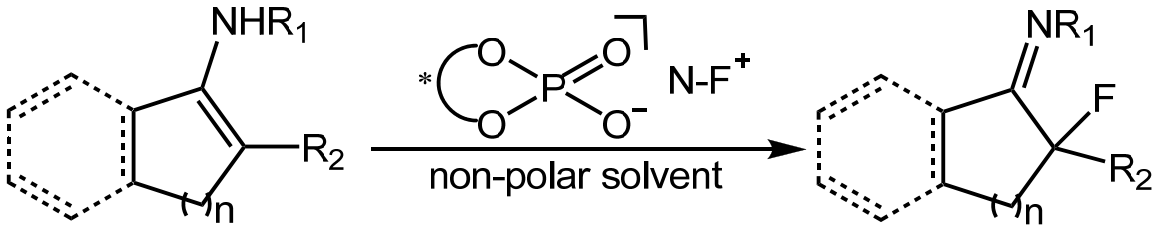
Literature Report

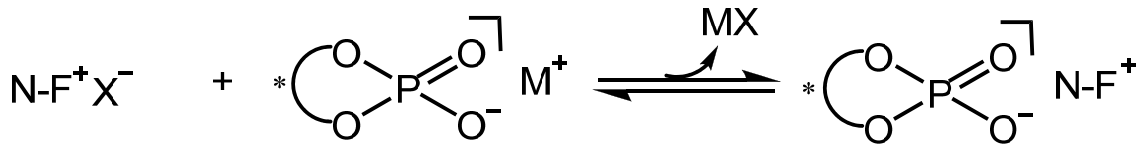
Asymmetric Fluorination of Enamides: Access to α-Fluoroimines Using an Anionic Chiral Phase-Transfer Catalyst

Reporter: Mu-Wang Chen
Checker: Zhi-Shi Ye

Toste, F. D. *et al.*
***J. Am. Chem. Soc.* 2012, *134,* 8376-8379**

Asymmetric Fluorination of Enamides



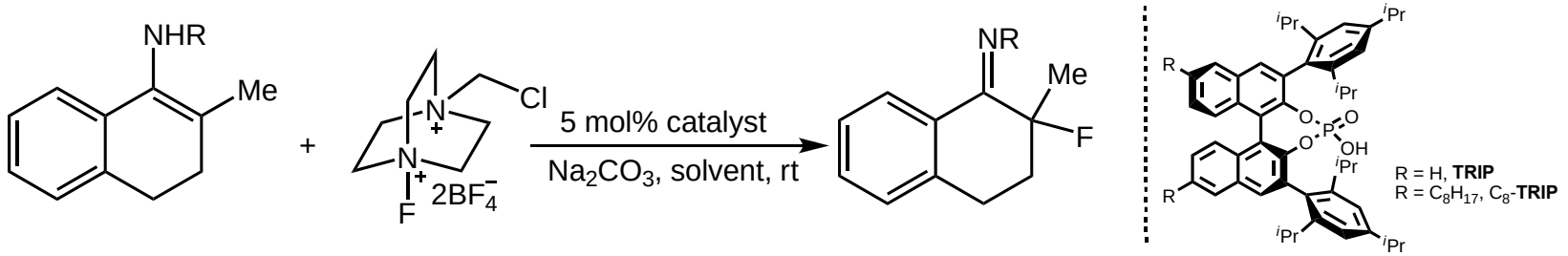


insoluble in non-polar solvent

soluble in non-polar solvent

soluble chiral fluorinating reagent

Optimization of the Enamide Fluorination Reaction

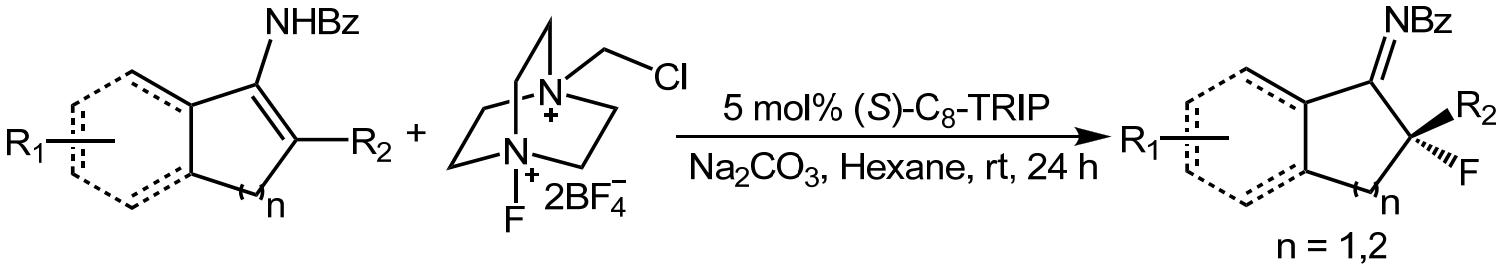


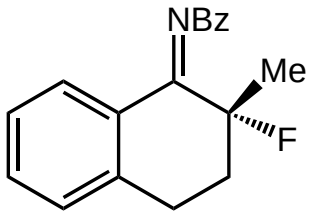
entry	R	catalyst	solvent, time	yield (%)[a]	ee (%)[b,c]
1	CO_2Bn (**1a**)	none	$PhCH_3$, 8 h	14[d]	-
2	CO_2Bn	(*S*)-C_8-TRIP	$PhCH_3$, 8 h	77	55 (*R*)
3	CO_2Me (**1b**)	(*S*)-C_8-TRIP	$PhCH_3$, 8 h	75	22 (*R*)
4	Ac (**1c**)	none	$PhCH_3$, 8 h	14[d]	-
5	Ac	(*S*)-C_8-TRIP	$PhCH_3$, 8 h	84	3
6	Bz (**1d**)	(*S*)-C_8-TRIP	$PhCH_3$, 8 h	91	90 (*R*)
7	Bz	none	$PhCH_3$, 8 h	6[d]	-
8	Bz	(*S*)-C_8-TRIP	PhF, 24 h	87	90 (*R*)

entry	R	catalyst	Solvent, time	yield (%)[a]	ee (%)[b,c]
9	Bz	(*S*)-C_8-TRIP	cyclohexane, 24 h	85	94 (*R*)
10	Bz	(*S*)-C_8-TRIP	hexane, 24 h	88	96 (*R*)
11	Bz	(*S*)-TRIP	$PhCH_3$, 24 h	83	92 (*R*)
12	Bz	(*S*)-TRIP	hexane, 24 h	83	92 (*R*)
13[e]	Bz	(*S*)-TRIP	hexane, 24 h	13	11 (*R*)

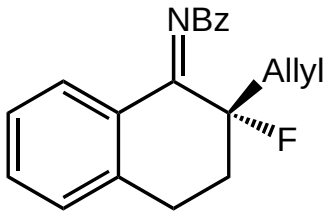
[a] Isolated yields after chromatography on silica gel, unless otherwise indicated. [b]Determined by HPLC. [c]Absolute configurations (in parentheses) were determined by hydrolysis and comparison of optical rotation with ref 13. [d]^{1}H NMR yield using 1,2-dimethoxyethane as an internal standard.[e]Reaction was run in the absence of Na_2CO_3 .

Exploration of the Scope of Substituted Enamides

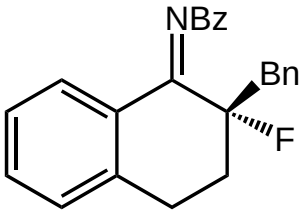




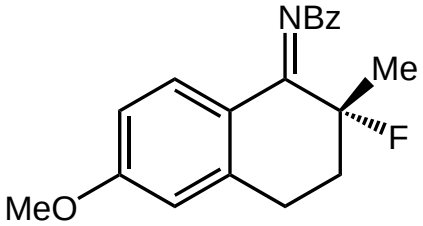
2d 96% (88%)



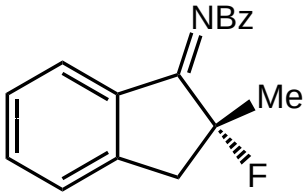
2e 96% (80%)



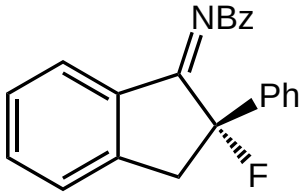
2f 99% (92%)



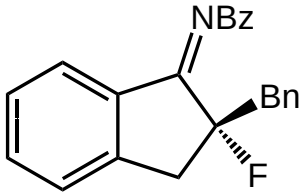
2g 92% (94%)



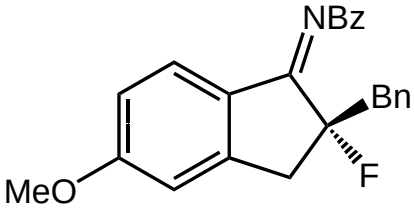
2h 96% (66%)



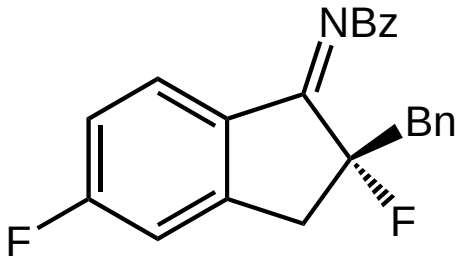
2i 90% (79%)



