phase-Transfer Catalysis

The use of chiral cation salts as phase-transfer catalysts for anionic reagents has enabled a vast set of enantioselective transformations.

To overcome the problem of background reaction of electrophilic fluorinating agent and starting material – Toste decided to keep low the concentration of electrophilic fluorine in organic solution by applying anionic phase –transfer catalysis



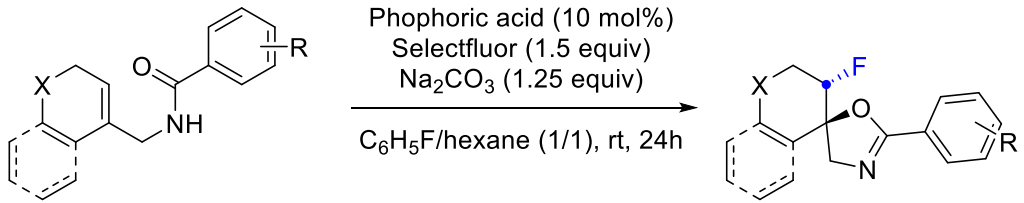
1. Lipophilic backbone phase –transfer catalyst
2. Bulky, chiral phosphonic acid
3. Selectfluor is not soluble in nonpolar solvents

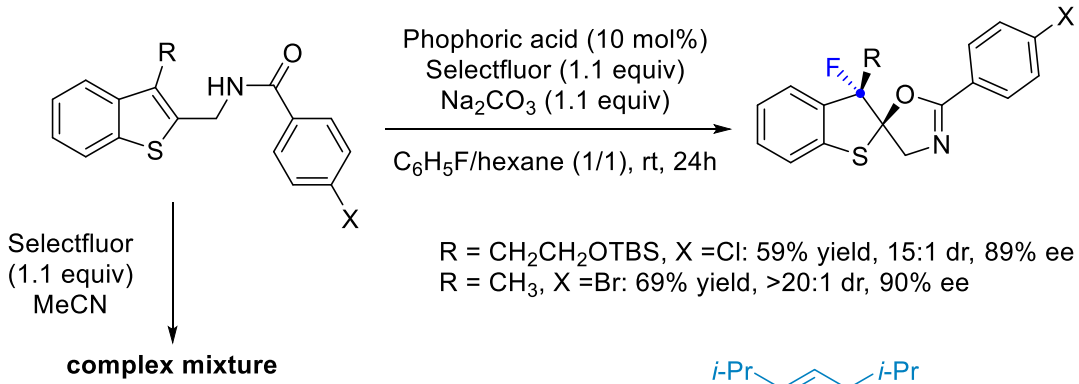


Toste, F.D. *Science* **2011**, *334*, 1681-1684

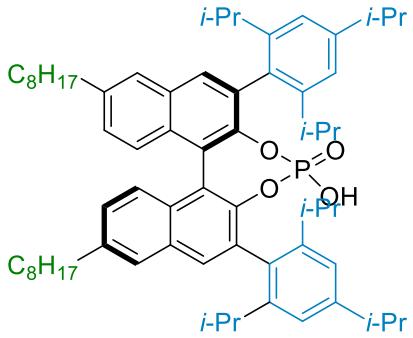
Anionic Phase-Transfer Catalysis

1. Fluorocyclization of olefins

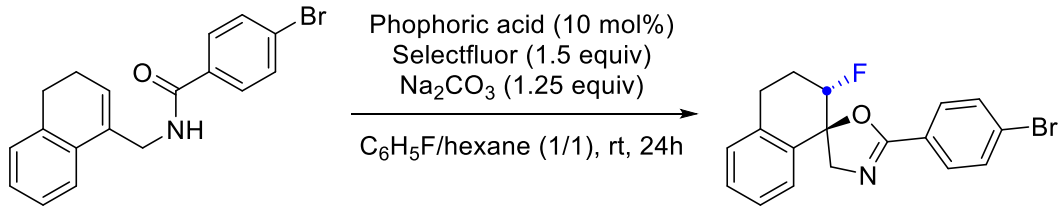


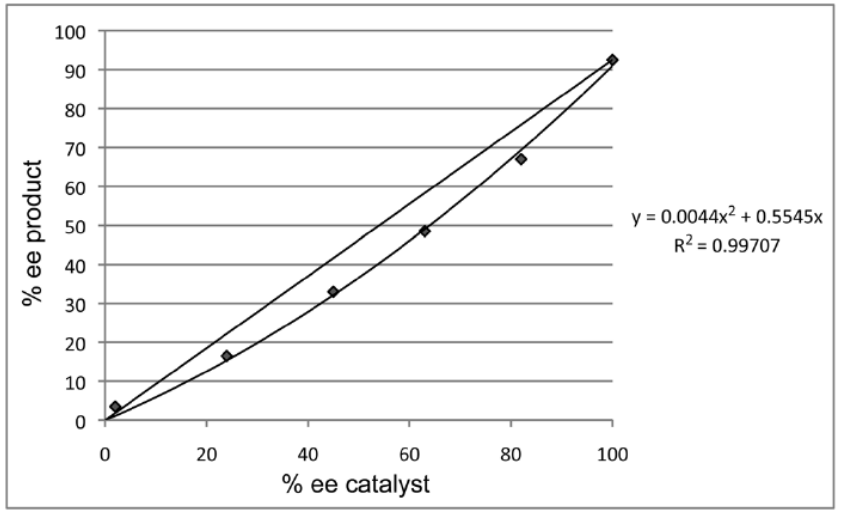


R = CH_2CH_2OTBS, X =Cl: 59% yield, 15:1 dr, 89% ee
R = CH_3, X =Br: 69% yield, >20:1 dr, 90% ee



Phosphoric acid





A nonlinear effect was observed, supporting a pathway in which both BF_4 anions are exchanged for chiral phosphates before the reaction with substrate.

