Asymmetric Fluorination

Rob Weintraub

SED Group Meeting

June 2nd, 2009

Fluorine

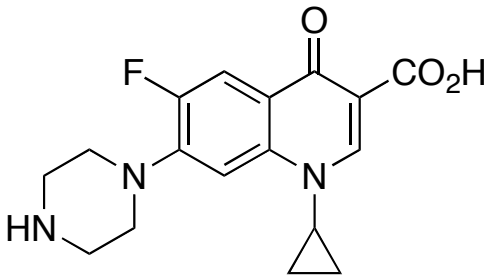
- First isolated by Henri Moissan in 1886, awarded Nobel Prize in Chemistry for work in 1906
- 13th most abundant element on Earth's crust
- Most electronegative element, only one oxidation state
- Capable of forming bonds with every element on the periodic table (except He, Ne, and Ar)
- C-F BDE 116 kcal/mol (C-H 99 kcal/mol)
- C-F bond length (1.41 Å), C-O (1.43 Å), C-H (1.1 Å)
- Fluorine van der Waals radius 1.51Å (H 1.11Å, O 1.50Å)

Why Fluorine?

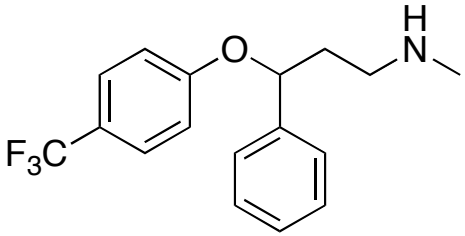
- Strengthens adjacent bonds
- Metabolically stable (incompatible with haloperoxidases)*
- Reduces the basicity of nearby amines**
- Hydrogen bond acceptor

*Kirk, K. L., *Org. Proc. Res. Dev.* **2008**, *12*, 305-321
Dolbier, W. R., *Journal of Fluorine Chemistry* **2005, *126*, 157-163

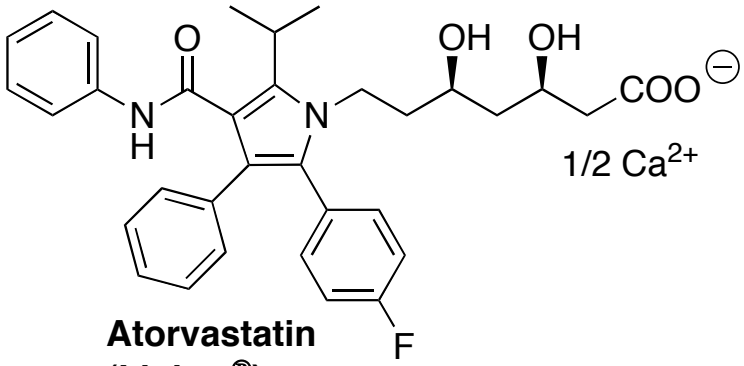
Well Known Fluorine-Containing Compounds



Ciprofloxacin (CIPRO®)

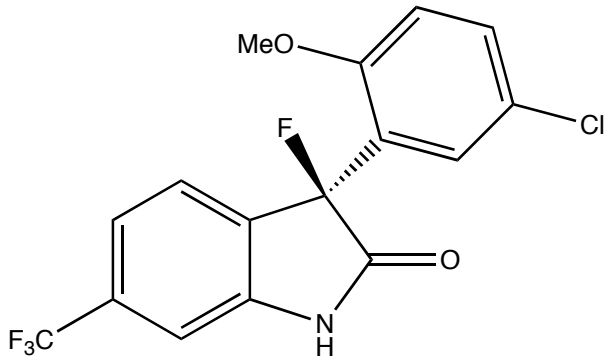


Fluoxetine (Prozac®)

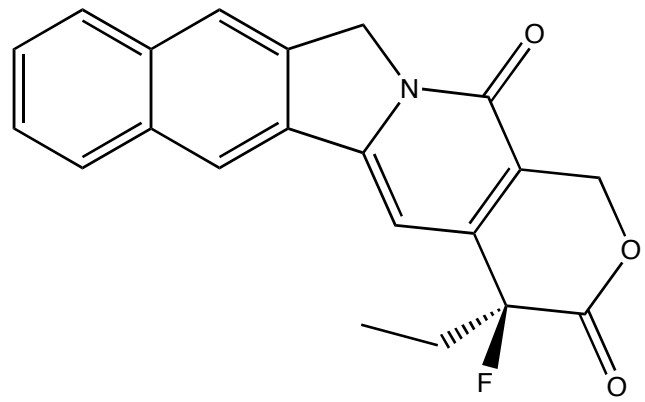


Atorvastatin (Lipitor®)

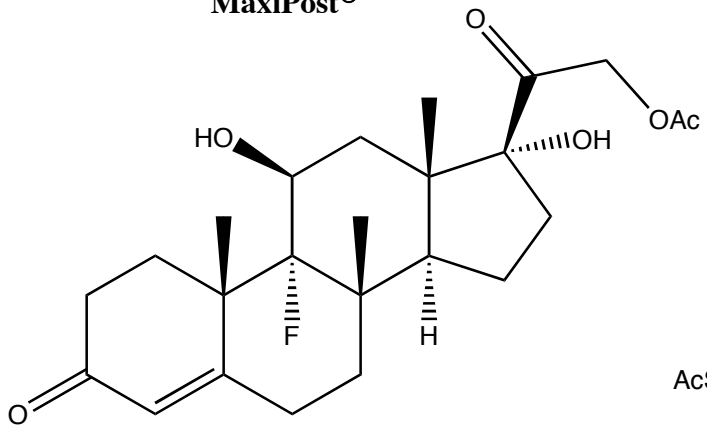
Biologically Active Compounds With Fluorine on a Stereogenic Center



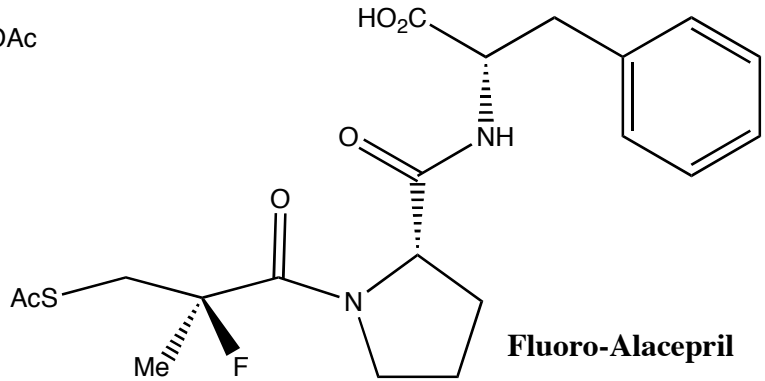
BMS-204352
MaxiPost®



20-deoxy-20-fluorocamptothecin
(20(S)-FluoroCPT)



9α-F-glucocorticoid

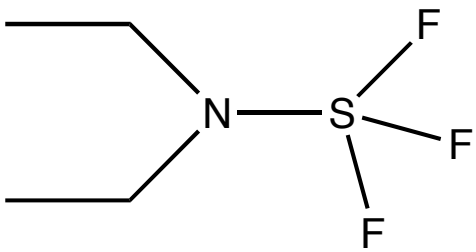


Fluoro-Alacepril

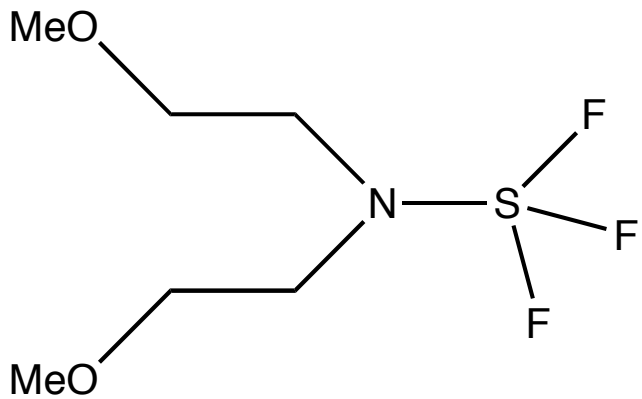
Electrophilic vs. Nucleophilic Fluoride Substitution

- Most common by electrophilic means
- Small anion
- Tight ion-pairs
- Well solvated

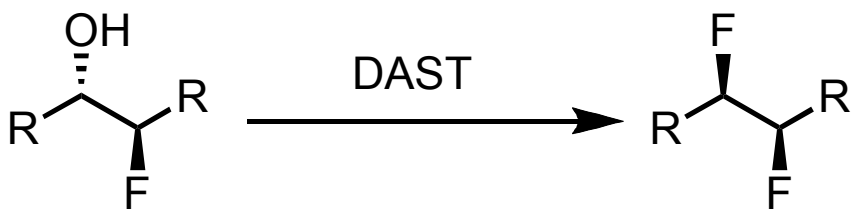
Nucleophilic Fluorinating Agents



Diethylaminosulfur trifluoride (DAST)



Deoxofluor



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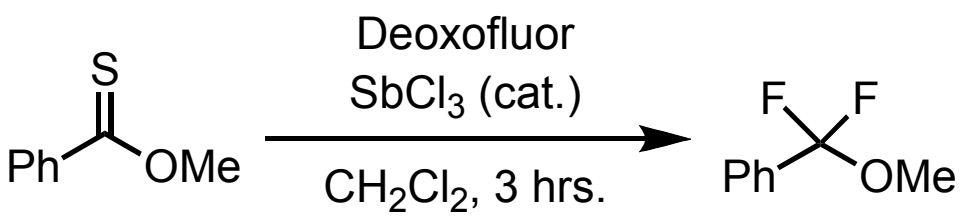
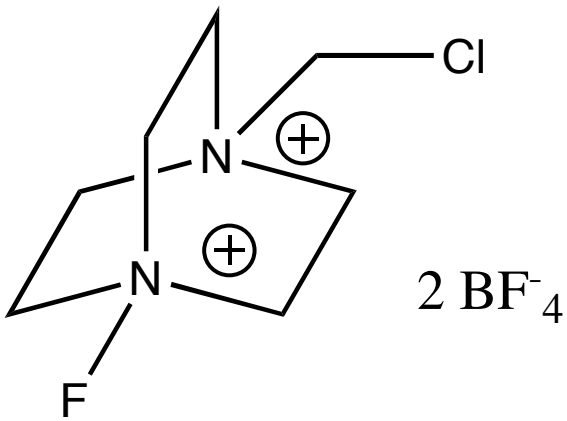


2

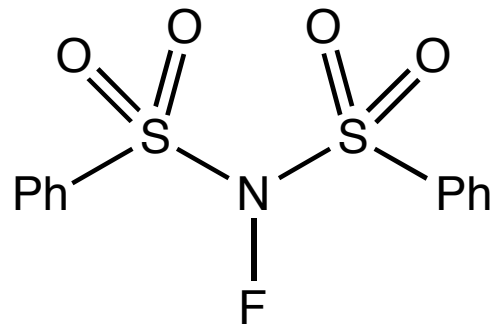
[1]Schlosser et al., *Tetrahedron* **1988**, *44*, 2875-2881