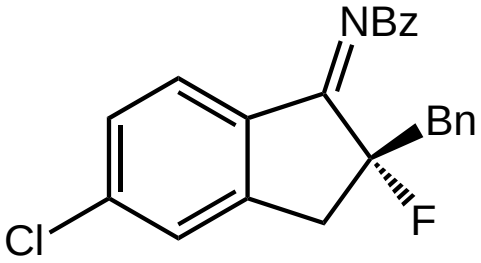
2j 98% (84%)



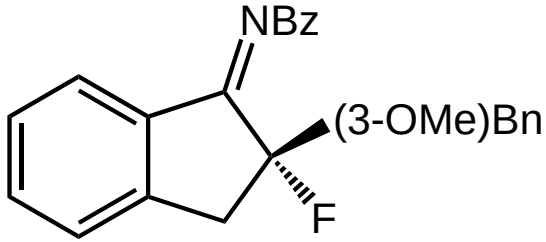
2k 96% (68%)



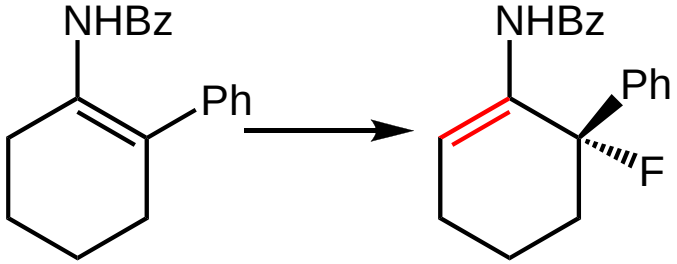
2l 94% (75%)



2m 93% (85%)

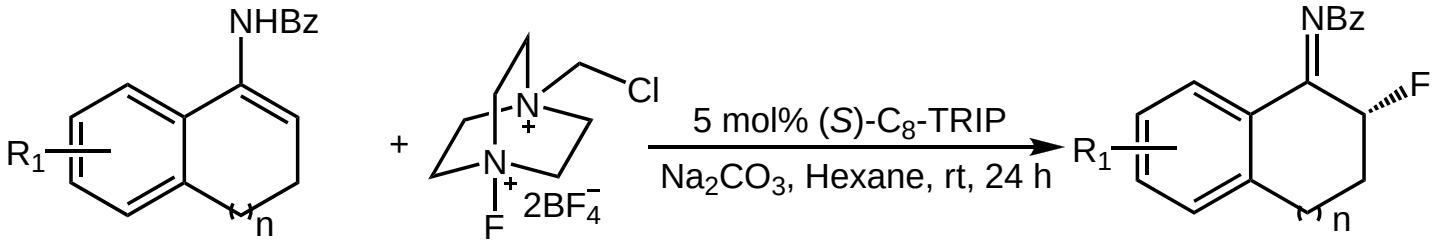


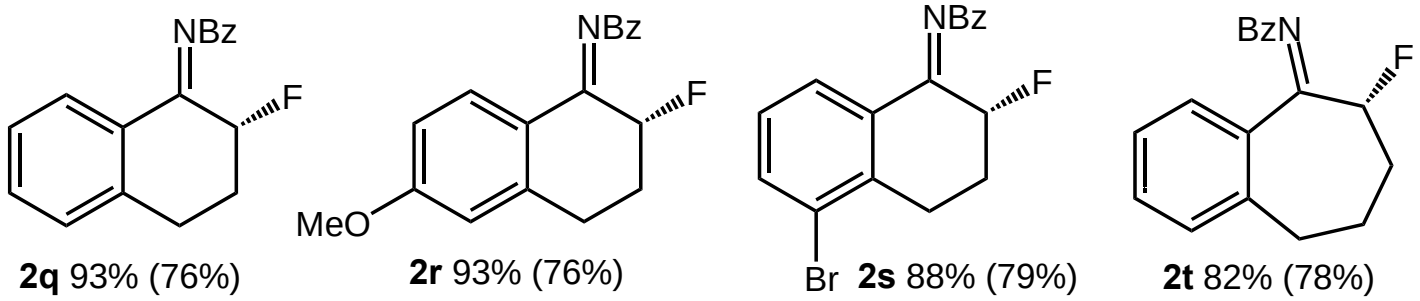
2n 98% (83%)



2o 87% (58%)

Fluorination of Unsubstituted Enamides



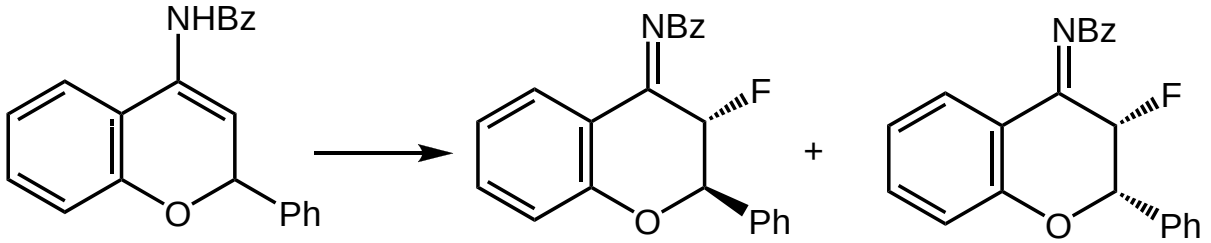


2q 93% (76%)

2r 93% (76%)

2s 88% (79%)

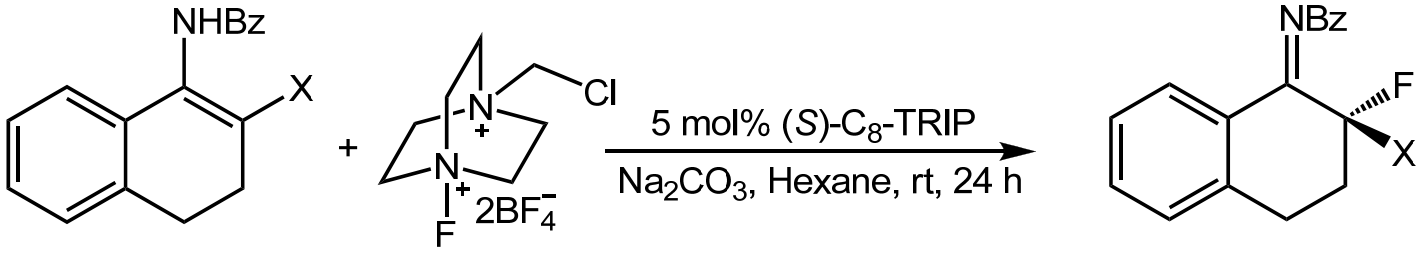
2t 82% (78%)

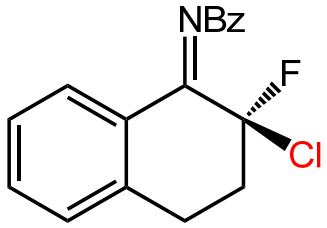


anti-**2u**, 93% (41%)

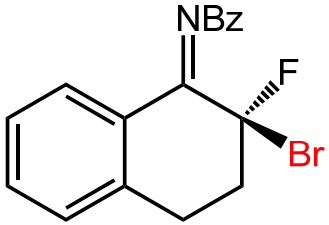
syn-**2u**, 99% (20%)

Fluorination of Halo-substituted Enamides



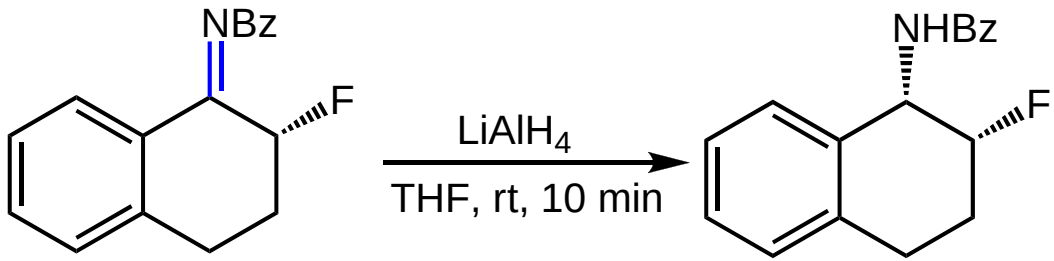


2v 95% (84%)



2w 83% (80%)