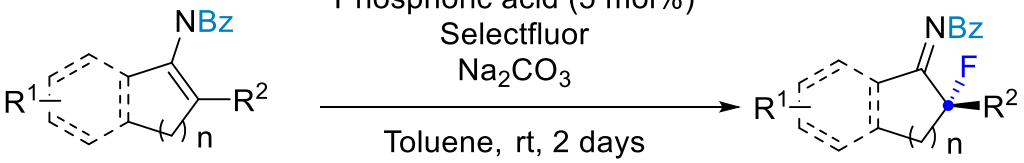
Toste, F.D. *Science* **2011**, *334*, 1681-1684

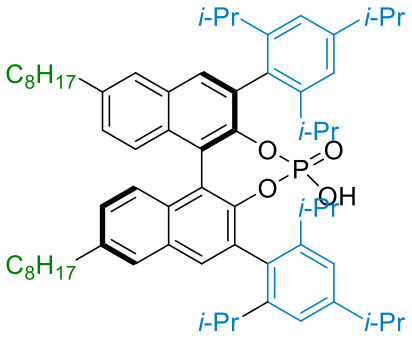
Anionic Phase-Transfer Catalysis

2. Fluorination of Enamides

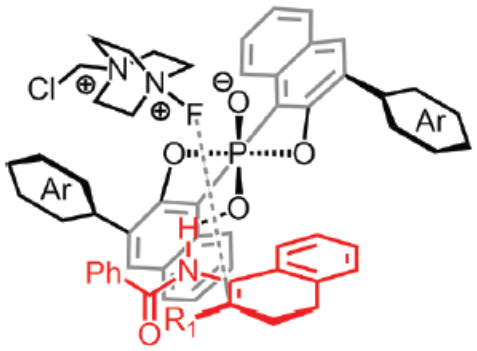
Asymmetric synthesis of β-fluoroamine

- Enantioselective fluorination of ketones and aldehydes
- Desymmetrization of fluoro-containing compounds

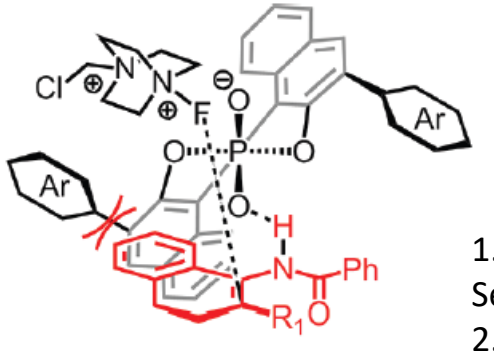




Phosphoric acid

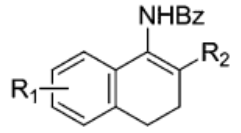
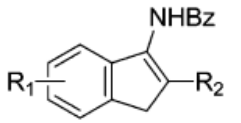
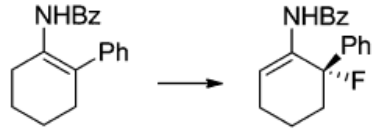


favored



disfavored

1. an ion pair with the Selectfluor reagent
2. activating the enamide through hydrogen bonding

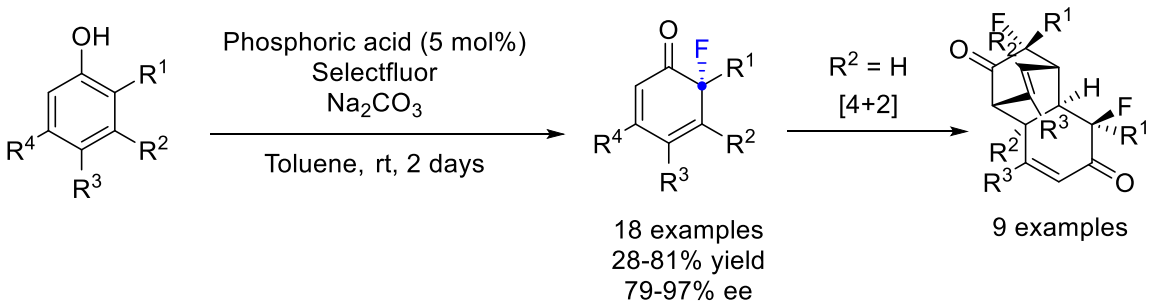
Entry	Substrate **1**	R_1	R_2	Product	% yield **2**[a]	%ee **2**[b,c]
1		H	Me	**2d**	88	96
2[d]		H	Allyl	**2e**	80	96
3		H	Bn	**2f**	92	99
4[e]		6-OMe	Me	**2g**	94	92
5		H	Me	**2h**	66	96
6[d,f]		H	Ph	**2i**	79	90
7		H	Bn	**2j**	84	98
8		5-OMe	Bn	**2k**	68	96
9[g]		5-F	Bn	**2l**	75	94
10[d]		5-Cl	Bn	**2m**	85	93
11		H	(3-OMe)Bn	**2n**	83	98
12[h]				**2o**	58	87