[2]Lal et al., *J. Org. Chem.* **1999**, *64*, 7048-7054

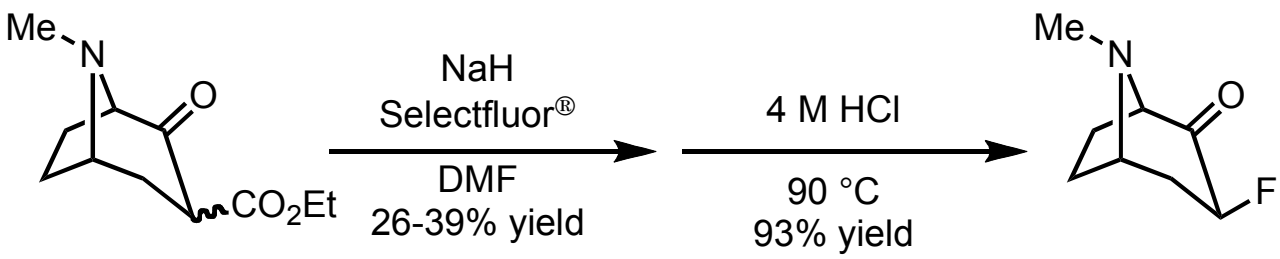
Electrophilic N-F Fluorinating Agents



Selectfluor®

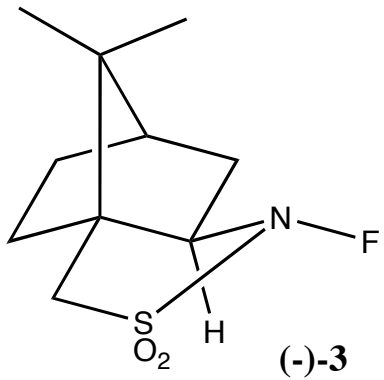


N-fluorodibenzenesulfonimde (NFSI)

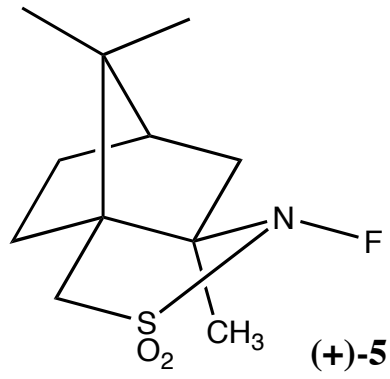


Denmark, S. E.; Matsuhashi, H., *J. Org. Chem.* **2002**, *67*, 3479-3486

First examples of Enantioselection

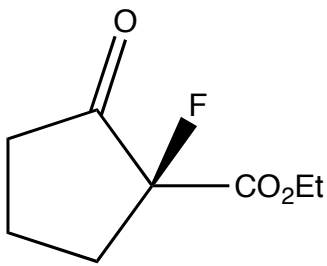


(-)-3



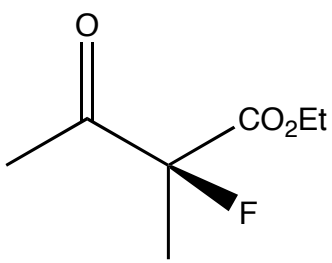
(+)-5

- NaH, KH, and LDA as bases
- Et_2O, THF, and toluene as solvents



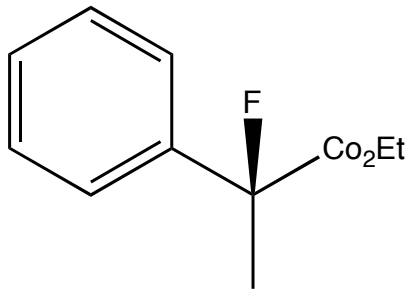
(-)-3

70 %ee, 60% yield



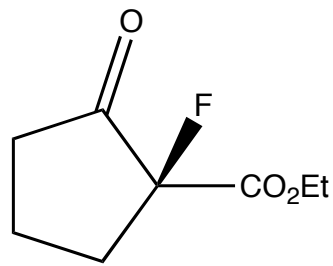
(-)-3

≤10 %ee, 31% yield



(-)-3

35 %ee, 27% yield



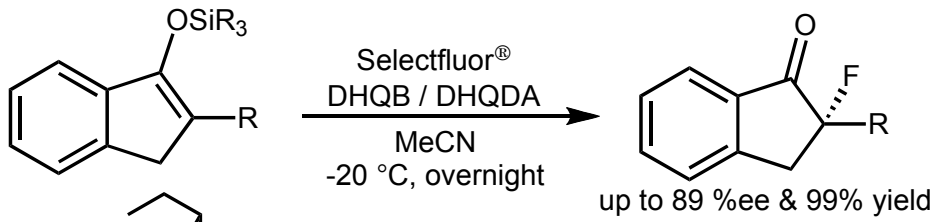
(+)-5

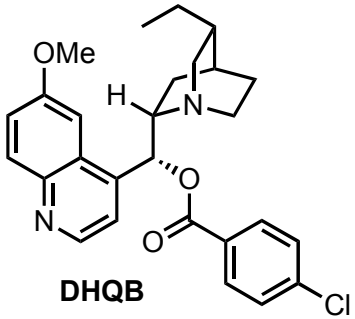
≤10 %ee, <5%yield

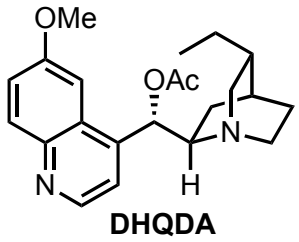
Lang, R. W.; Differding, E., *Tet. Lett.* **1988**, *29(47)*, 6087-6090

Enantioselective Fluorination with Cinchona alkaloids/Selectfluor® Combinations

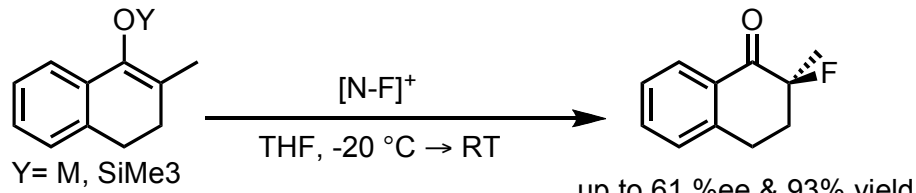
Takeuchi et. al.

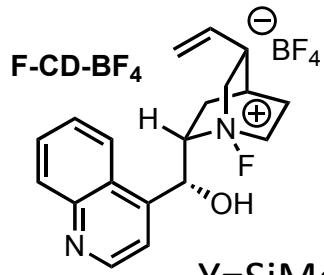






Cahard et. al.



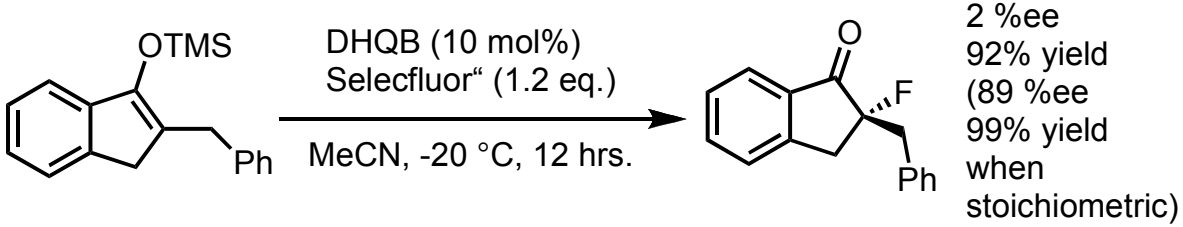


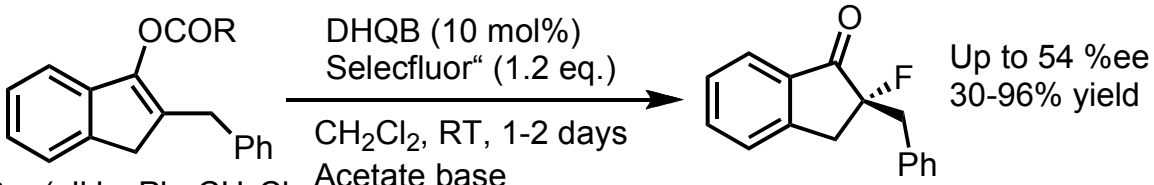
Y=$SiMe_3$, NaOH was added, improved yield and selectivity

Takeuchi et al., *J. Am. Chem. Soc.* **2000**, *122*, 10728-10729

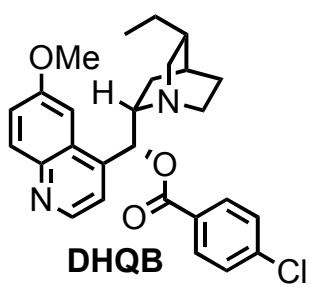
Cahard et al., *Org. Lett.* ***2000***, 2, *3699-3701*

Catalytic Enantioselective Fluorination in Cinchona/Selectfluor® Systems





R = (alkly, Ph, CH_2Cl_2 OEt, CF_3)

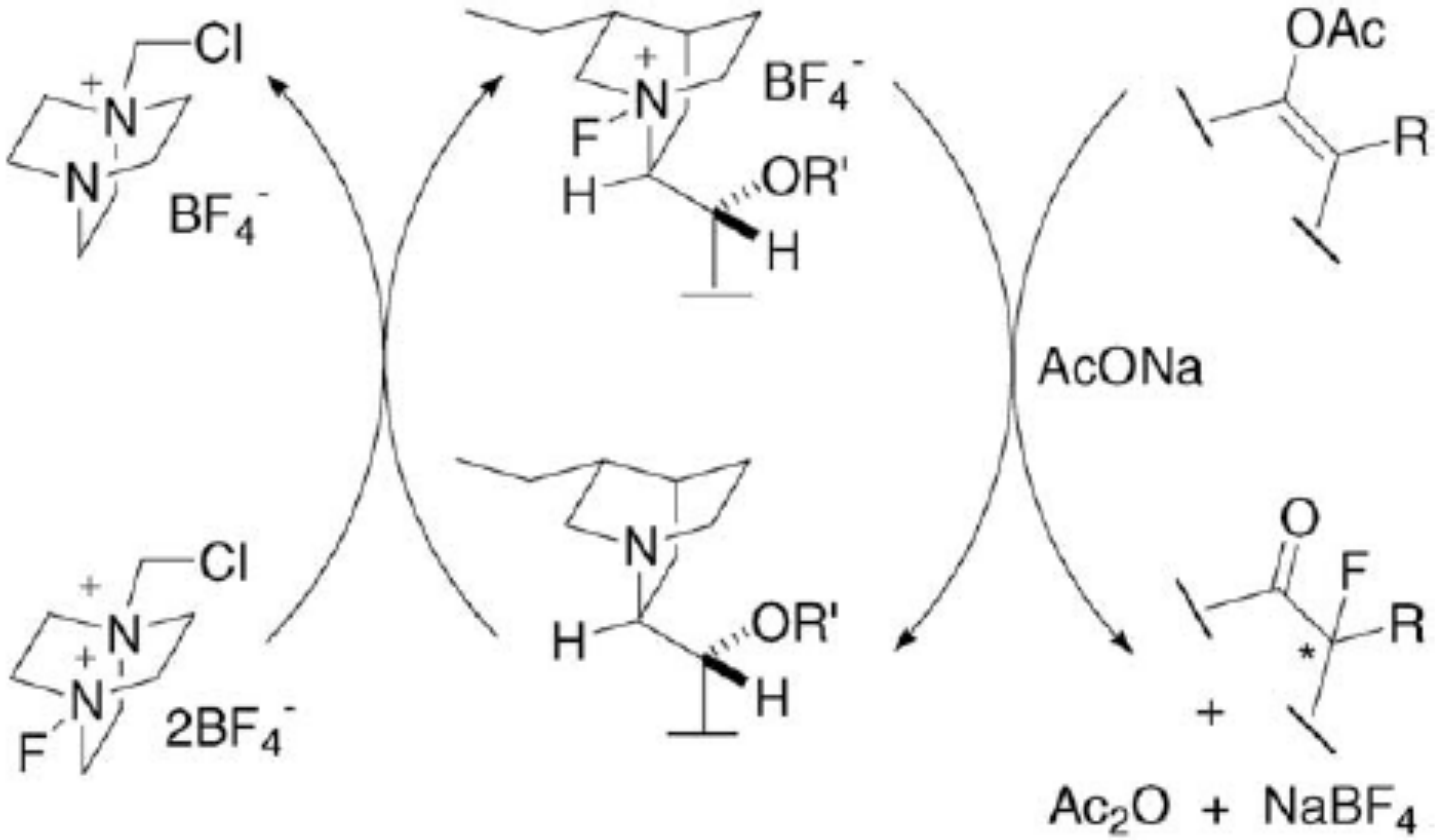


DHQB

- Acetate bases (NaOAc, NH_4OAc, etc.) needed to activate acetly enol ethers
- Selectfluor® insoluble in CH_2Cl_2
- Opposite enantiomer when R = CF_3 (18 %ee)