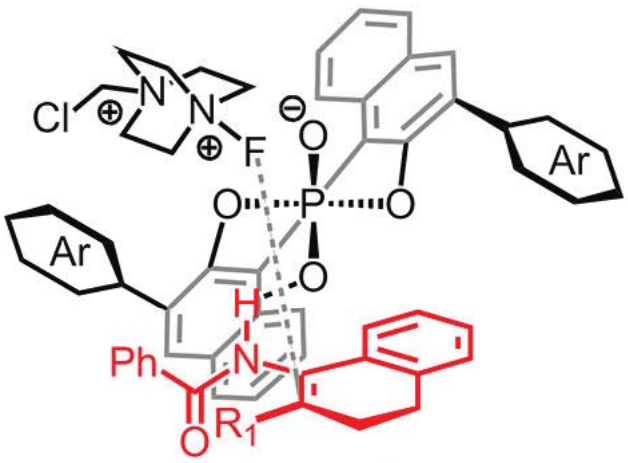
Reduction of 2q without Racemization



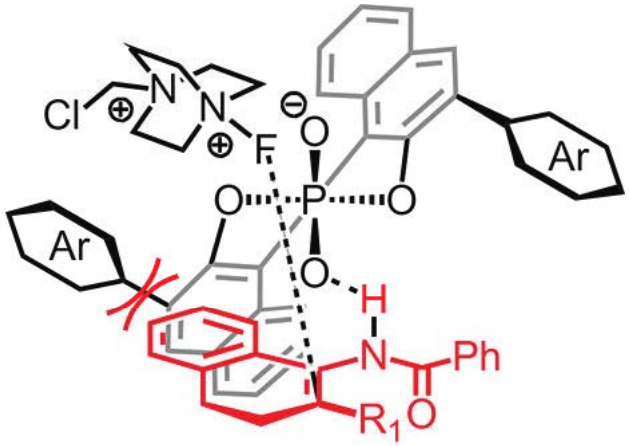
2q ee: 92%

3q 92% (79%)
dr 7:1

Mechanistic proposal for observed absolute stereochemistry

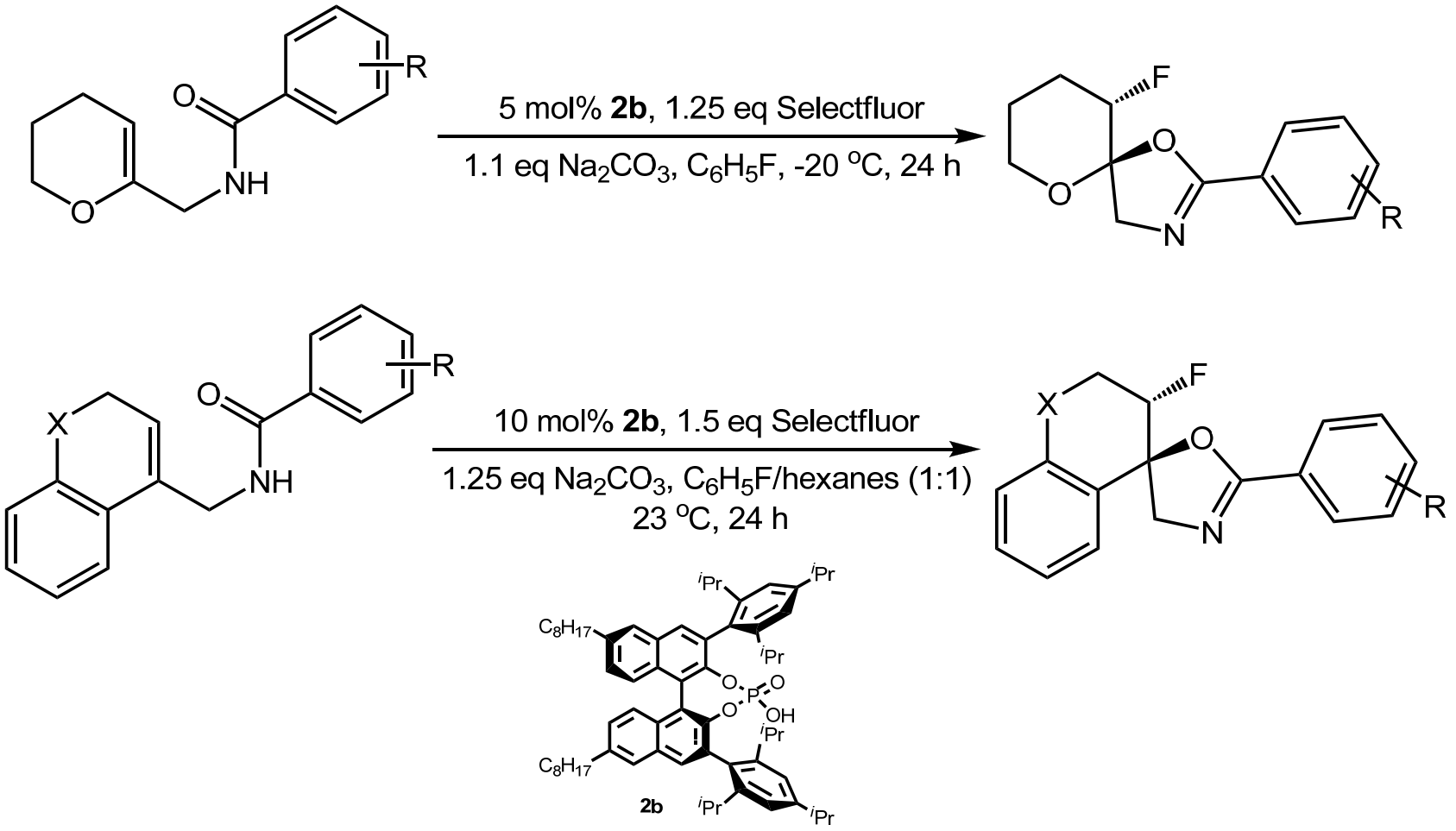


favored

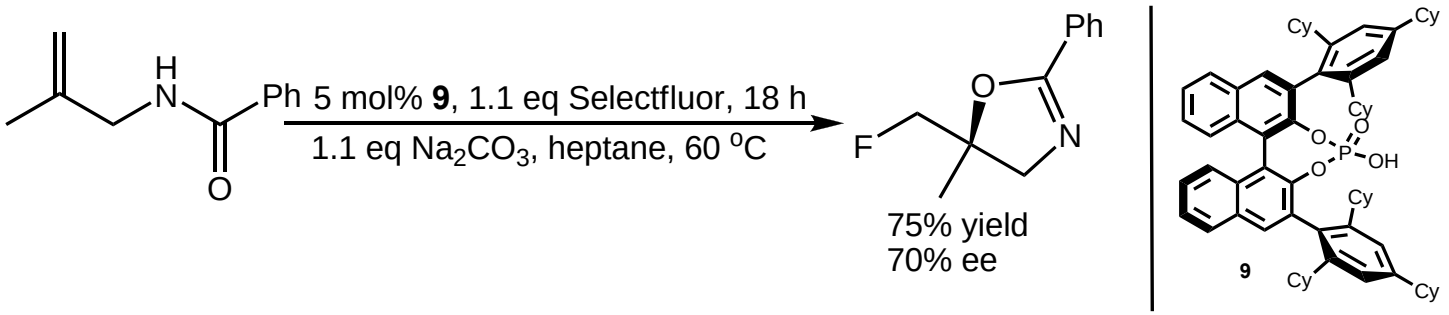


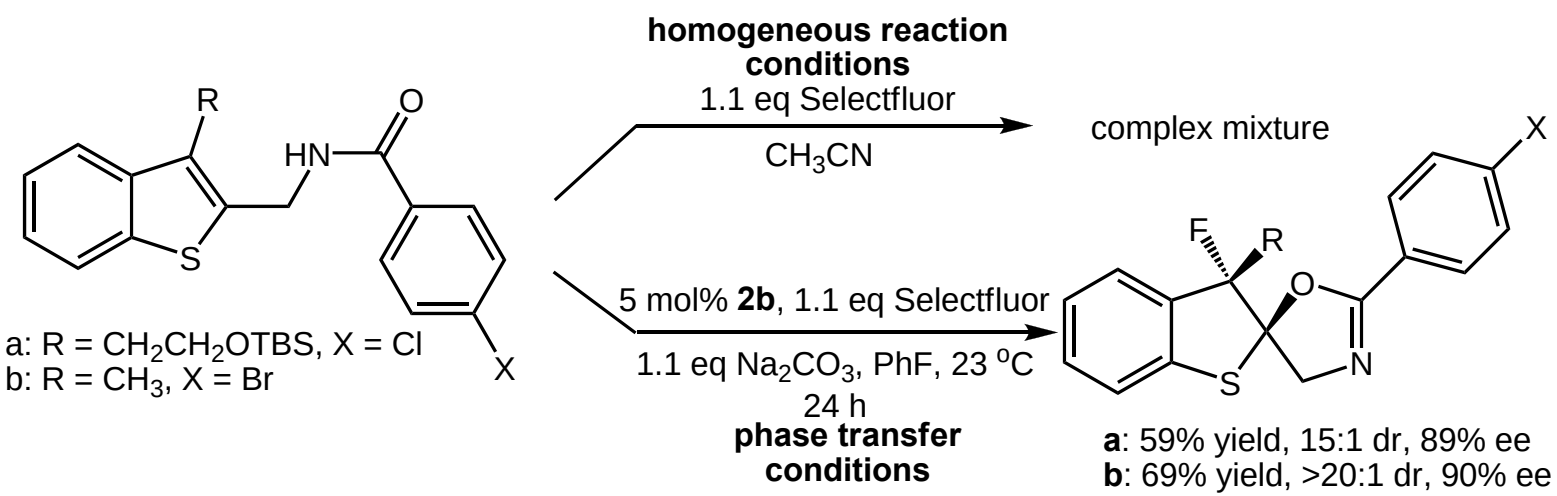
disfavored

Asymmetric Electrophilic Fluorination Using an Anionic Chiral Phase-Transfer Catalyst