Toste, F.D. *JACS* **2012**, *134*, 8376-8379

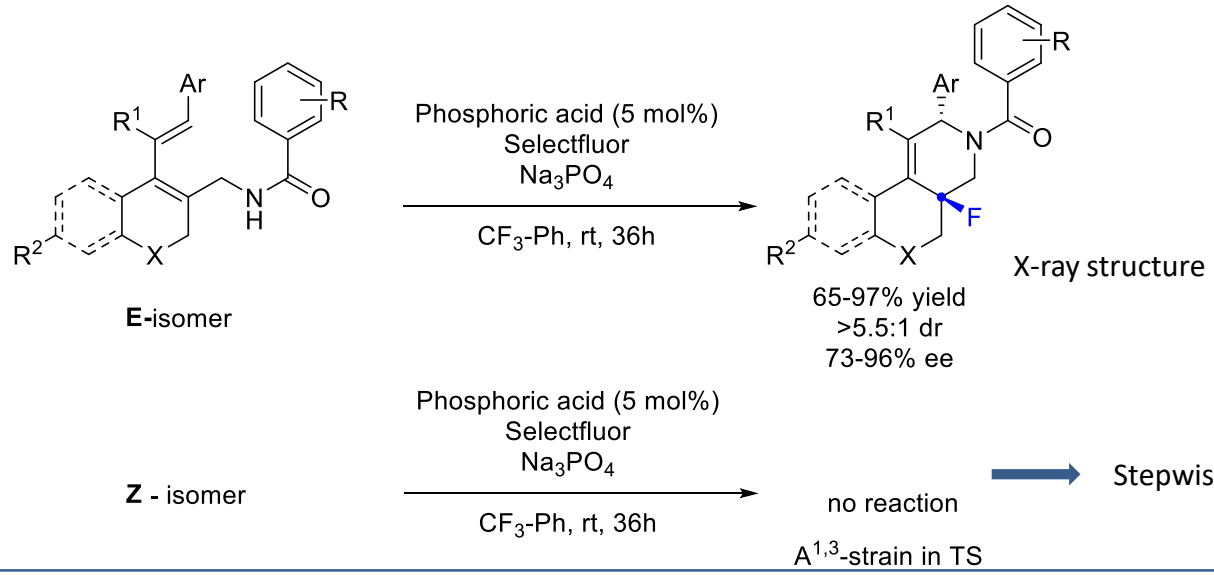
Anionic Phase-Transfer Catalysis

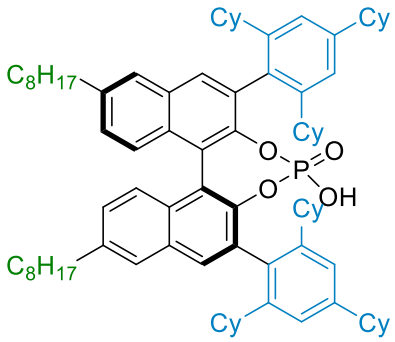
3. Dearomatization of phenols

Direct asymmetric dearomatization through discrimination between the enantiotopic faces of the arene



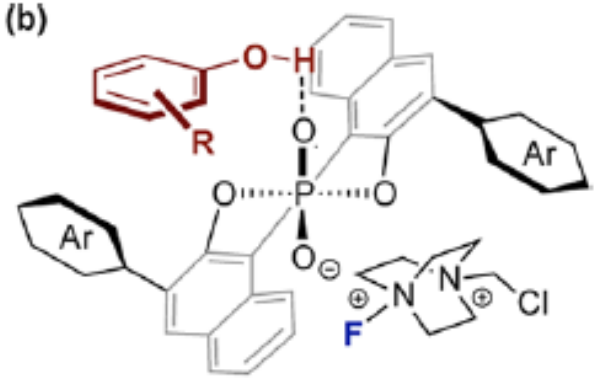
4. Aminofluorination: 1,4-Addition to Conjugated Dienes



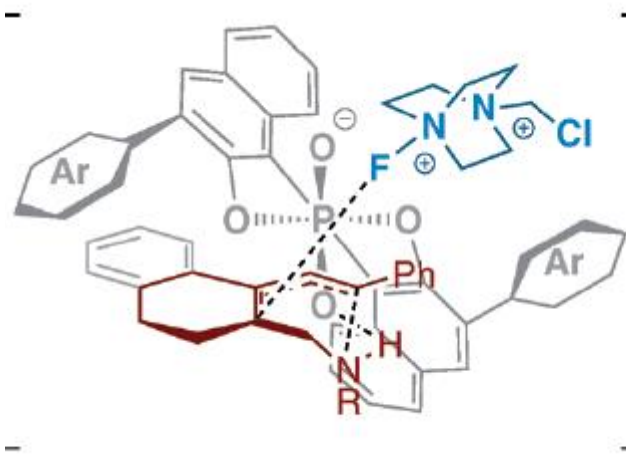


Phosphoric acid

(b)



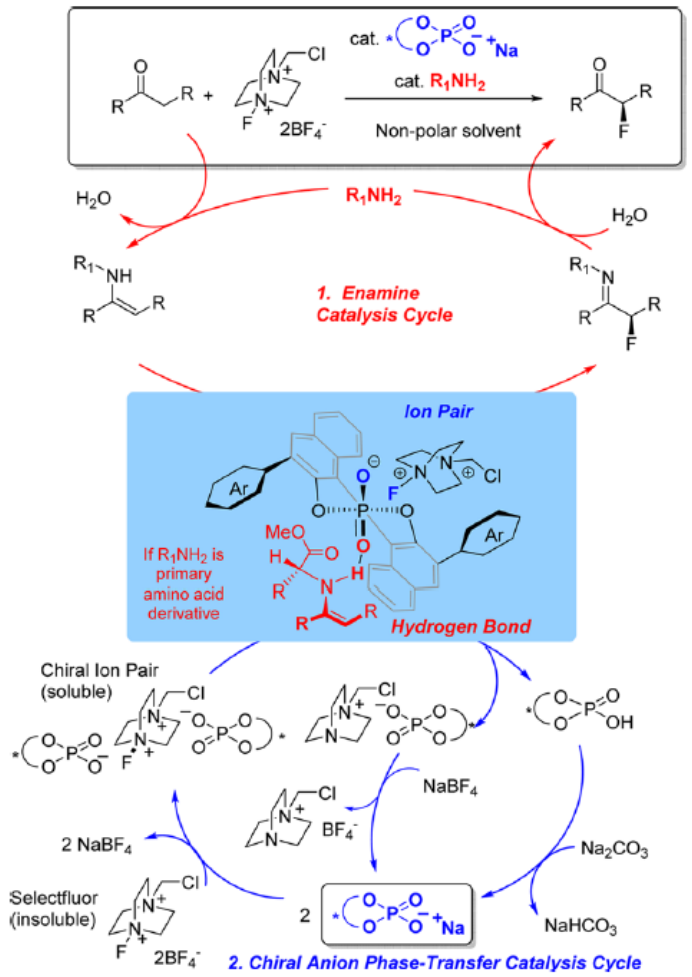
Interaction of non-symmetrical phenol with catalyst may allow face-selective fluorinative dearomatization