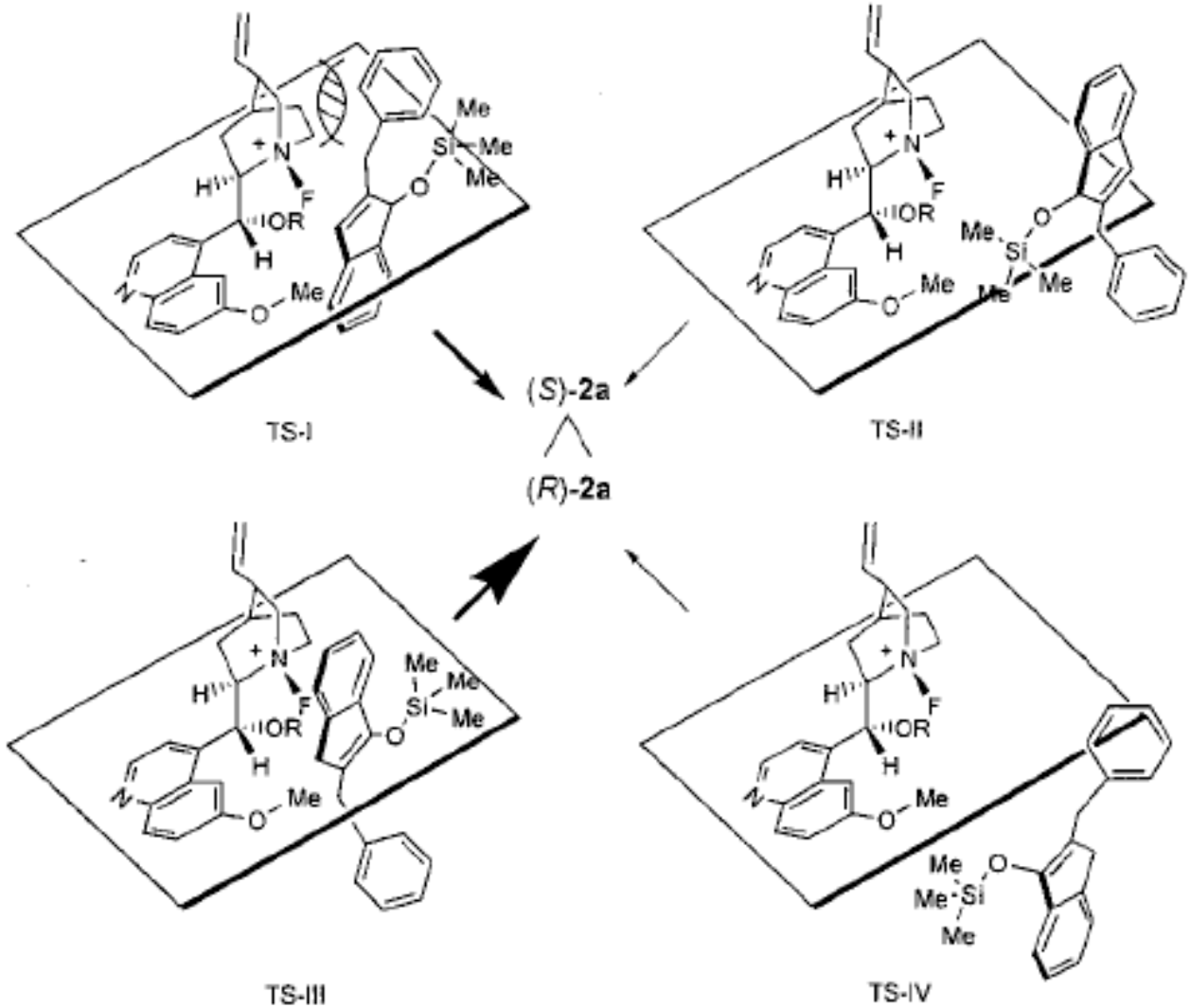
Toru et al., *Journal of Fluorine Chemistry* **2006**, *127*, 548-551

Proposed Catalyst Turnover Cycle



Toru et al., *Journal of Fluorine Chemistry* **2006**, *127*, 548-551

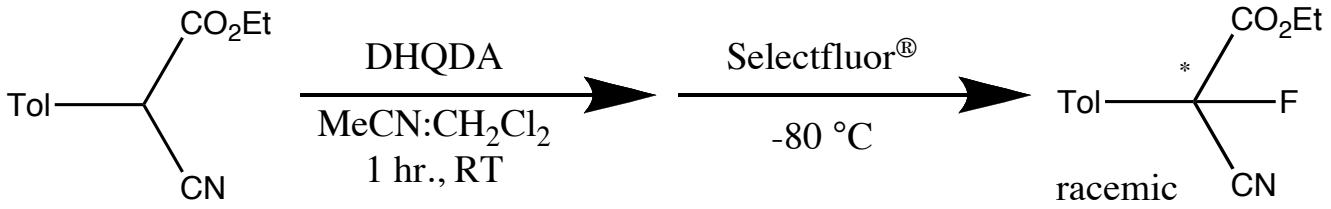
Proposed Transition Structures



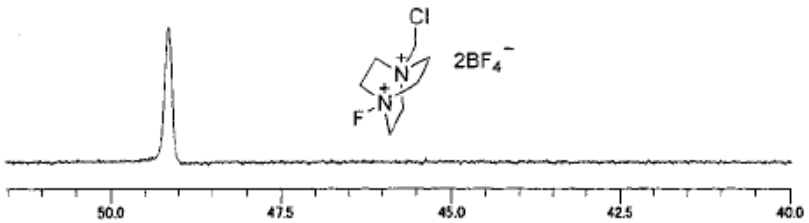
- Likely typo in TS-I and TS-II in alkene position

Shibata et al., *J. Am. Chem. Soc.* **2001**, *123*, 7001-7009

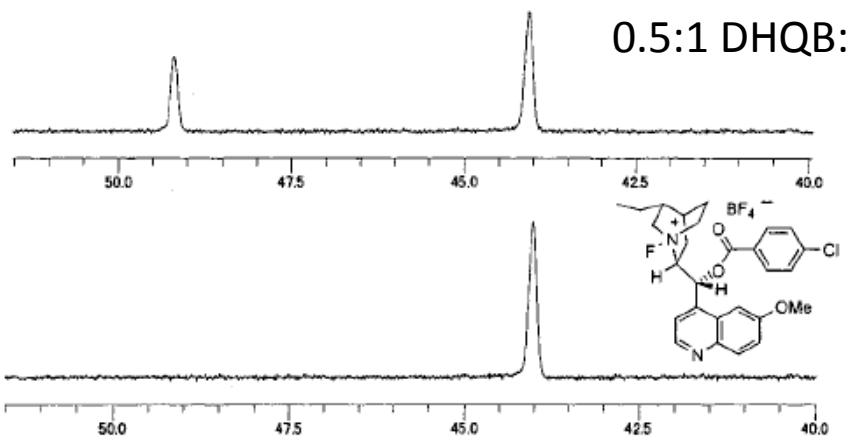
Fluorine Transfer and Enantioselectivity



^{19}F NMR

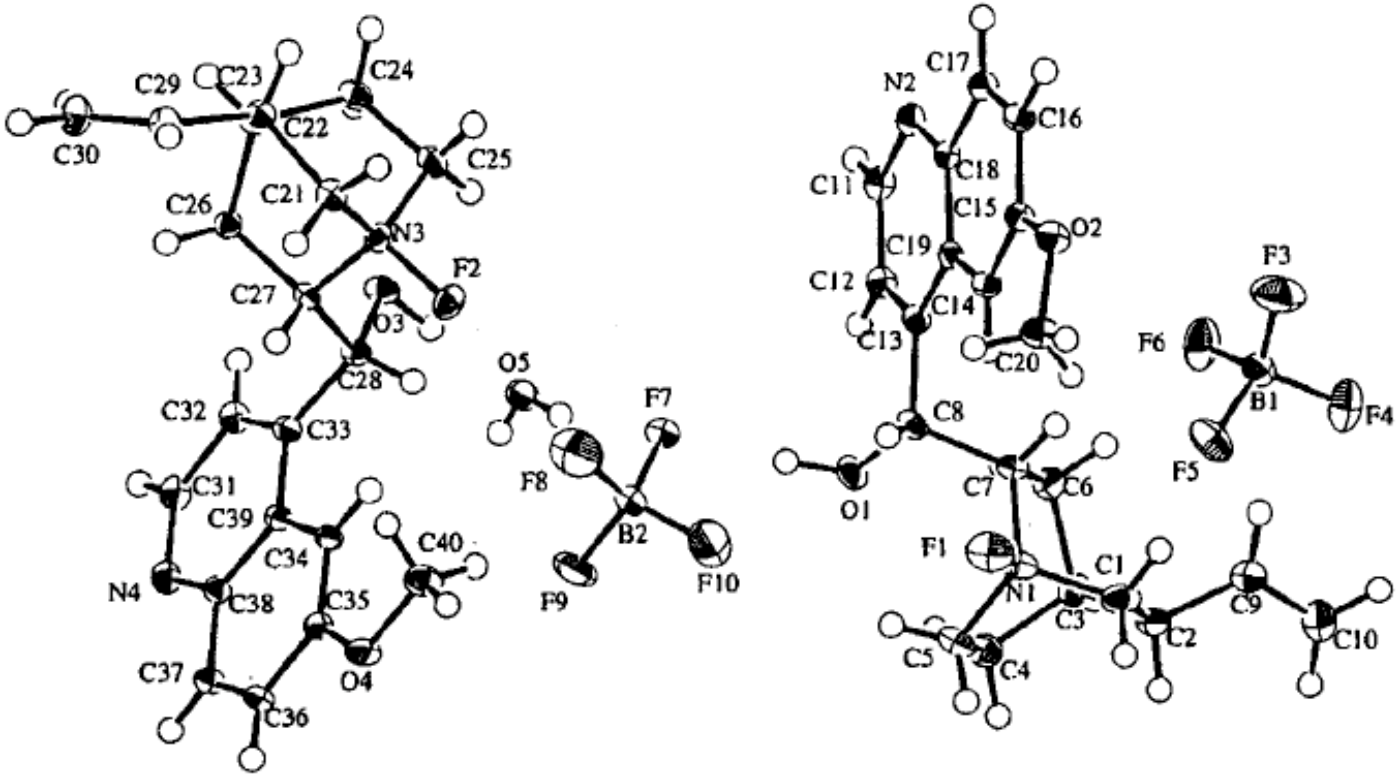


0.5:1 DHQB:Selecfluor®



Shibata et al., *J. Am. Chem. Soc.* **2001**, *123*, 7001-7009

NF-Q•BF_4 X-Ray Structure



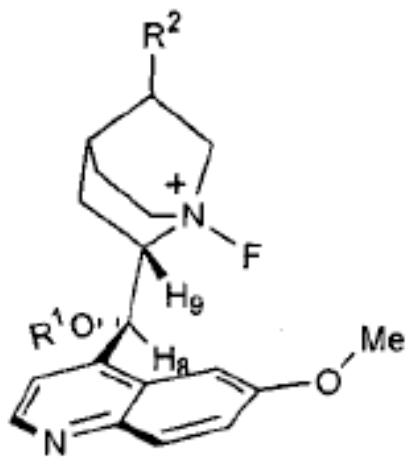
•Difference the result of vinyl chain torsion angle (-138.0° and 137.5°, left to right)