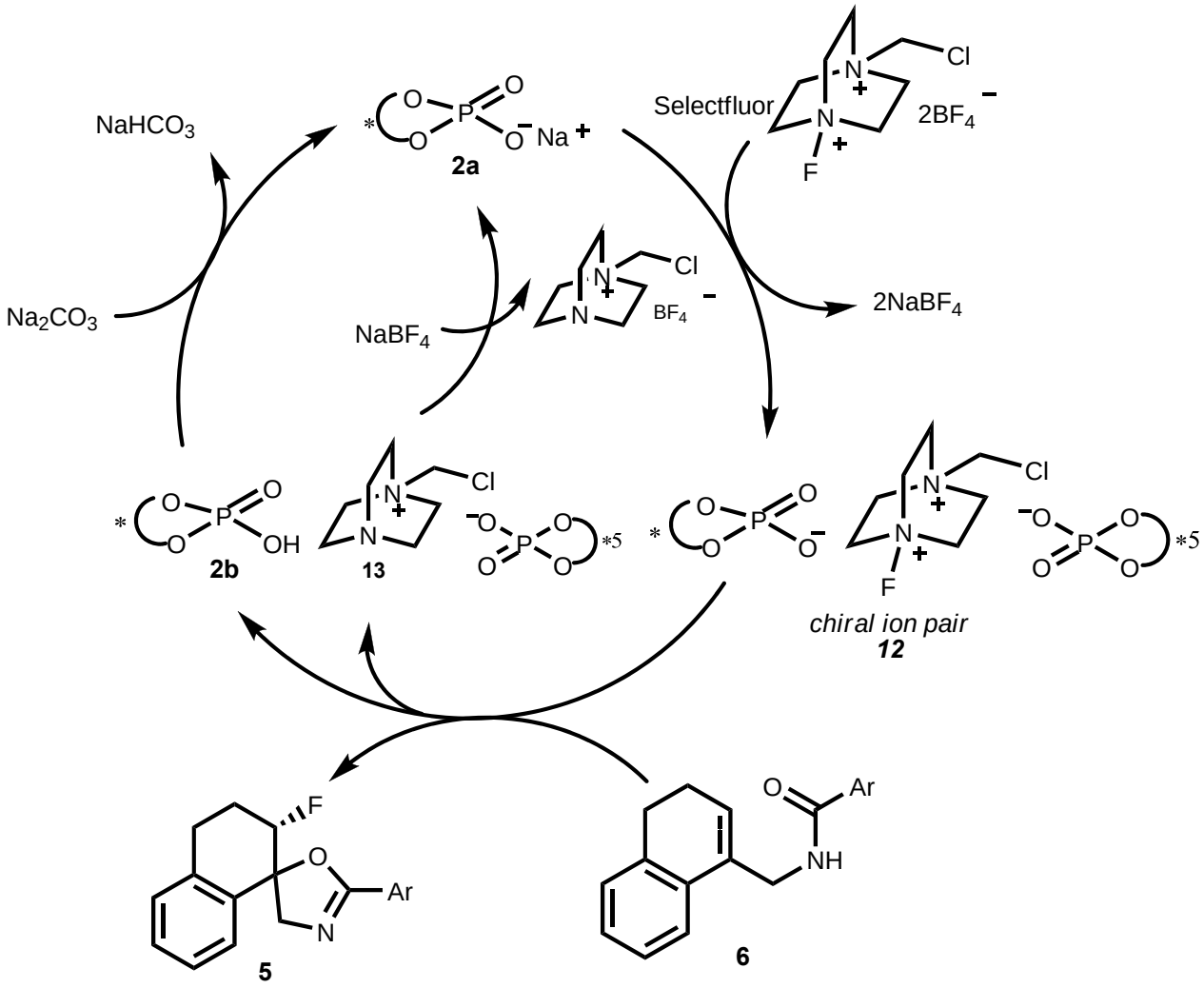


Toste, F. D. *et al. Science* **2011**, *334*, 1681-1684

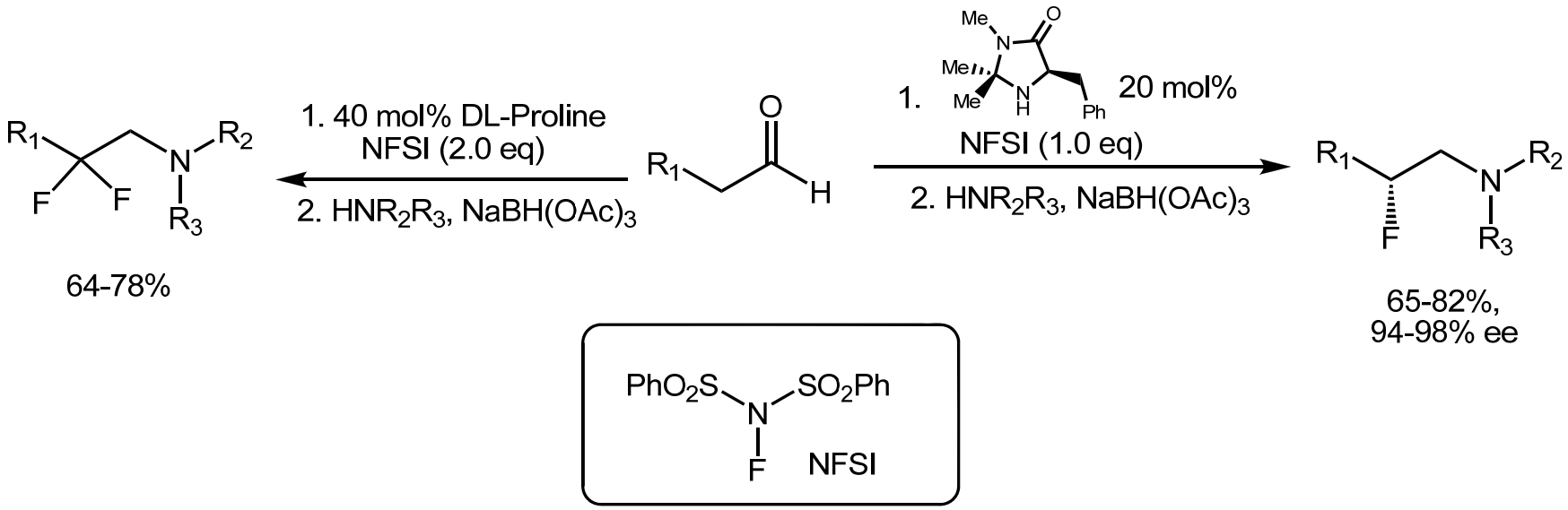

H
N
Ph
O
5 mol% 9, 1.1 eq Selectfluor, 18 h
1.1 eq Na2CO3, heptane, 60 °C
Ph
O
N
F
75% yield
70% ee
Cy
Cy
Cy
O
O
P
OH
O
Cy
Cy
Cy
9


R
HN
O
S
X
a: R = CH2CH2OTBS, X = Cl
b: R = CH3, X = Br
homogeneous reaction conditions
1.1 eq Selectfluor
CH3CN
complex mixture
5 mol% 2b, 1.1 eq Selectfluor
1.1 eq Na2CO3, PhF, 23 °C
24 h
phase transfer conditions
F
R
O
N
S
X
a: 59% yield, 15:1 dr, 89% ee
b: 69% yield, >20:1 dr, 90% ee

The proposed catalytic cycle supported by the observed nonlinear effect

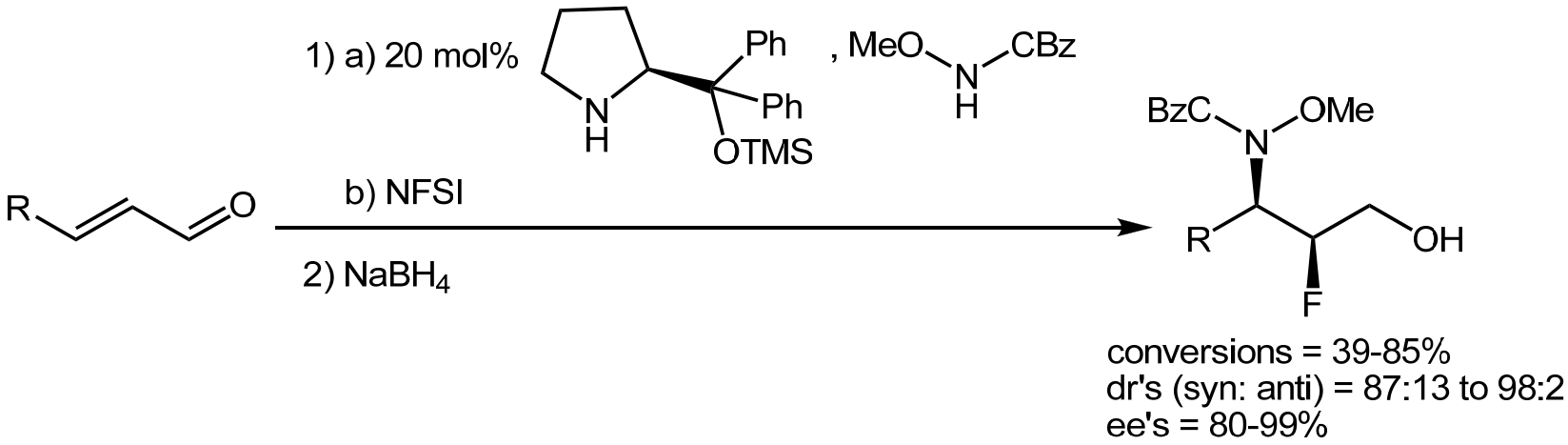


Rapid, General Access to Chiral β-Fluoroamines and β,β-Difluoroamines via Organocatalysis