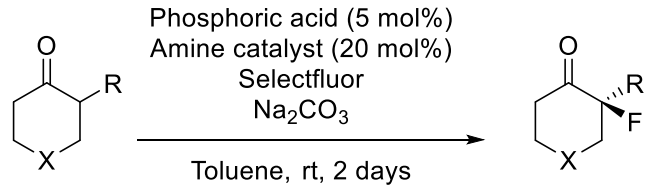


Toste, F.D. *JACS* **2013**, *135*, 1268-1271; *ACIE* **2013**, *52*, 7724-7727

Anionic Phase-Transfer Catalysis

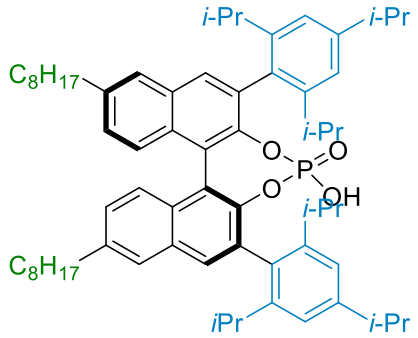
5. Fluorination of α-Branched Cyclohexanones Enabled by a Combination of Chiral Anion Phase-Transfer Catalysis and Enamine Catalysis



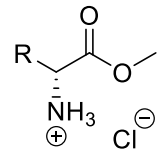


2 equiv
Excess

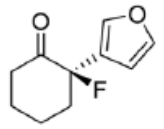
17 examples
48-86% yield
77-94% ee



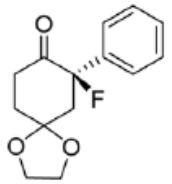
Phosphoric acid



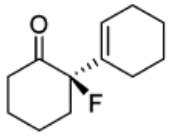
Amino acid catalyst



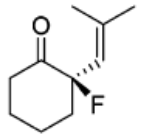
2i, with **A12**
31% (62%) yield,
89% ee



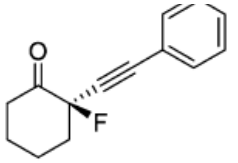
2k, with **A13**
32% (63%) yield,
92% ee



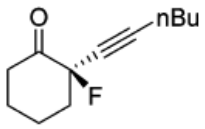
2n, with **A13**
26% (52%) yield,
86% ee



2o, with **A12**
35% (70%) yield,
85% ee



2p, with **A12**
43% (86%) yield,
78% ee

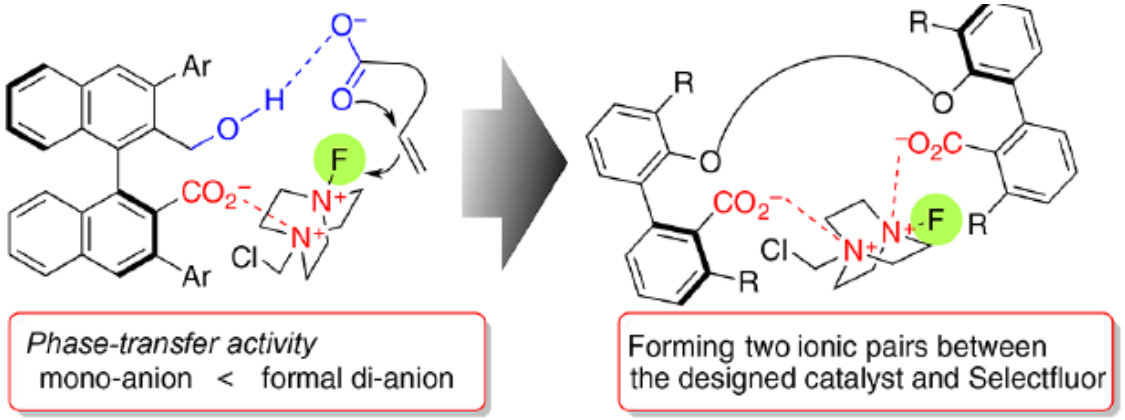


2q, with **A12**
39% (77%) yield,
77% ee

Toste, F.D. *JACS* **2014**, *136*, 5225-5228

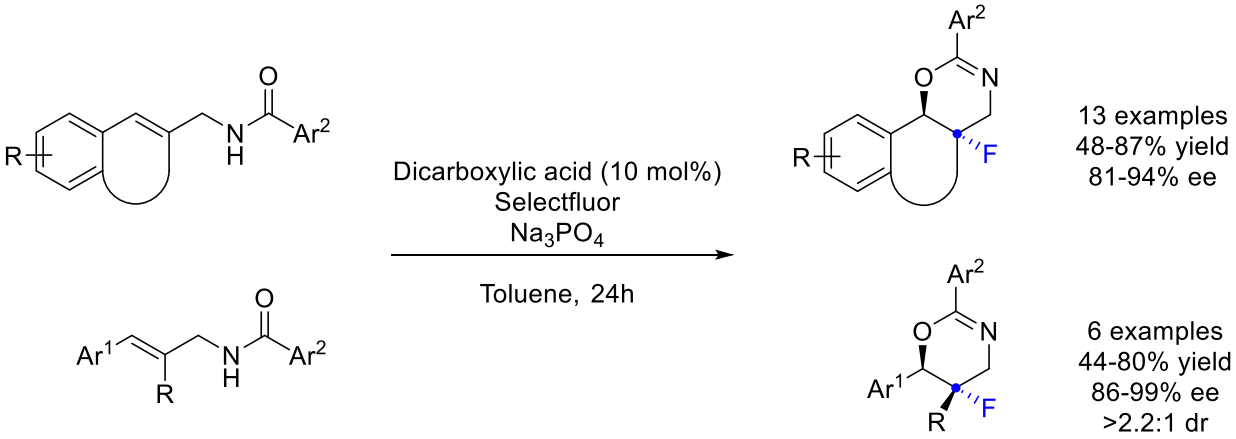
Anionic Phase-Transfer Catalysis

6. Fluocyclization with dicarboxylic chiral acids

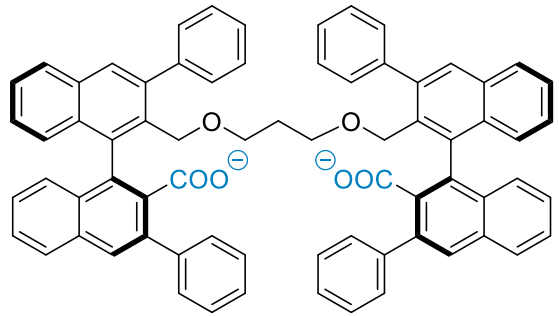


The designed catalysts are conformationally flexible, but the two-point ionic pairing of the catalyst with Selectfluor would form a well-defined chiral environment.