•N(1)-F(1) 1.4912Å
•N-F 1.37 (Selectfluor®) 1.37Å
Δ=0.1212Å

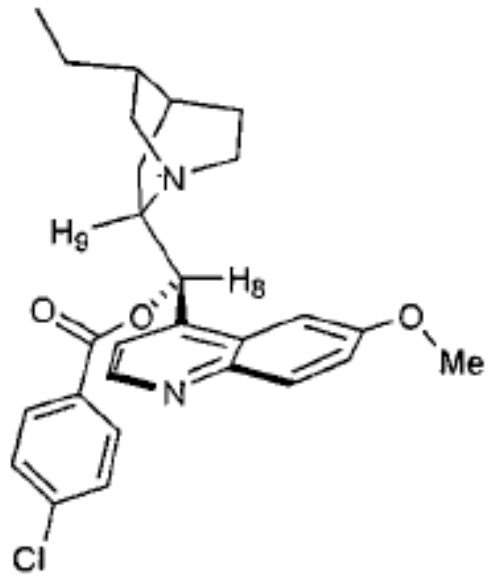
•Exists as open conformation III*

*Wynberg et al., *J. Org. Chem.* **1990**, *55*, 6121-6131
Shibata et al., *J. Am. Chem. Soc.* **2001**, *123*, 7001-7009

Closed vs. Open Quinine



Open



Closed

*N*F-Q-BF_4: $^3J_{H8,H9}$= 2.9 Hz

*N*F-DHQB·BF_4: $^3J_{H8,H9}$= 2.6 Hz

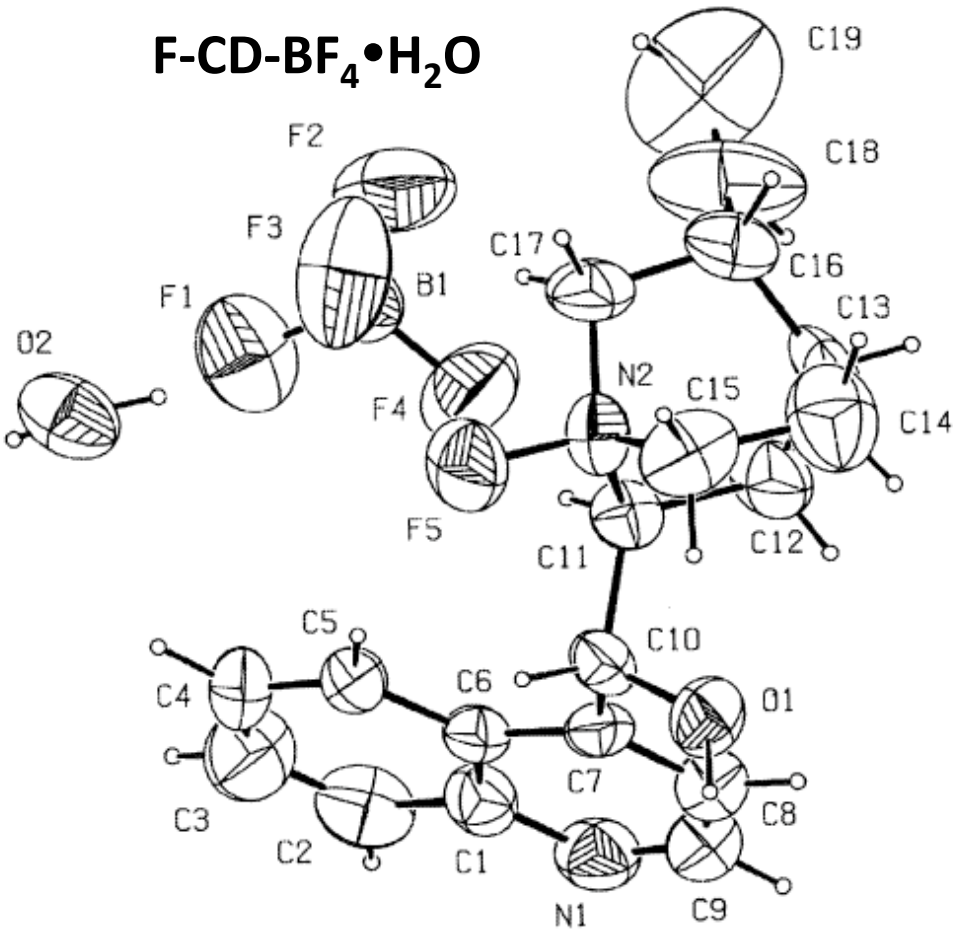
DHQB: $^3J_{H8,H9}$= 7.8 Hz

•No π-π stacking between NF-Q•BF_4 and substrate in transition state

Shibata et al., *J. Am. Chem. Soc.* **2001**, *123*, 7001-7009

Cinchona $[N\text{-}F]^+$ X-Ray Structure

F-CD-BF_4•H_2O

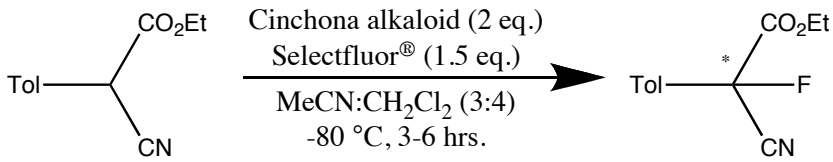


- Crystal structure contains a molar equivalent of H_2O
- N-F (cinchona) 1.409 Å, N-F (Selectfluor®)1.37 Å
- Prepared by Bank's fluorine-transfer procedure*

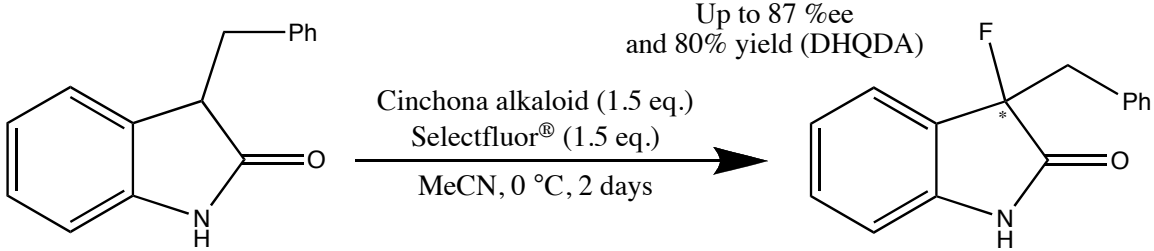
* Banks et al., *Journal of Fluorine Chemistry* **1995**, *73*, 255-257

Cahard et al., *Tet. Lett.* **2001**, *42*, 1867-1869

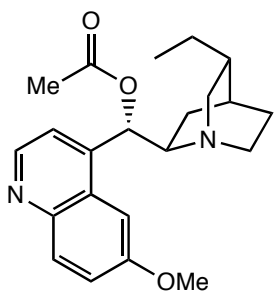
Expanding Reaction Scope



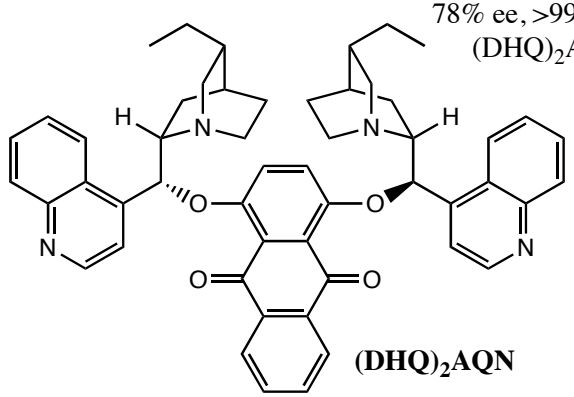
Up to 87 %ee
and 80% yield (DHQDA)



78% ee, >99% yield
$(DHQ)_2AQN$

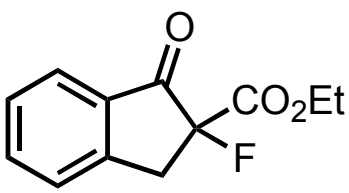


DHQDA

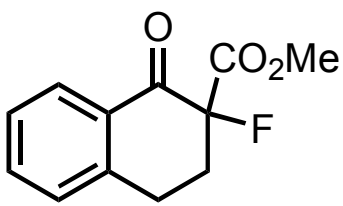


$(DHQ)_2AQN$

- Selectfluor® and cinchona alkaloid must be mixed prior to substrate introduction
- DHQDA showed poor %ee and yield with some β-ketoesters
- Unprotected hydroxyl improved selectivity and yield for oxindoles
- Screening conditions indicates extra alkaloid eq. increases yield