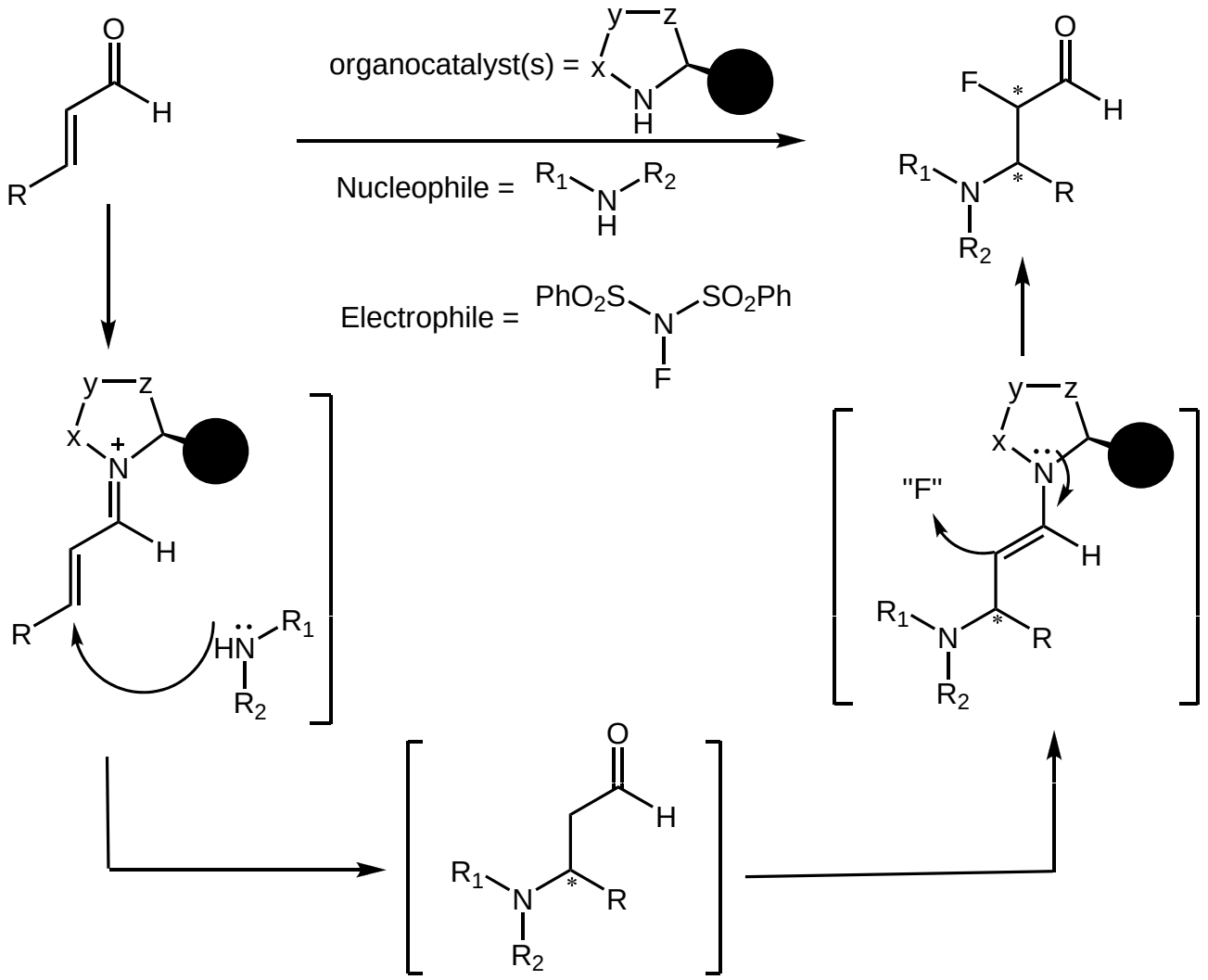
Lindsley, C. W. *et al. Org. Lett.* **2009**, *11*, 943-946