Enantioselective fluorocyclization of allylic amides



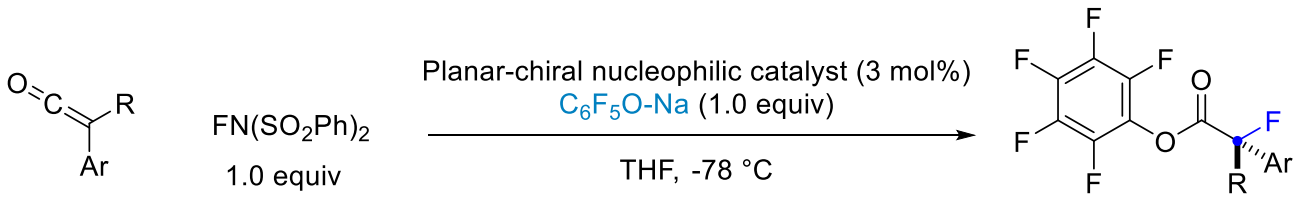
Mosher's ester method



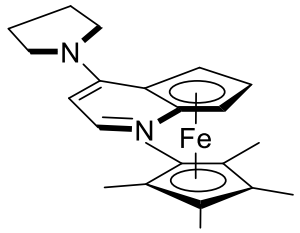
Dicarboxylic acid

Planar-chiral nucleophilic catalysis

1. α-Fluorination of Ketenes

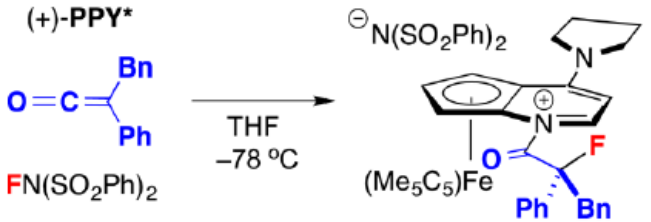


11 examples
86-98% yield
78-99% ee

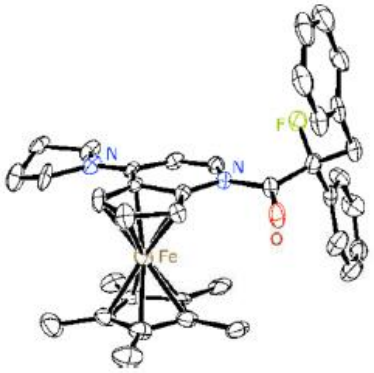


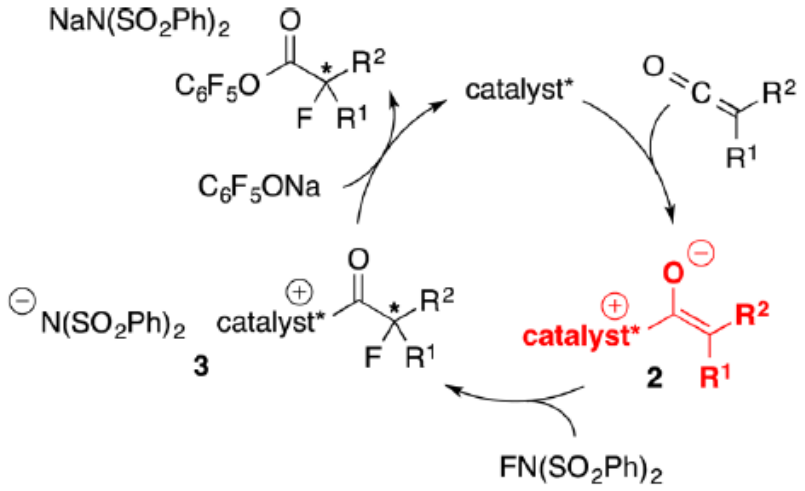
Planar-chiral nucleophilic catalyst
(-)-PPY

entry	Ar	R	ee (%)	yield (%)[b]
1	Ph	Et	99	98
2	Ph	Me	98	92
3	Ph	*i*-Bu	95	95
4	Ph	Bn	78	96
5[c]	Ph	cyclopentyl	80	84
6	4-ClC$_6$H$_4$	Et	97	86
7	4-MeC$_6$H$_4$	Et	97	92
8	4-(OMe)C$_6$H$_4$	Et	97	91
9	3-MeC$_6$H$_4$	Et	97	97
10	2-naphthyl	Et	94	89
11	3-thiophenyl	*i*-Bu	98	94



N-acylated
intermediate

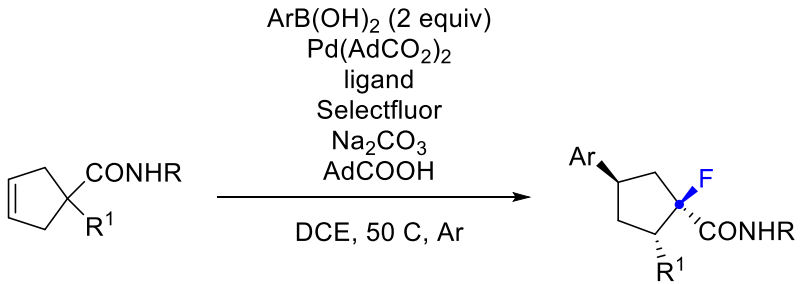




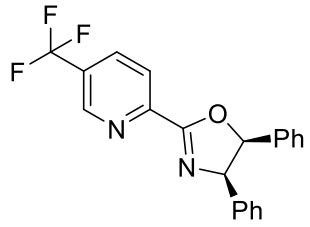
Fu, G.C. *JACS* **2014**, *136*, 8899-8902