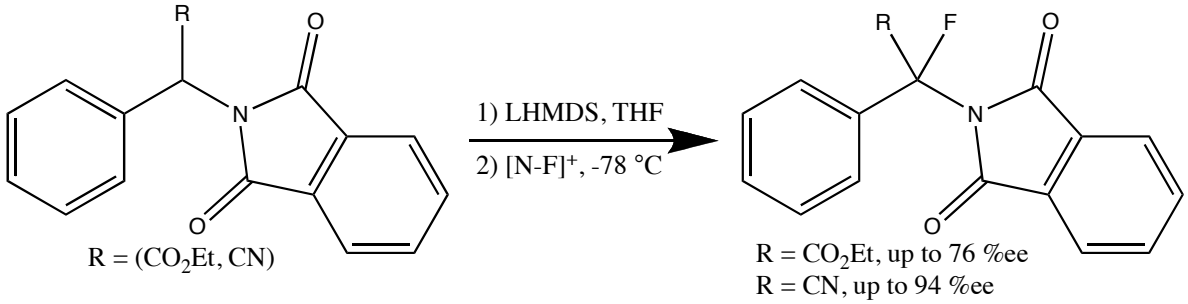
DHQDA
78 %ee, 89% yield

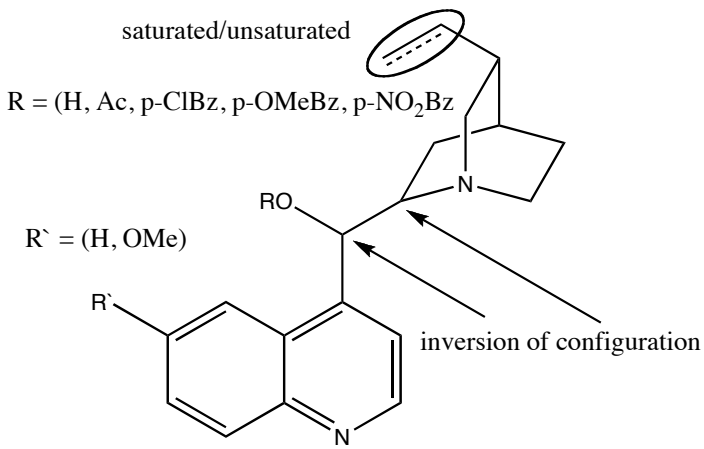


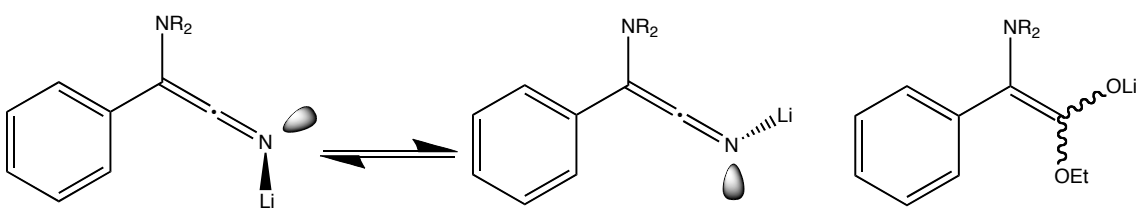
DHQDA
2 %ee, 26% yield

Shibata et al., *J. Am. Chem. Soc.* **2001**, *123*, 7001-7009

Enantioselective Fluorination of α-Amino Acid Derivatives



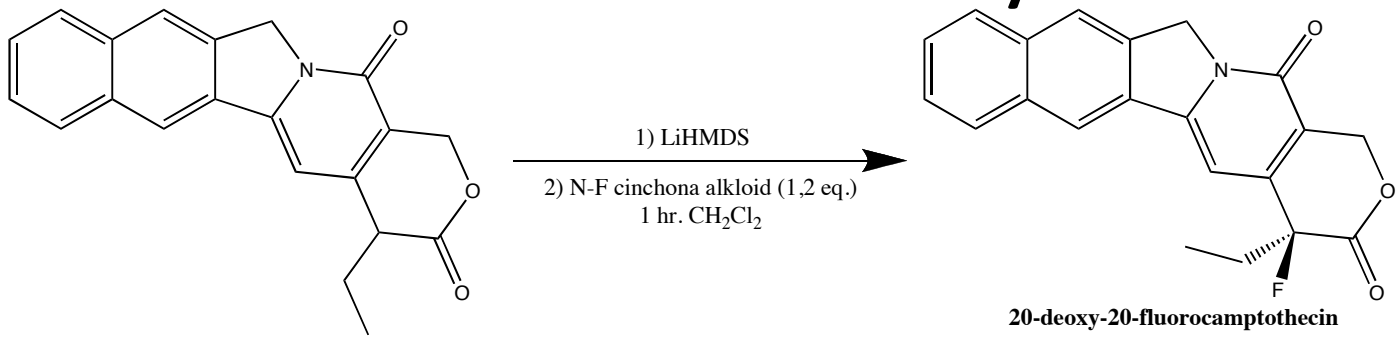




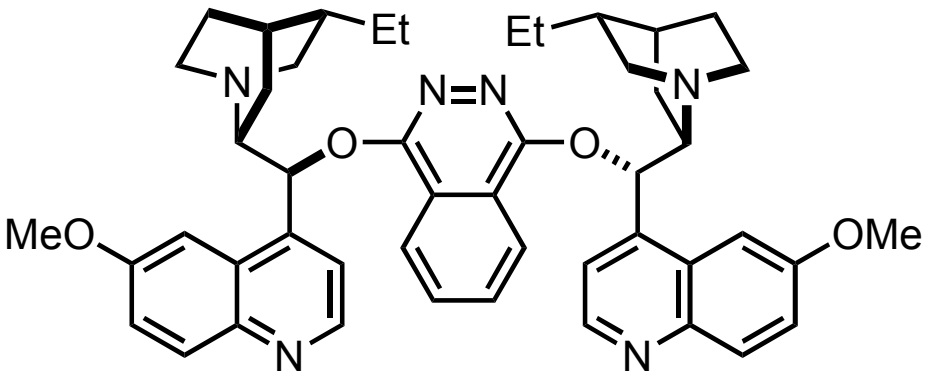
- Investigated structure-enantioselectivity relationship
- R` = OMe better %ee
- R = EDG or EWG little difference
- Quinine core best selectivity
- Ester substrate, R = Ac, better selectivity
- Nitrile substrate, R = benzoyl better selectivity
- Nitriles enantioselectivity from DKR
- Esters enantioselectivity from facial differentiation

Cahard et al., *Angew. Chem. Int. Ed.* **2001**, *40(22)*, 4214-4216

Enantioselective α-Fluorination with Cinchona Alkaloid in Synthesis



88 %ee, 87% yield, R enantiomer obtained

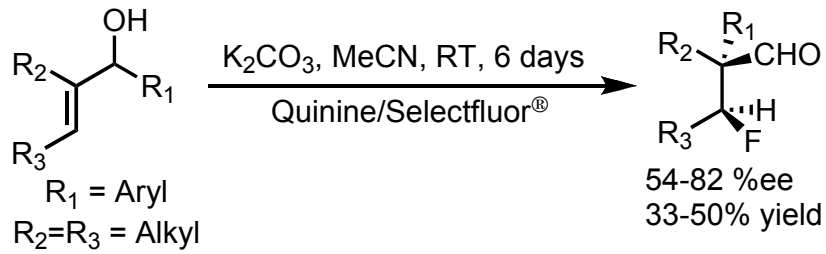


$(DHQD)_2PHAL$

- $[N\text{-}F]^+$ generated either with Selectfluor® in MeCN or with NFSI in THF (both at -80 °C)
- Generated with 1.2 eq. Selectfluor®
- Inhibits DNA topoisomerase I with CPT where F=OH
- Fluorine substitution thought to make lactone less reactive

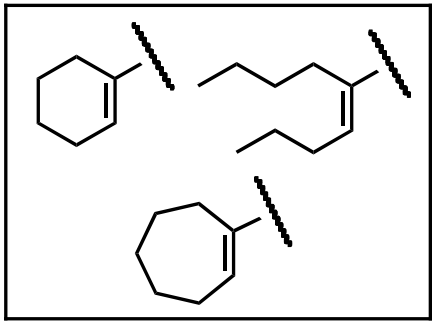
Shibata, N.; Toru, T.; Ishimaru, T., *Synlett.* **2004**, *14*, 2509-2512

Asymmetric Semipinacol Rearrangment with Allylic Alcohols

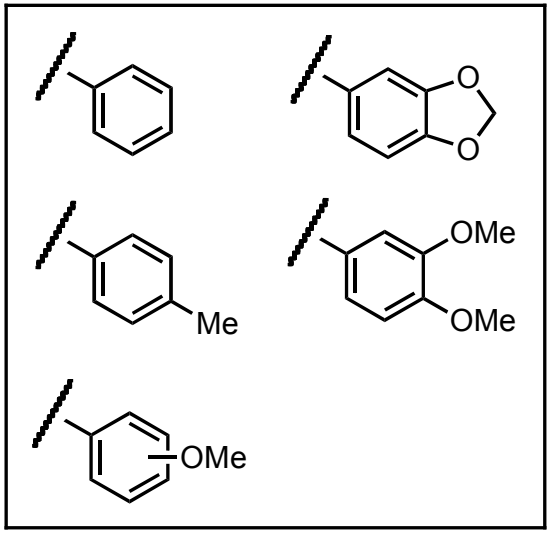


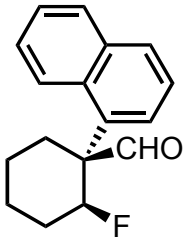
- Cinchona dimers found to be less selective
- 0.6 eq. of inorganic base was found to increase yields and selectivity

Akyl Groups



Aryl Groups





82 %ee
45% yield

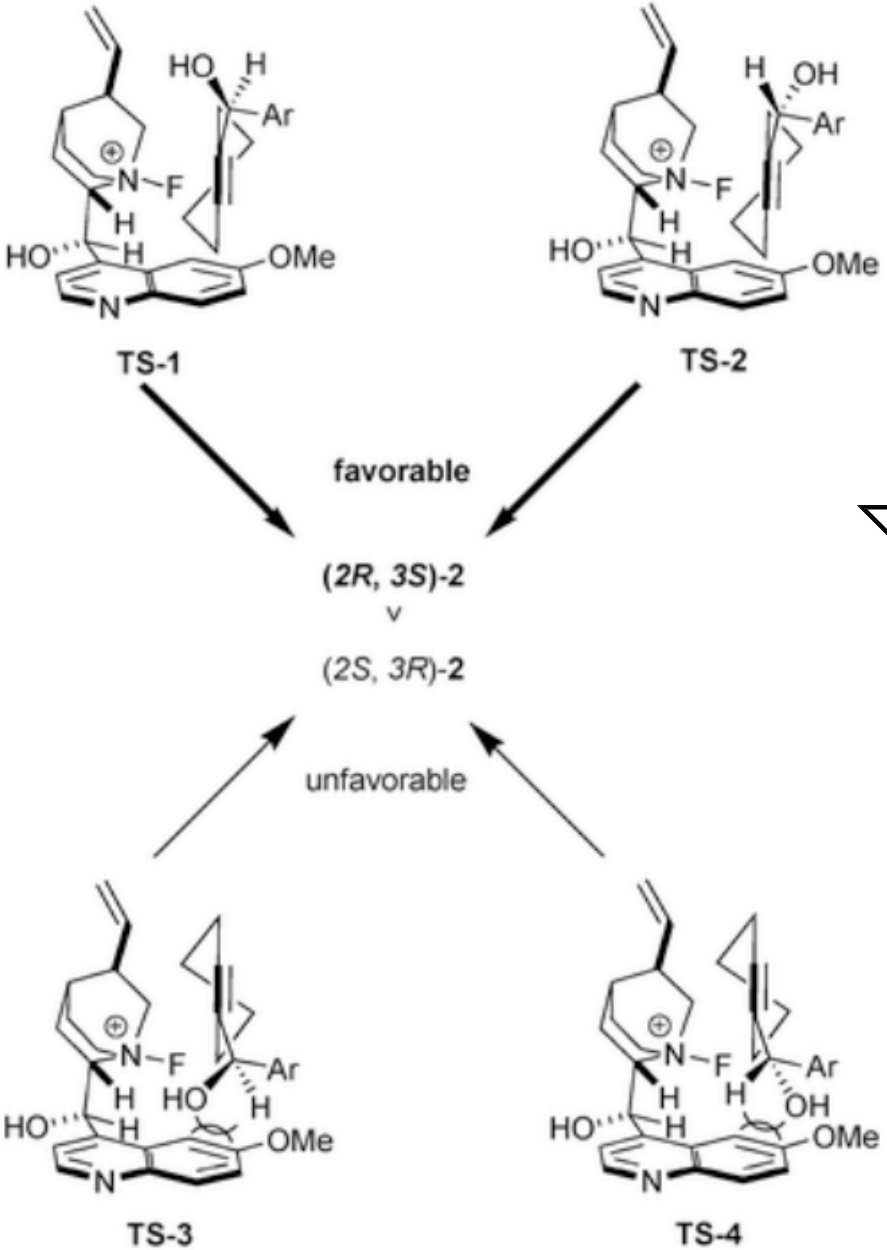
- Tertiary alcohols don't react
- Recovered starting material was racemic