Organocatalytic Enantioselestive Olefin Aminofluorination

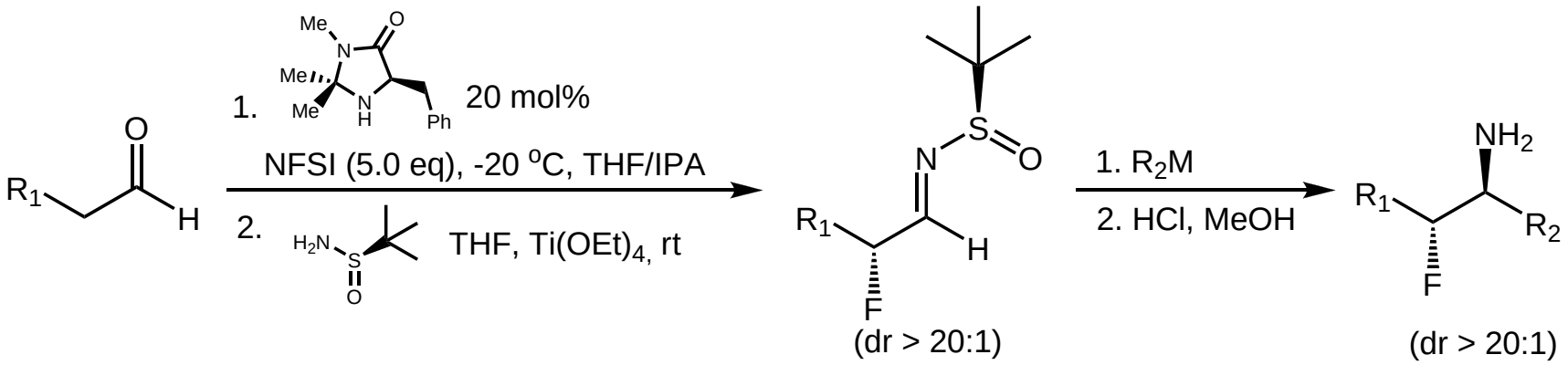


Brenner-Moyer, S. E. *et al. Org. Lett*. **2010**, *12*, 3356-3359

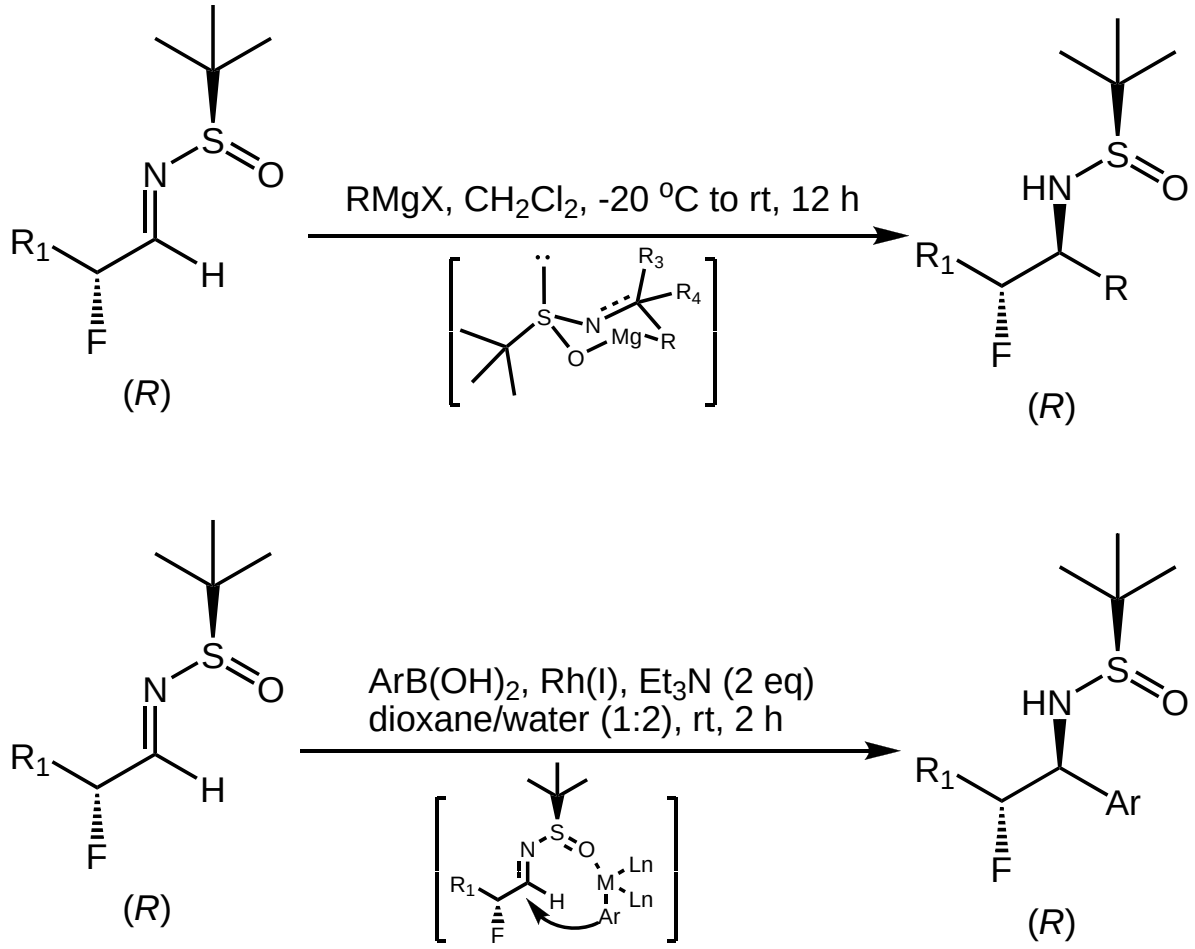
Proposed One-Pot Organocascade Reaction

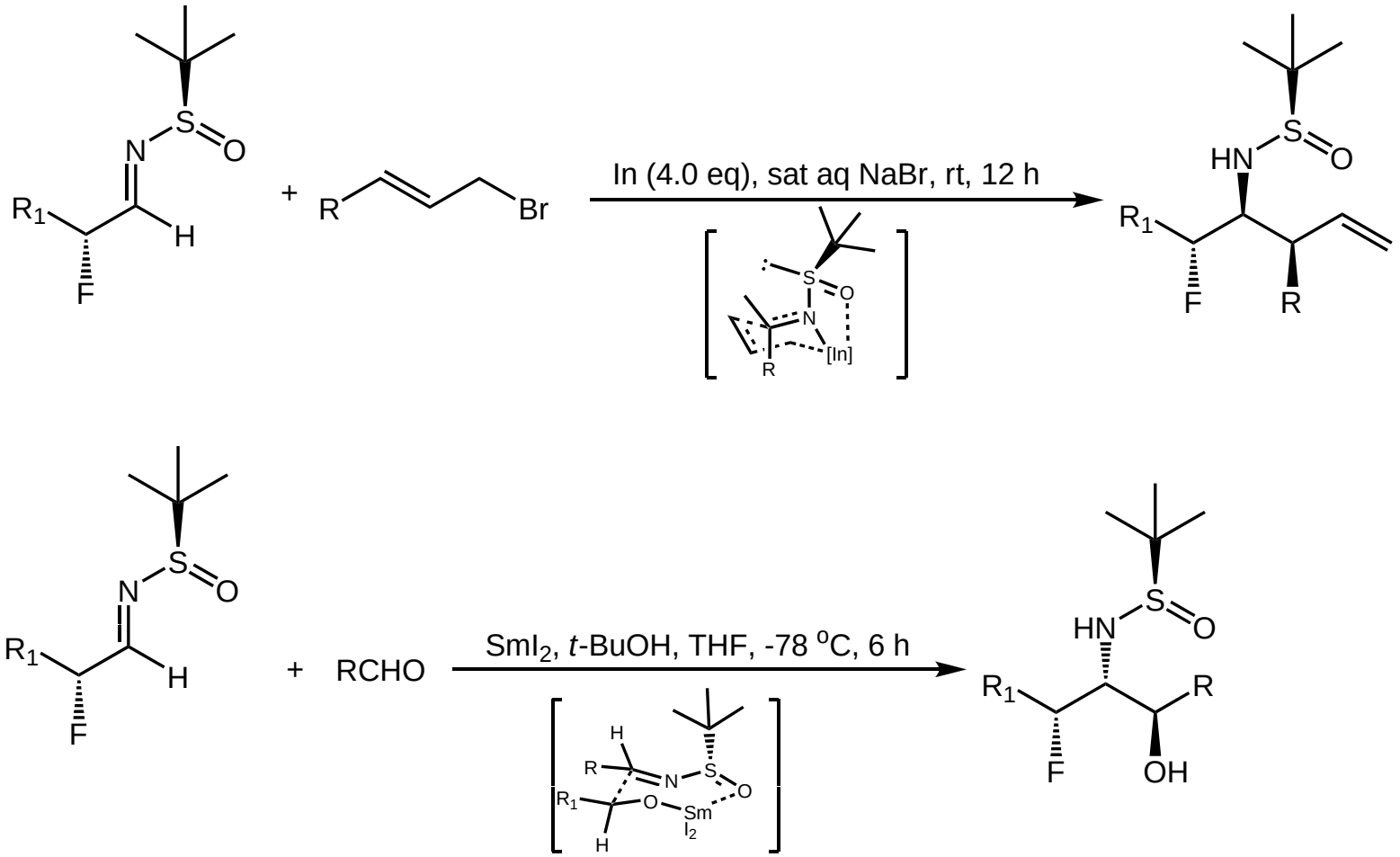


Highly Diastereoselective and General Synthesis of Primary β-Fluoroamines

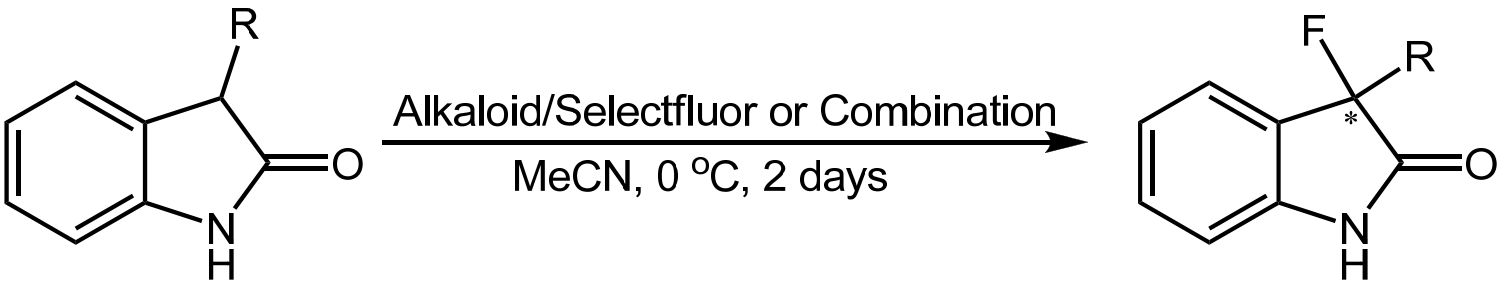


Lindsley. C. W. *et al. Org. Lett.* **2011**, *13*, 5684-5687


RMgX, CH2Cl2, -20 °C to rt, 12 h
(R)
(R)
ArB(OH)2, Rh(I), Et3N (2 eq)
dioxane/water (1:2), rt, 2 h
(R)
(R)

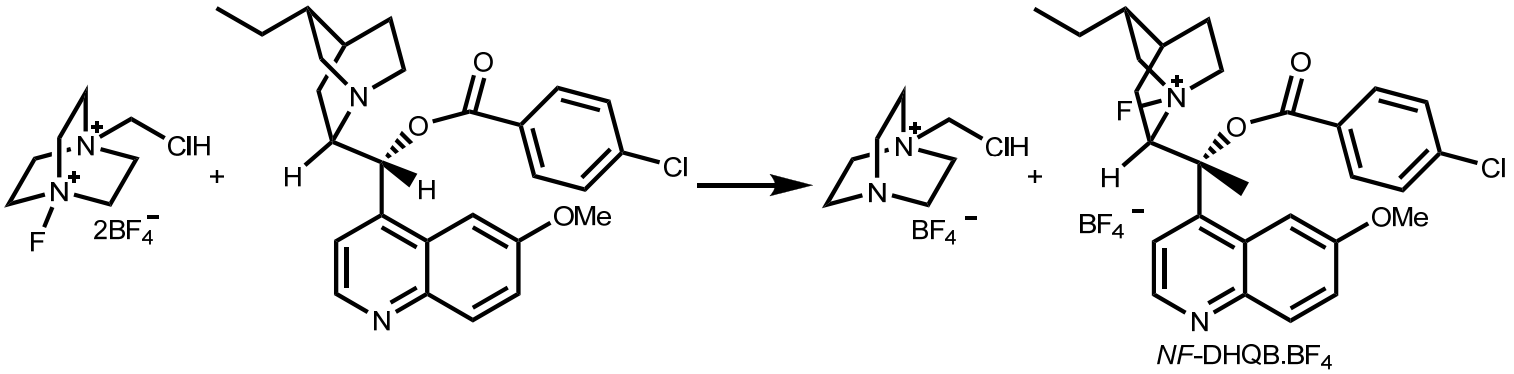

In (4.0 eq), sat aq NaBr, rt, 12 h
SmI2, t-BuOH, THF, -78 °C, 6 h
RCHO

Enantioselective Fluorination Mediated by Cinchona Alkaloid Derivatives/Selectfluor Combinations: Reaction Scope and Structural Information for *N*-Fluorocinchona Alkaloids



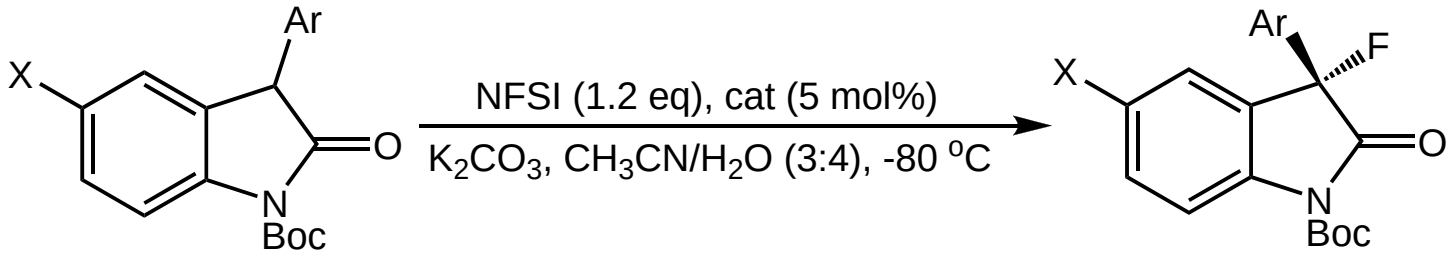
R = Bn, Me, Et, CO_2Et, *p*-MeOBn, *i*-Pr

up to 82% ee



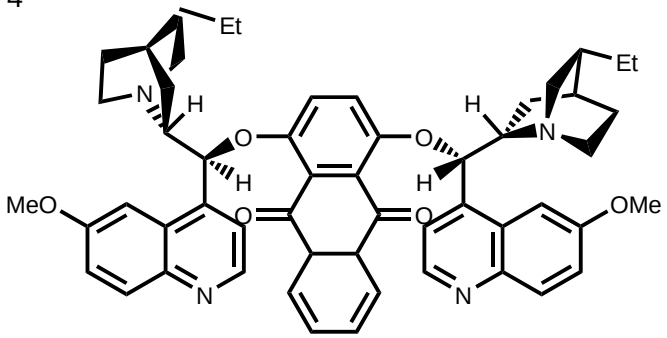
Shibata, N. *et al. J. Am. Chem. Soc.* **2001**, *123*, 7001-7009