Transition-metal catalyzed transformations

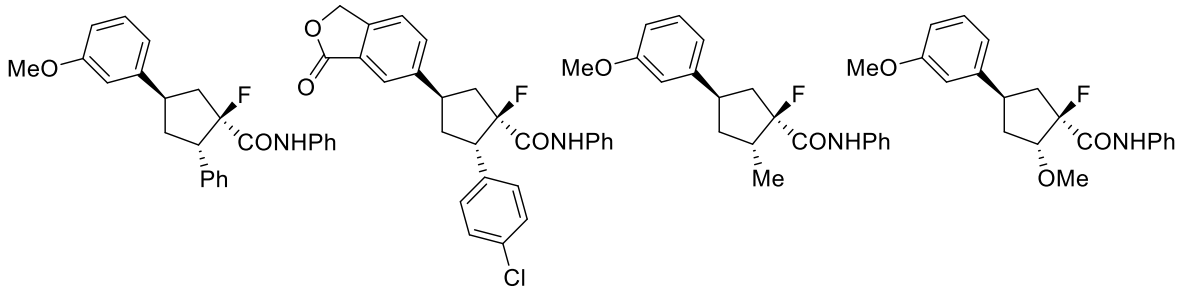
1. Dyotropic rearrengement with Pd(IV)



26 examples
27-72% yield
74-95% ee



Ligand

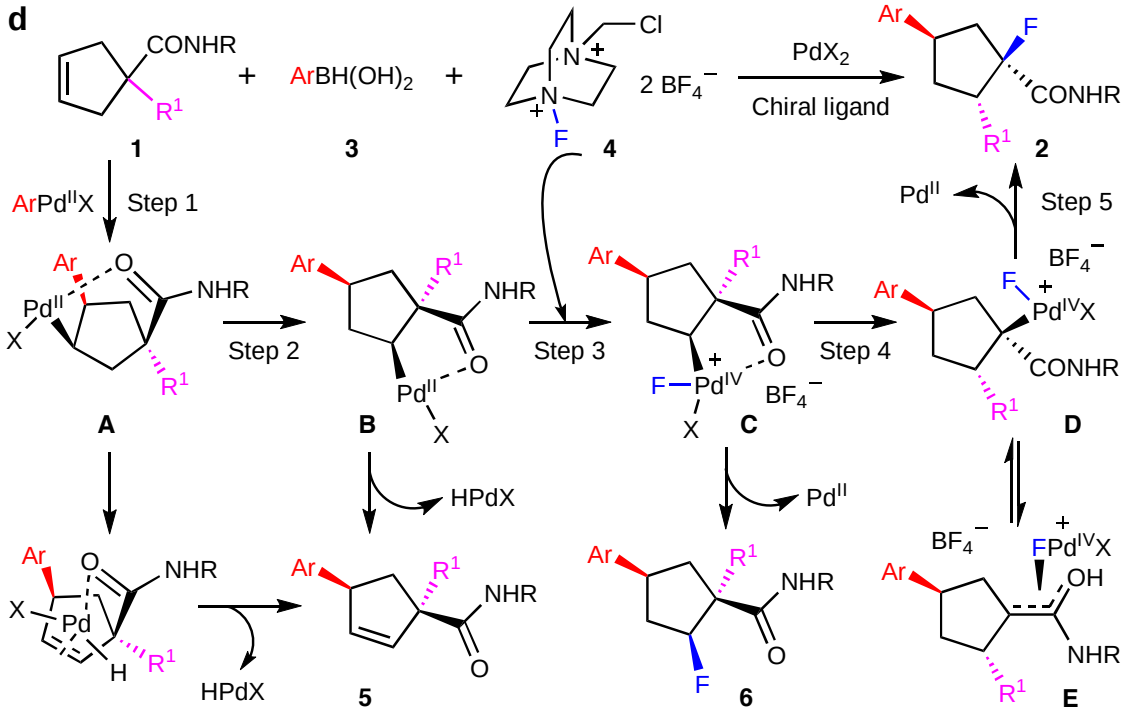


70% yield
92% ee

51% yield
89% ee

27% yield
95% ee

26% yield
80% ee



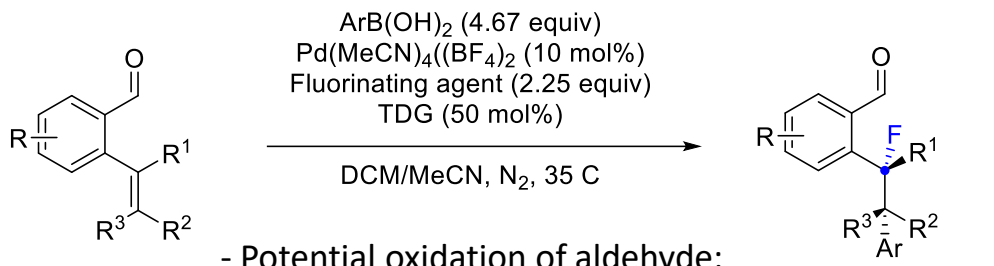
(1) the β-hydride elimination of intermediates **A** and **B** to alkene **5**;
(2) the premature oxidation of Pd(ii) intermediate **A;**
(3) C(*sp*3)–F reductive elimination of Pd(iv) species **C** (isolated)**.**

The whole catalytic process would create three stereocentres including one quaternary C–F bond from a prochiral substrate, the whole sequence would be diastereoselective if the initial carbopalladation be effectively directed.