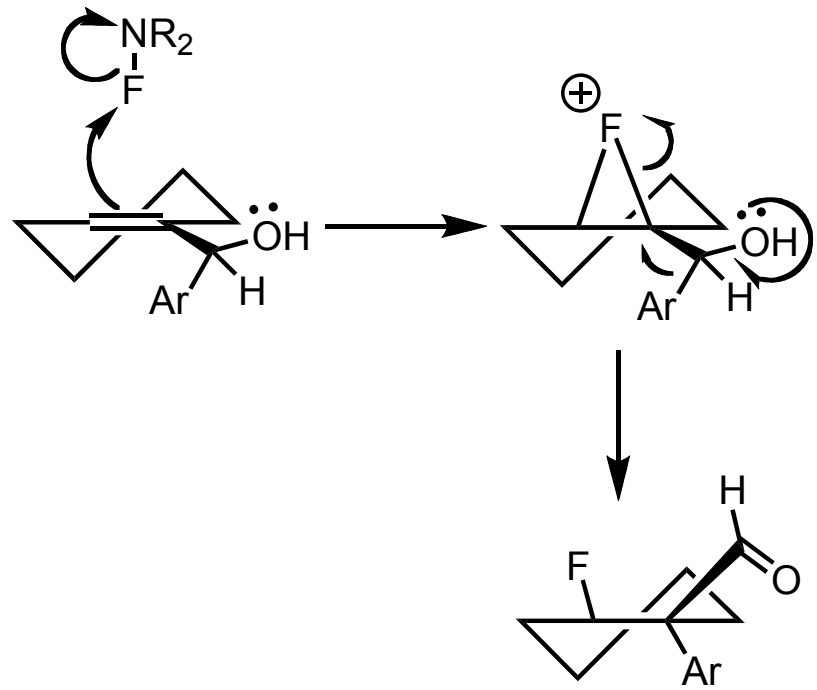
Tu et al., *Chem. Commun.* **2005**, 5580-5582

Group Question

- Show mechanism of this semi-pinacol rearrangement.
- Propose a transition state model that explains both observed product stereochemistry and account for the racemic starting material recovered.

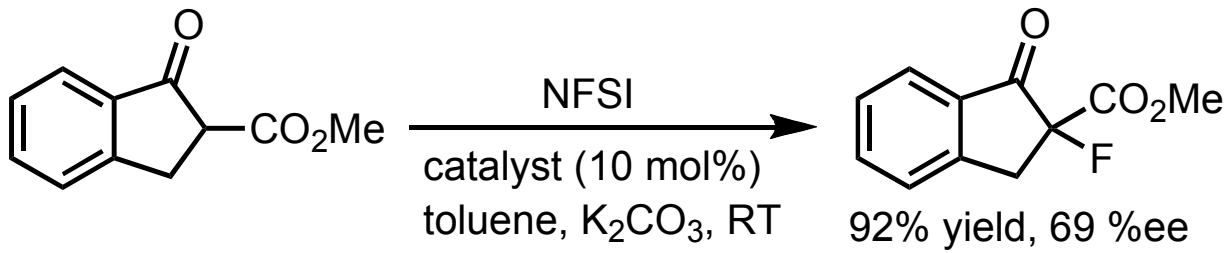
Proposed Transition State and Mechanism



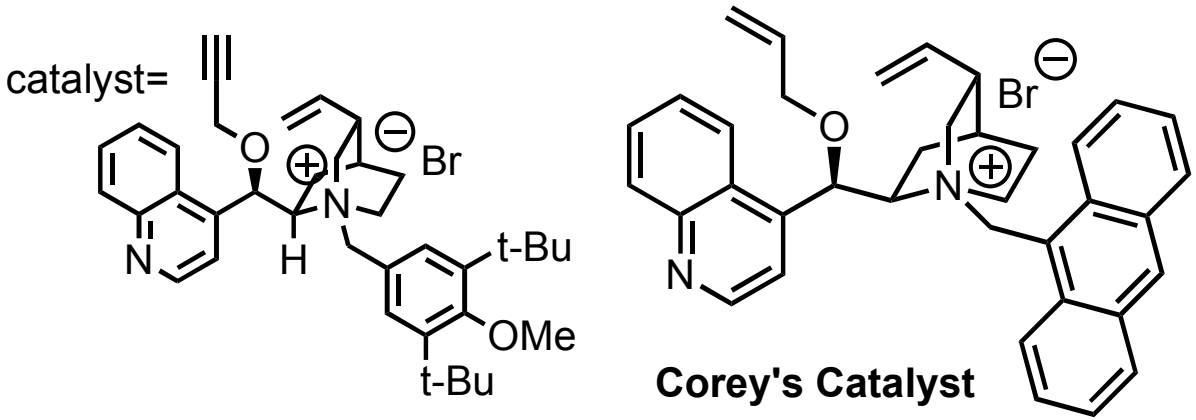


Tu et al., *Chem. Commun.* **2005**, 5580-5582

Phase-Transfer Catalytic Fluorination



- At -78 °C, only 36 %ee



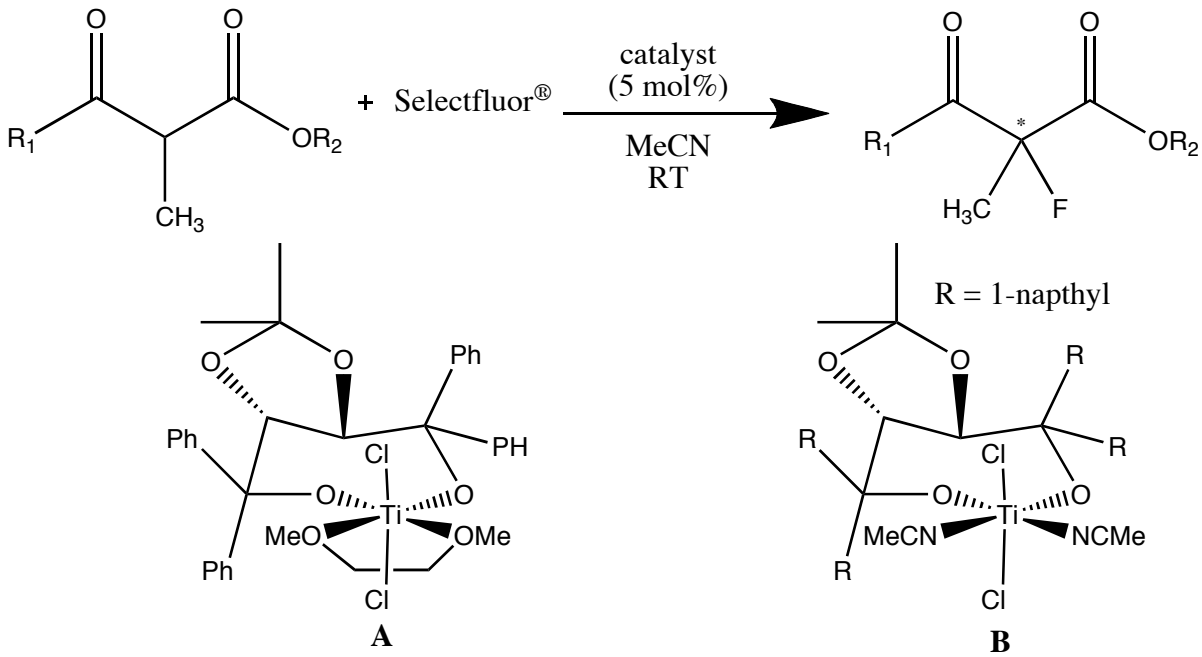
- Corey's catalyst also worked
- 66 %ee, 90% yield

Kim, D. Y.; Park, E. J., *Org. Lett.* **2002**, *4(4)*, 545-547

Cinchona Alkaloid Summary

- Advantages
  - Cheap source of chiral material
  - Lots of potential for modification
- Disadvantages
  - Competing background reactions and selectivity issues when substoichiometric

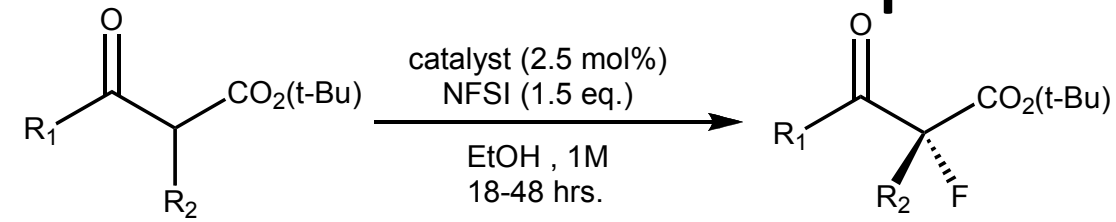
First Lewis Acid-Catalyzed Enantioselective α-Fluorination of β-Keto Esters



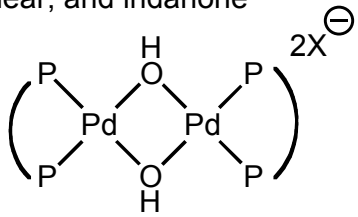
- Lewis acid activates the nucleophile
- R_1 three examples R_2 six examples
- Up to 59 %ee with **A** and 90 %ee with **B**

Togni, A.; Hintermann, L., *Angew. Chem. Int. Ed.* **2000**, *39(23)*, 4359-4362

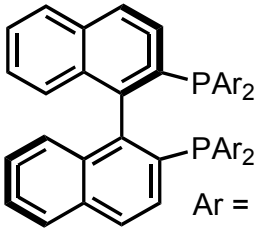
Efficient and Enantioselective Pd complexes



cyclic, linear, and indanone

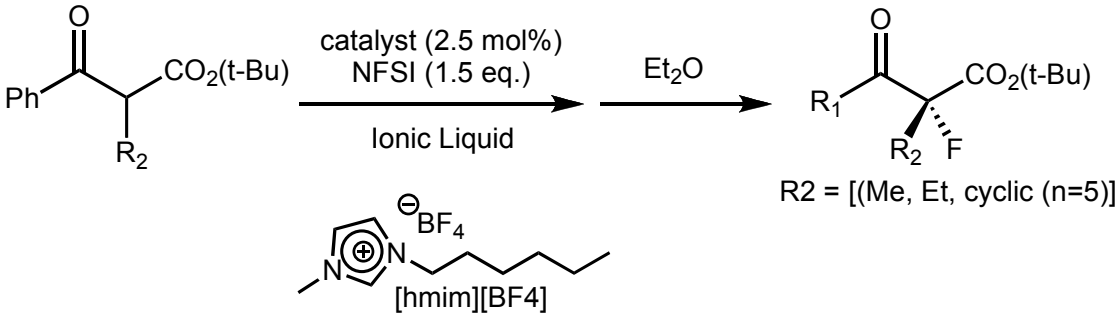


X = (TfO, $^-BF_4$)



Ar = (Ph, 3,5-dimethylphenyl)

- Insensitive to H_2O, scaled up to 1g
- 83-94 %ee, 82-96% yield
- High selectivity even at RT



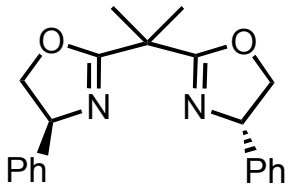
R2 = [(Me, Et, cyclic (n=5)]

- Up to 91 %ee (60 hrs.), catalyst recycled up to ten times without loss of %ee

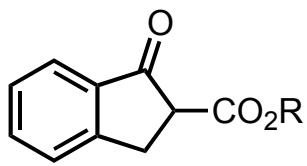
Sodeaka et. al., *Org. Lett.* **2003**, *5(18)*, 3225-3228

Sodeaka et. al., *J. Am. Chem. Soc.* **2002**, *124*, 14530-14531

Catalytic Enantioselective Fluorination with Metal Bis(oxazoline)



(S,S)-Bis(oxazoline)-Ph
(Box-Ph)

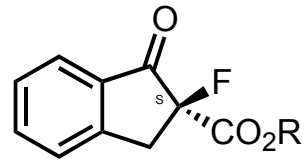


Box-Ph
10 mol%
NFSI
1.2 eq.