Cinchona Alkaloid Catalyzed Enantioselective Fluoroination of Allyl silanes,Silyl Enol Ethers, and Oxindoles



X = H, Me, OMe;
Ar = Ph, *p*-Tol, *p*-FC_6H_4

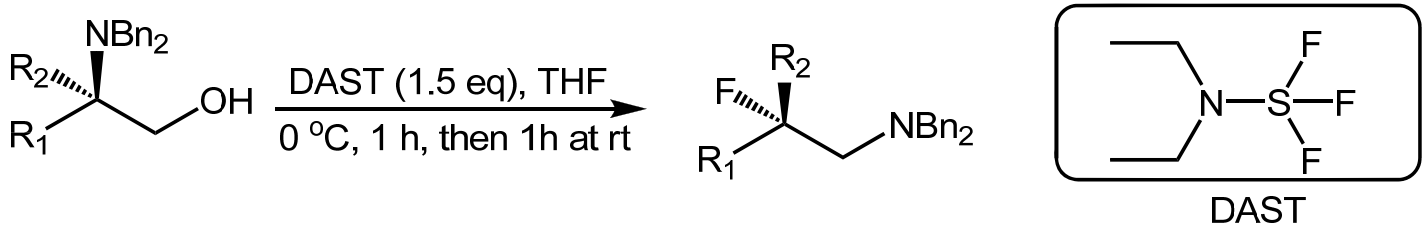
up to 87% ee

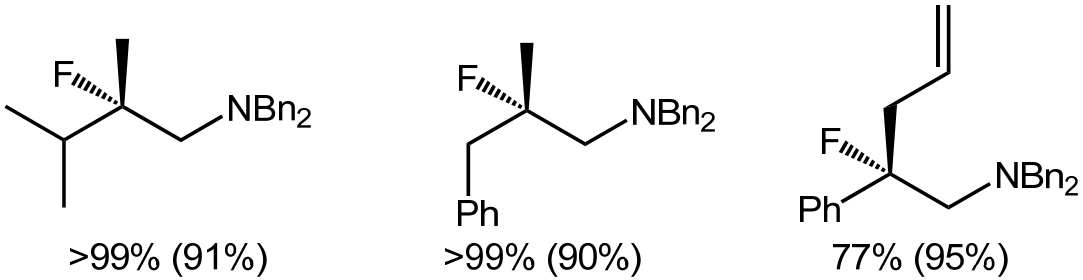


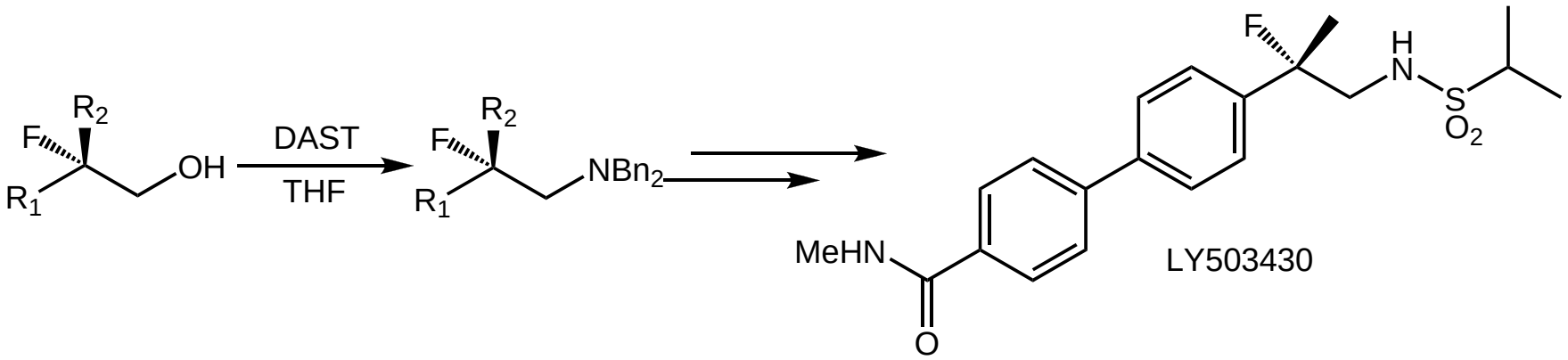
$(DHQD)_2AQN$

Shibata, N. *et al.* *Angew. Chem. Int. Ed.* **2008**, *47*, 4157-4161

Enantioselective Synthesis of β-Fluoroamines from β-Amino Alcohols: Application To the Synthesis of LY503430