Zhu, J. *Nat.Chem.* **2021**, *13*, 671-676

Transition-metal catalyzed transformations

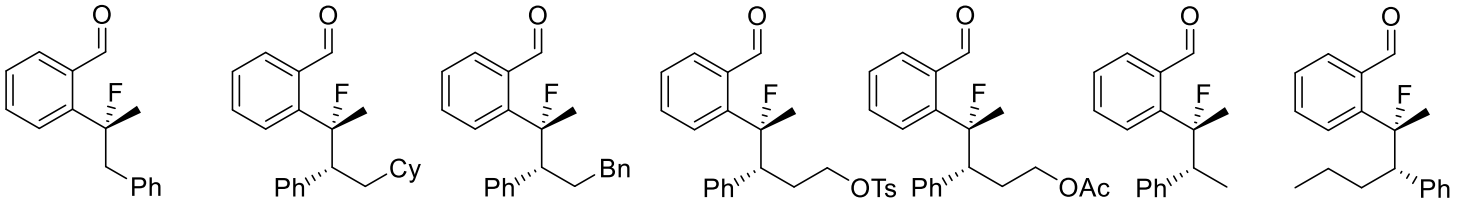
2. Transient directing group arylfluorination

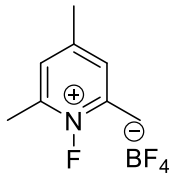


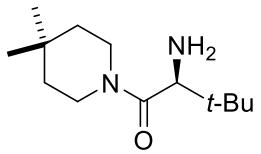
- Potential oxidation of aldehyde;
- Homocoupling of boronic acid;
- Interactions of F(+) with TDG.

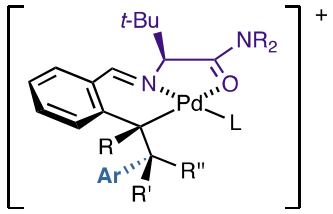
R^1 = H, 29 examples
91-99% ee

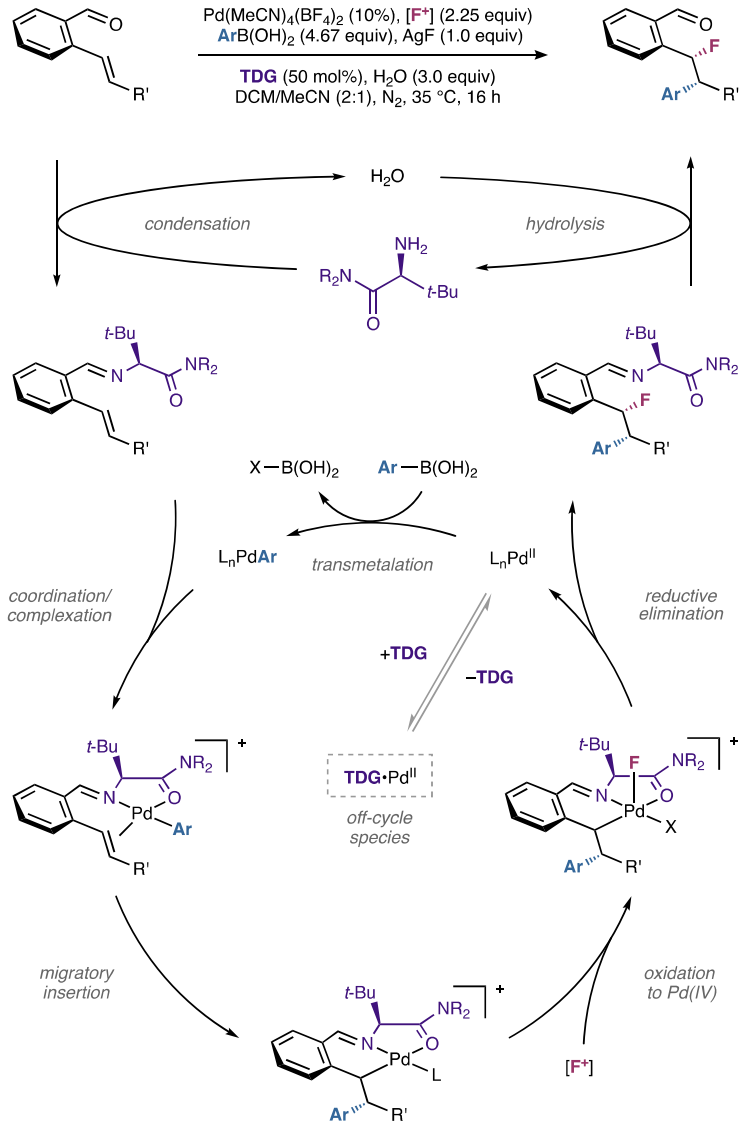
Design of experiments (DoE)