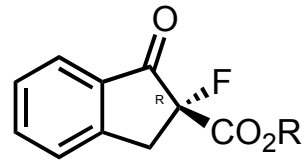
$Cu(OTf)_2$ (10 mol%)

$Ni(ClO_4)_2 \cdot 6H_2O$
(10 mol%)

(4A MS)



84 %ee, R = 1-adamantyl



93 %ee, R = t-butyl

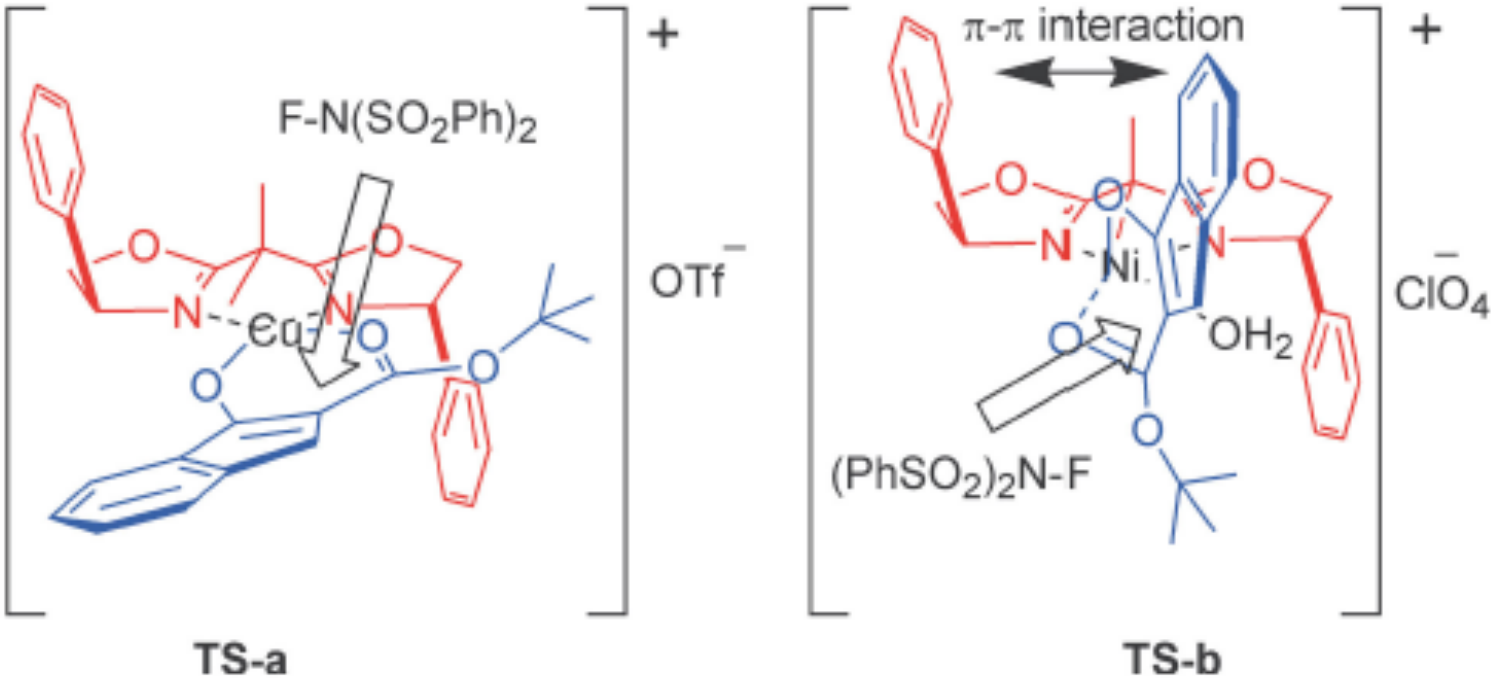
R = (L-menthyl, t-Butyl, 1-adamantyl)

Solvents = (THF, CH_2Cl_2, Et_2O, MTBE)

- Without ligand product was 13% diastereomerically enriched (R = L-menthyl)
- Authors propose metal center geometry responsible for opposite stereoinduction
- For [Ni], CH_2Cl_2 was best
- For [Cu], increased temp, better %ee in CH_2Cl_2, Et_2O, & MTBE

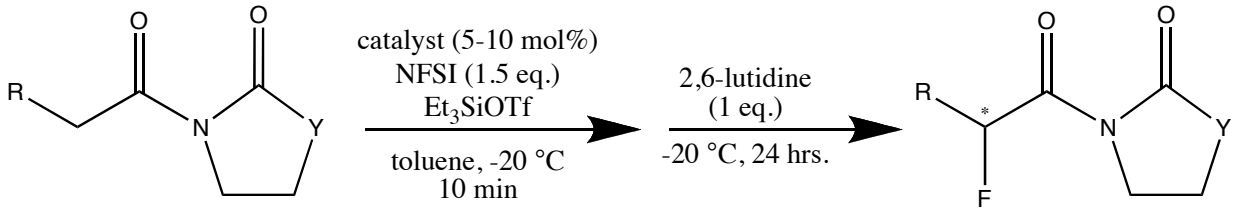
Toru and Shibata et al., *Synlett.* **2004**, *10*, 1703-1706

Proposed Transition Structures



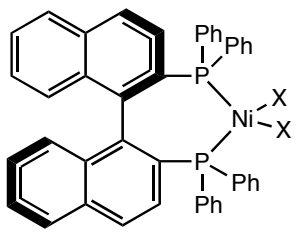
Toru and Shibata et al., *Synlett.* **2004**, *10*, 1703-1706

Catalytic Enantioselective Fluorination of α-Aryl Acetic Acid Derivatives with $NiCl_2$-BINAP



Y = (S, O)

catalyst =



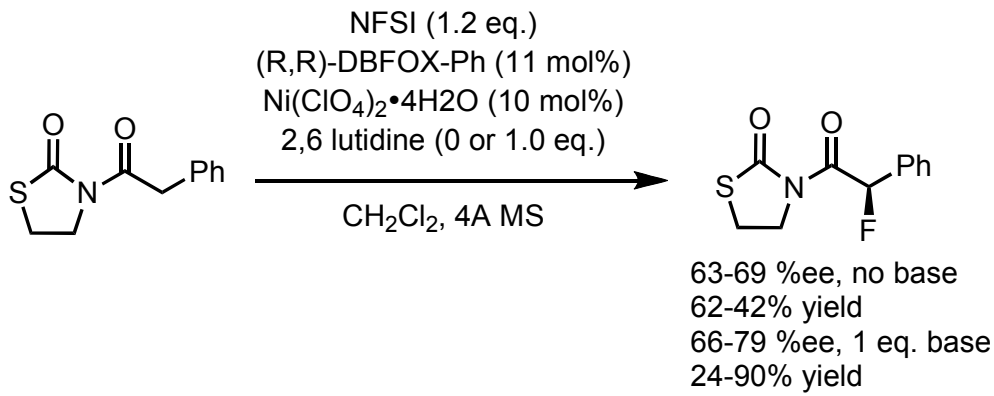
X = (OTf, Cl)

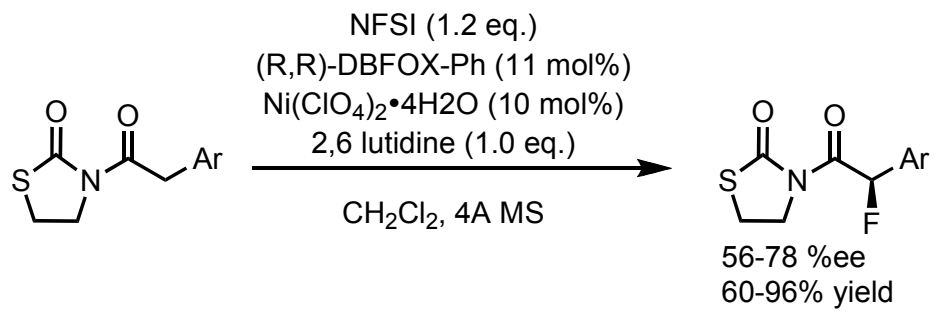
- Up to 88 %ee, 99% yield (R = Ph)
- Et_3SiOTf needed to activate NFSI
- Racemic pathway suppressed by conditions
- No difluorination or racemization observed

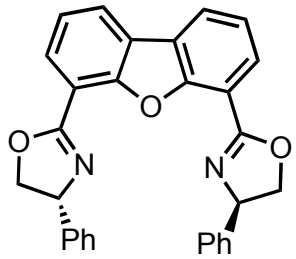
Entry	4	X	R	1b [mol%]	Et_3SiOTf [equiv]	Yield[a] [%]	ee[b] [%]
1	**4a**	S	Ph	5	0.75	99	88
2	**4c**	S	*p*-FC_6H_4	5	0.75	90	83
3	**4d**	S	*p*-$MeOC_6H_4$	5	0.75	92	81
4	**4e**	S	*m*-$MeOC_6H_4$	5	0.75	56	69
5	**4e**	S	*m*-$MeOC_6H_4$	10	1.5	95	82
6	**4f**	S	*o*-$MeOC_6H_4$	5	0.75	73	61
7	**4f**	S	*o*-$MeOC_6H_4$	10	1.5	87	78
8	**4g**	S	2-naphthyl	10	1.5	99	83
9	**4h**	S	1-naphthyl	5	0.75	94	87
10	**4b**	O	Ph	10	1.5	95	87
11[c]	**4i**	S	*n*-propyl	10	1.5	15	11

Sodeoka et al., *Angew. Chem. Int. Ed.* **2007**, *46*, 5435-5439

DBFOX-Ph Ligand with α-Aryl Acetic Acid Derivatives



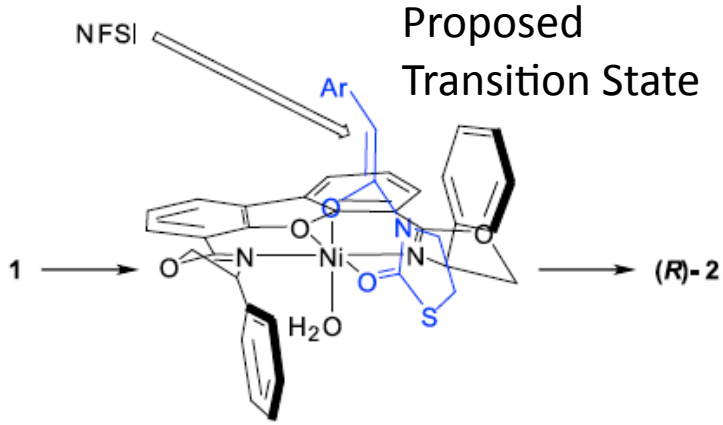




(R,R)-DBFOX-Ph

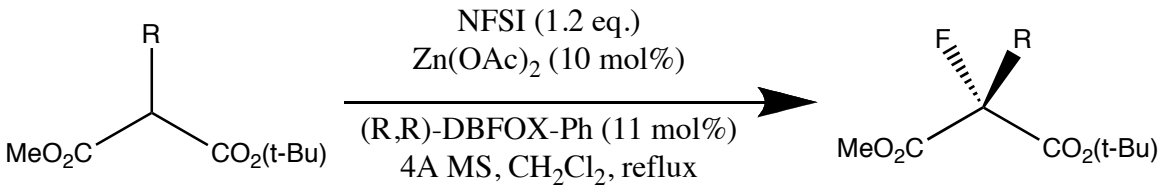
- Reaction can be preformed without base or extra lewis acid
- At 0 °C, reaction takes 20 hrs.
- $Cu(OTf)_2$ and $Zn(OAc)_2$ tested with base, no reaction
- (S,S)-BOX-Ph ligand tested with $Ni(ClO_4)_2 \cdot 6H_2O$, 15%ee, 33% yield
- Aryl groups with EWG groups slightly lower selectivity, 56-62 %ee

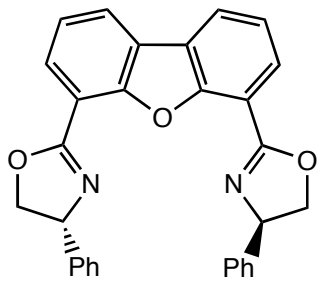
Proposed Transition State



Toru and Shibata et al., *Beilstein Journal of Organic Chemistry* **2008**, *4*, 16

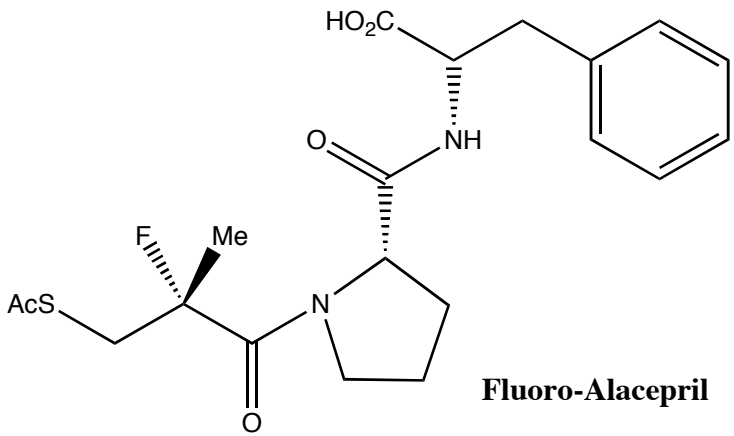
Highly Enantioselective Catalytic Fluorination of Unsymmetrical Malonates





(R,R)-DBFOX-Ph

- 99 %ee when R = Me, Bu, or Ph (isolated yields 90%, 93%, 95%)
- $Ni(ClO_4)_2 \bullet 6H_2O$ also used
- MS essential for selectivity



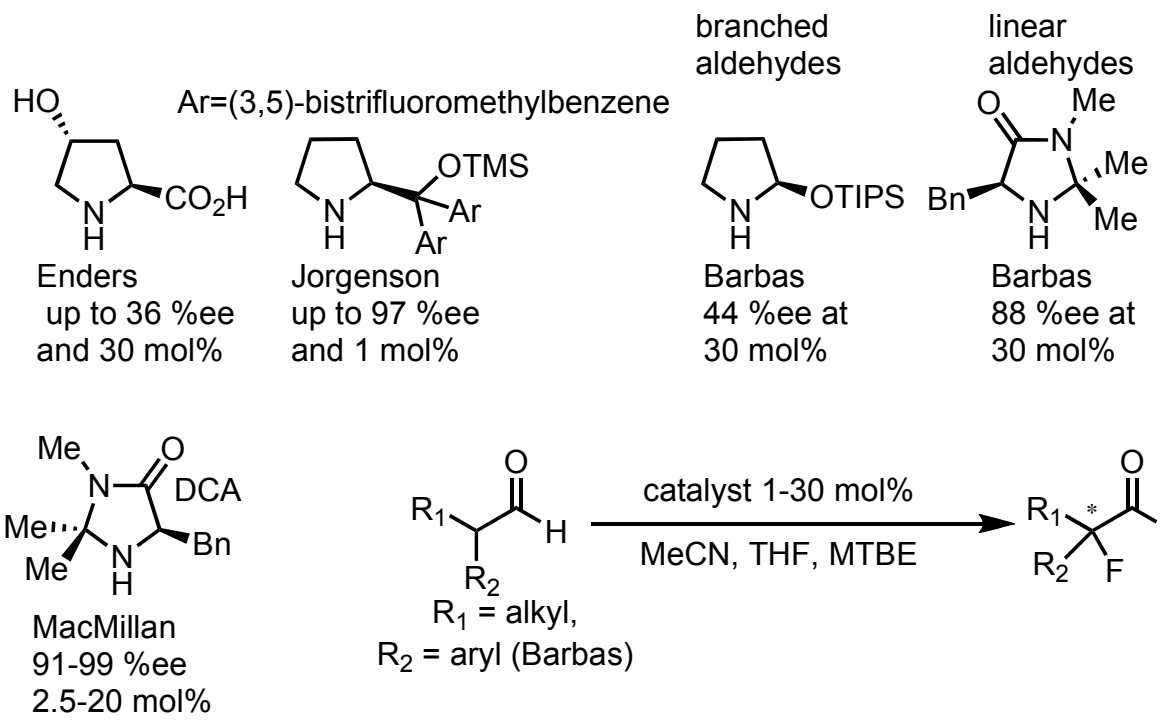
Fluoro-Alacepril

- 18.2% overall yield over 8 steps

Toru and Shibata et. al., *Angew. Chem. Int. Ed.* **2008**, *47*, 164-168

Organocatalytic Enantioselective Fluorination

•Simultaneous reported by four groups in 2005 by Enders[1], Jørgensen[2], Barbas[3], MacMillan[4],



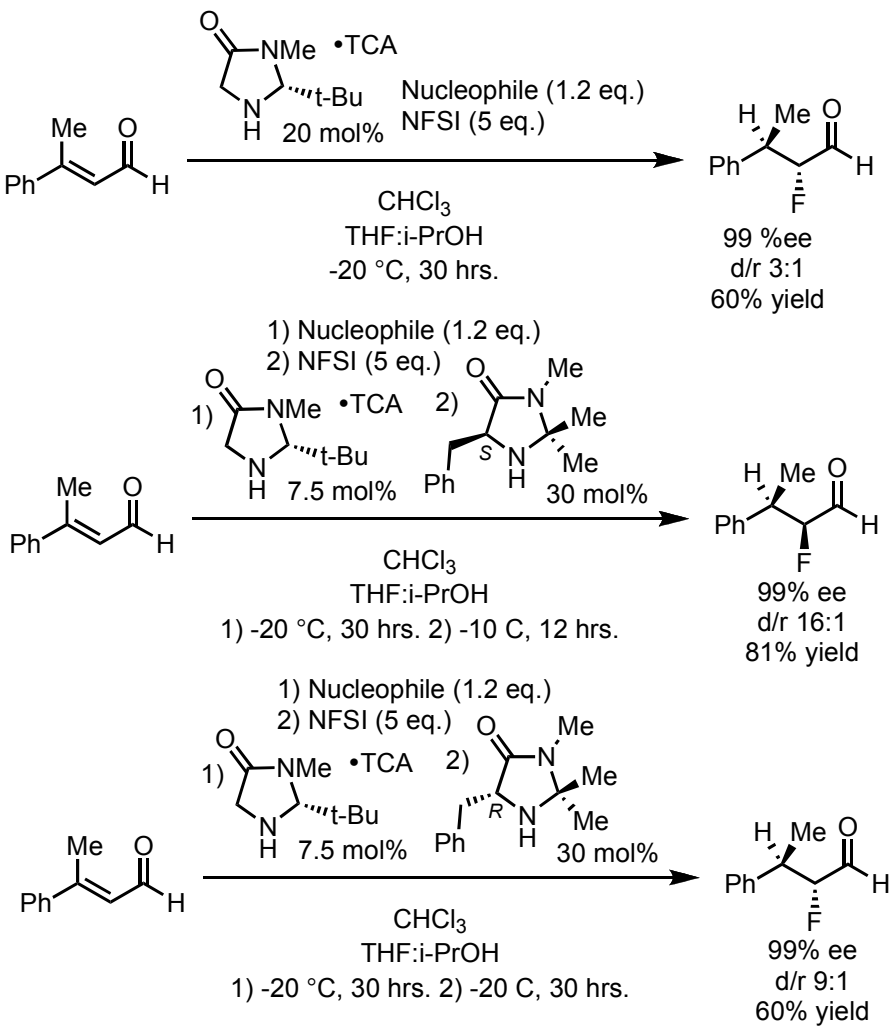
[1] Enders, D.; Huttl, M. R.M., *Synlett.* **2005**, *6*, 991-993

[2] Jorgensen et al., *Angew. Chem. Int. Ed.* **2005**, *44*, 3703-3706

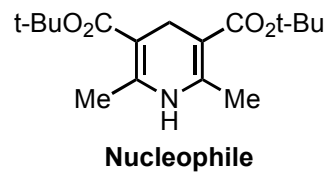
[3] Barbas et al., *Angew. Chem. Int. Ed.* **2005**, *44*, 3706-3710

[4] MacMillan, D. W.C.; Beeson, T., *J. Am. Chem. Soc.* **2005**, *127*, 8826-8828

Diastereoselective H-F Addition to α-β-Unsaturated Aldehydes via Organocatalysis



Hantzsch Ester



Nucleophile

- For combination catalysts, NFSI and enamine catalyst added only after Nu consumed

MacMillan et al., *J. Am. Chem. Soc.* **2005**, *127*, 15051-15053

Conclusion

- Substrates capable of asymmetric fluorination include, silyl enol ethers β-ketoesters, α-cyanoacetates, α-unbranched and branched aldehydes, oxindoles, and lactones.
- High levels of yield and selectivity only possible with efficient fluorinating agents

Toru and Shibata et al., *Journal of Fluorine Chemistry* **2007**, *128*, 469-483

Cahard, D.; Ma, J., *Chem. Rev.* **2004**, *104*, 6119-6146 (Update 2008)

O'Hagan, D.; Brunet, V. A., *Angew. Chem. Int. Ed.* **2008**, *47*, 1179-1182