Fluorinating agent A


TDG


TDG-stabilized Pd



Engle, K.M *JACS.* **2021**, *143*, 8962-8969

Conclusion

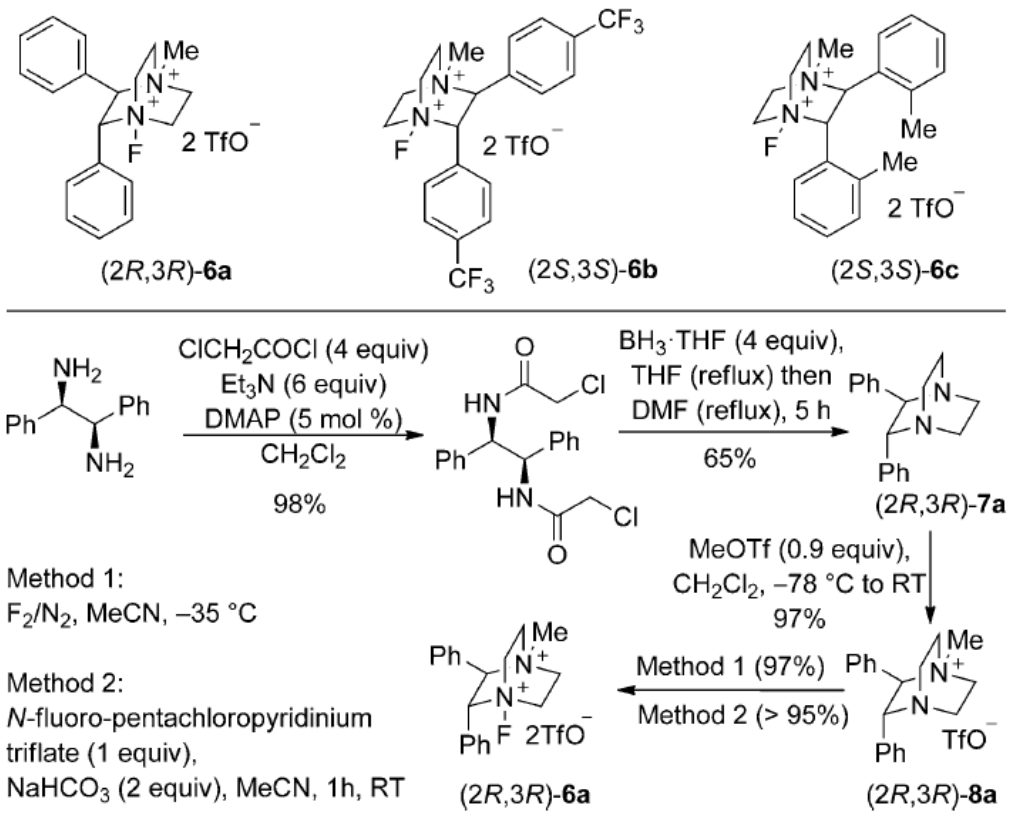
- Enantioselective formation of carbon-fluorine bond has become a field of great interest, due to the beneficial pharmarcokinetic properties that judiciously placed fluorine atoms can confer.

- Even though many methods have been discovered to perform such transformation with high enantioselectivity, still number catalytic transformations are still limited, especcialy in case of formation of quaternary center.

Thank you for your attention

Synthesis of chiral Selectfluor

2. Fluorocyclization of prochiral polyenes



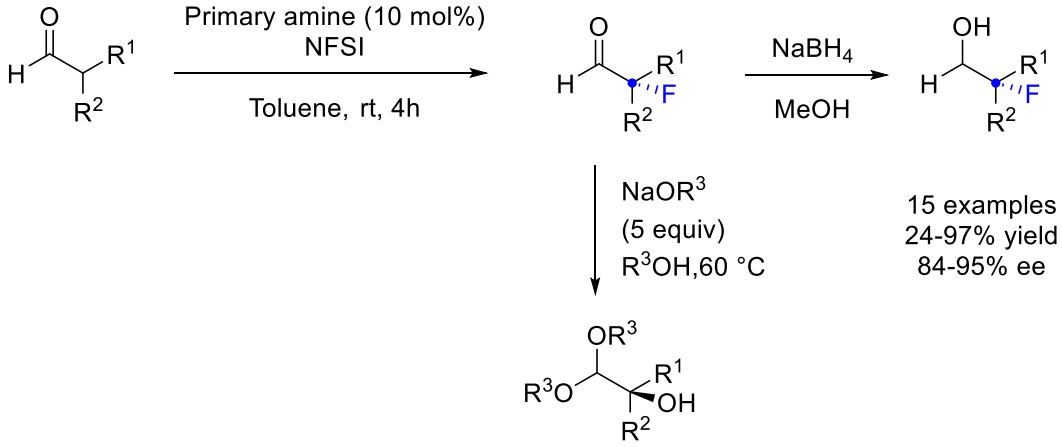
Scheme 3. Chiral reagents (2*R*,3*R*)-**6a**, (2*S*,3*S*)-**6b**, and (2*S*,3*S*)-**6c**. DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

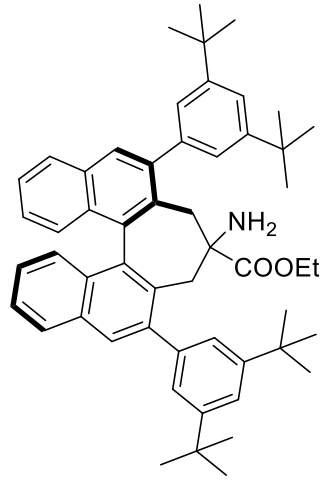
Gouverneur, V. *ACIE.* **2013**, *52*, 9796-9800

Primary Amine Catalysis

1. α-Fluorinations of Branched Aldehydes

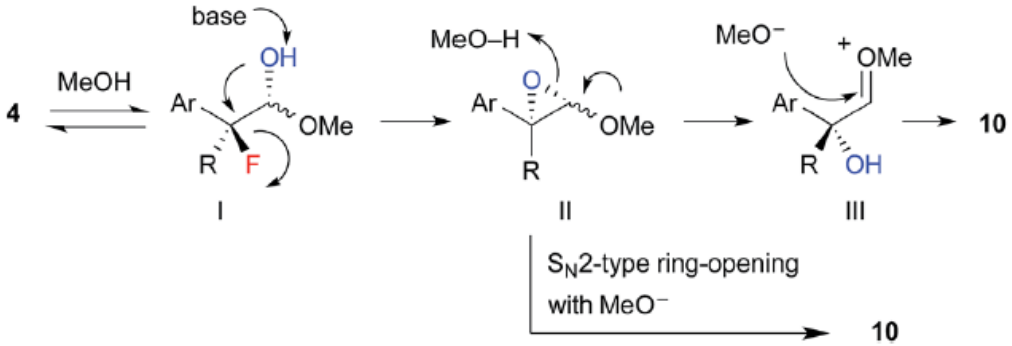
Iwasa





Primary amine

Various α-alkyl-α-aryl aldehydes were successfully fluorinated to afford the corresponding α-fluoroaldehydes in high yields with high ee.
The reaction with α, α-dialkyl aldehydes yielded the products with worse results.



Iwasa, S. *Chem.Sci.* **2016**, *7*, 1388-1392