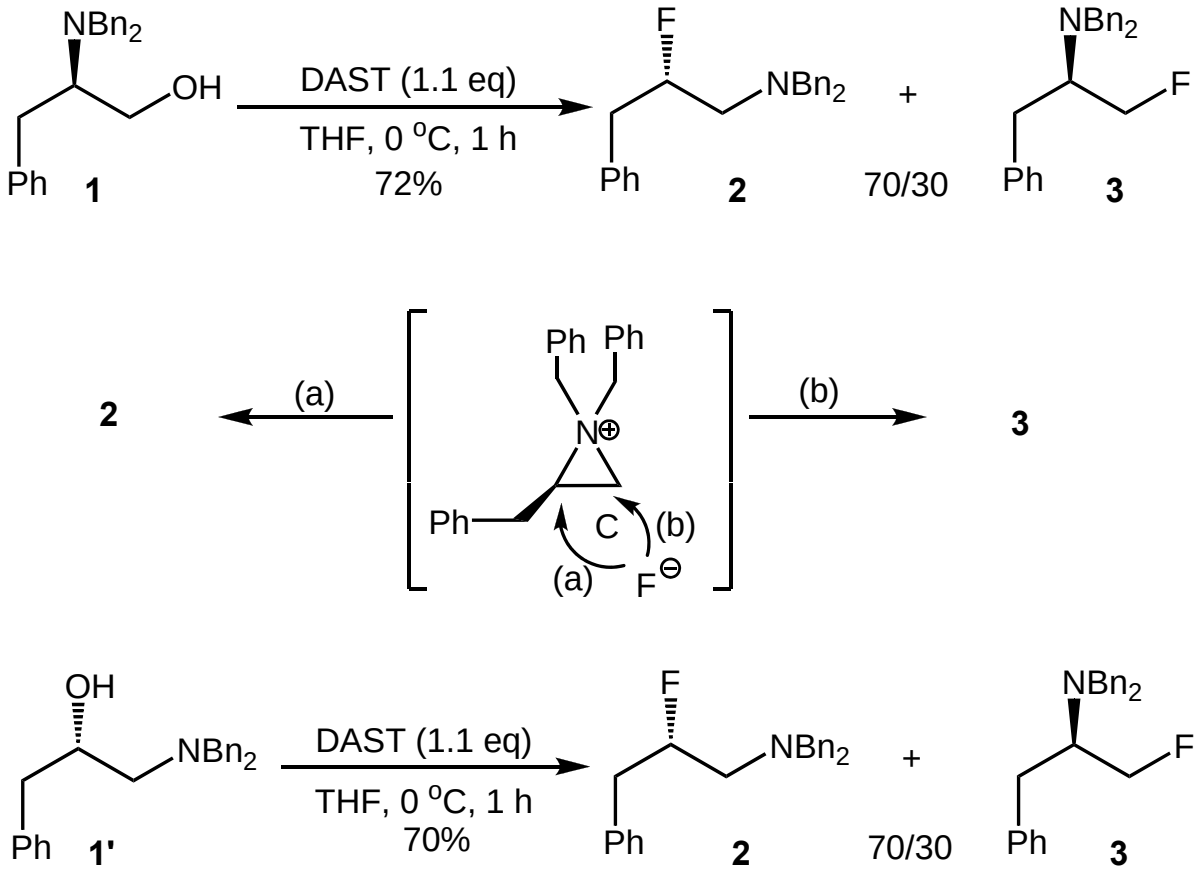




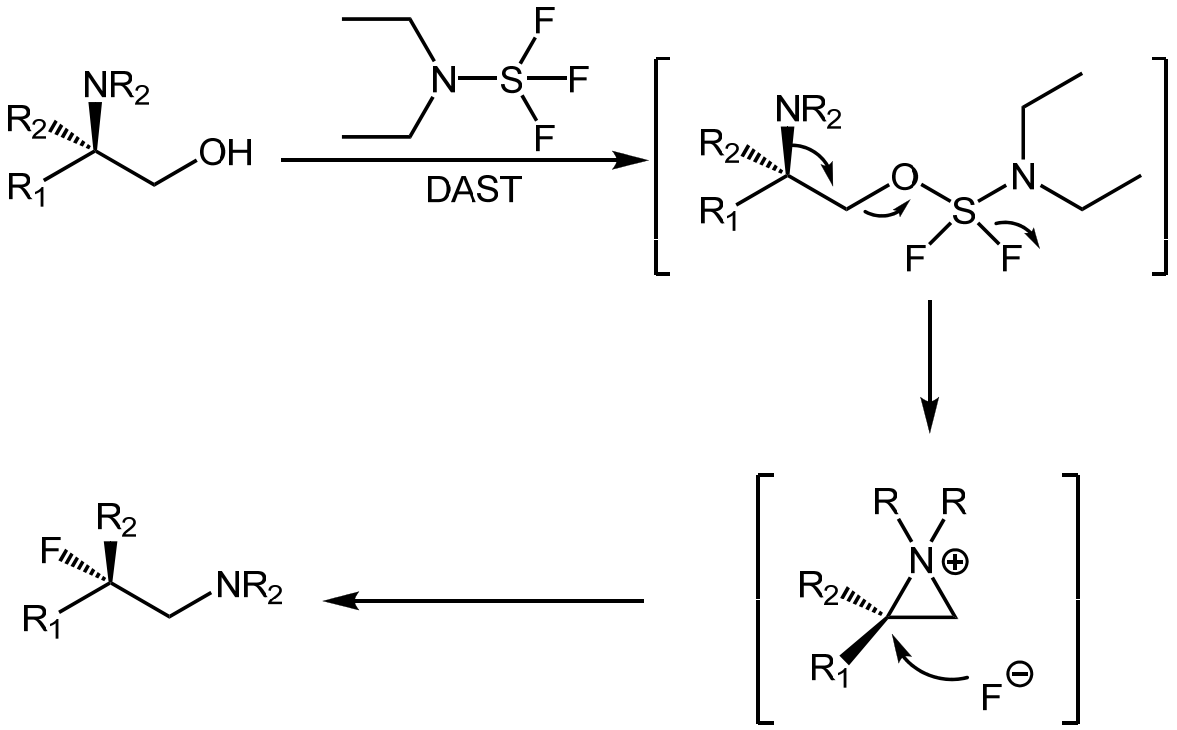


Cossy, J. *et al*. *Org. Lett.* **2010**, *12*, 4620-4623

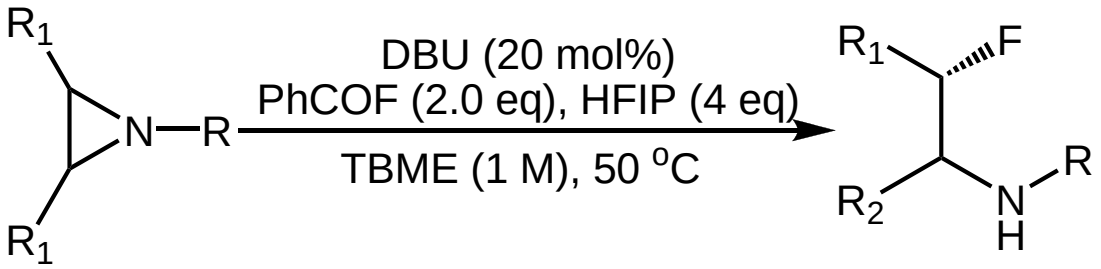
Rearrangement of 1 and 1’

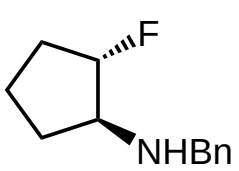


Mechanism of the Rearrangement

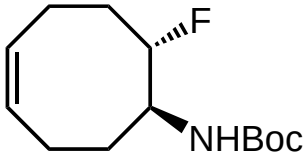


Synthesis of β-Fluoroamines by Lewis Base Catalyzed Hydrofluorination of Aziridines

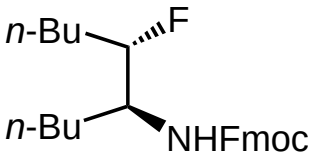




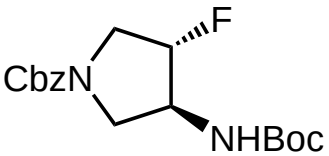
82%



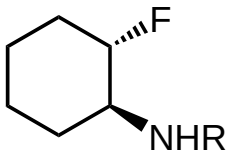
81%



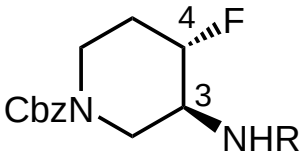
92%



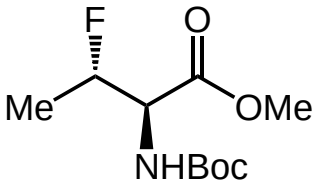
82%



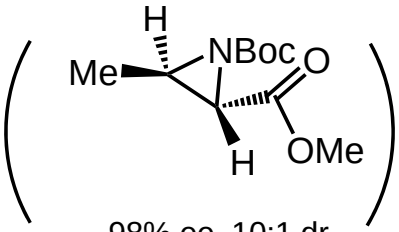
R = Boc, Cbz, Bn, *et al.*



76% 11:1 4-F:3-F

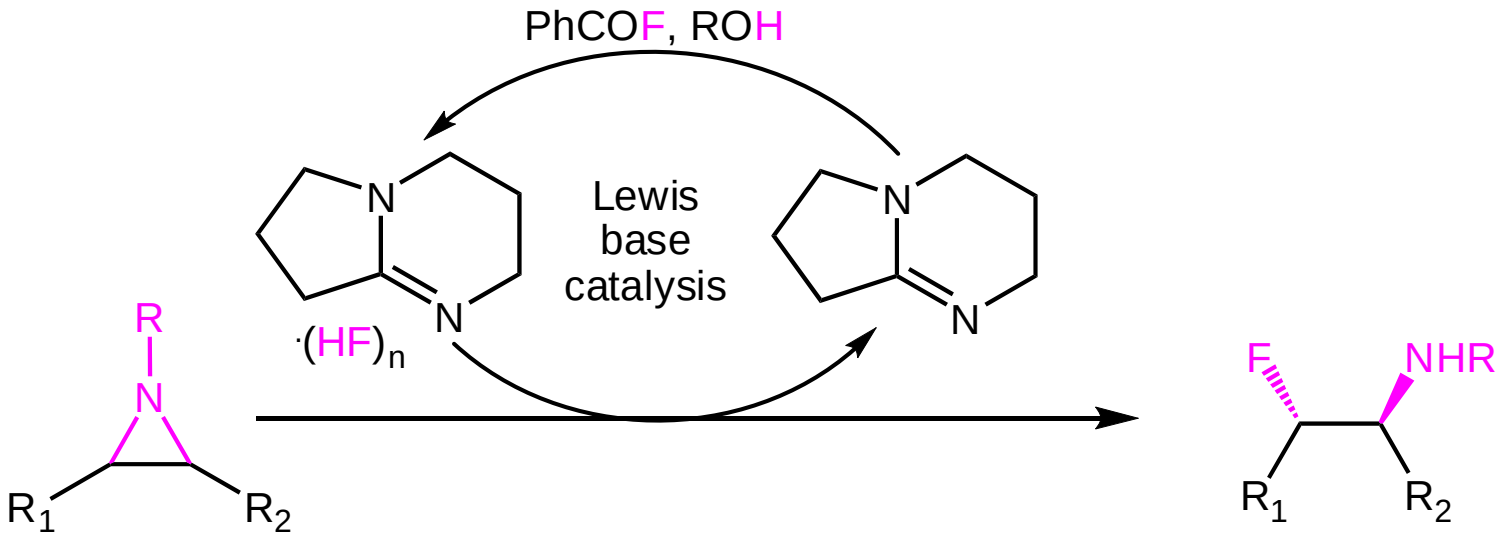


82% (98% ee), 10:1 dr



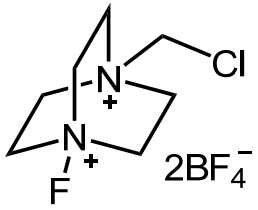
98% ee, 10:1 dr

Doyle, A. G. *et al. J. Org. Chem.* **2012**, *77*, 4177-4183

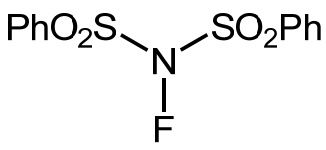

PhCOF, ROH
Lewis
base
catalysis
N
N
N
N
·(HF)n
R
N
R1
R2
F
NHR
R1
R2

Summary

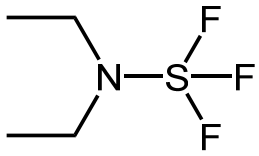
1. Fluorination reagent:



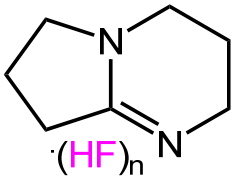
Selectfluor



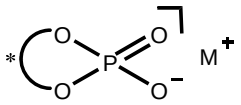
NFSI

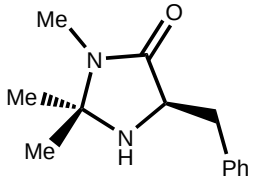


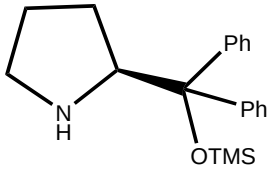
DAST

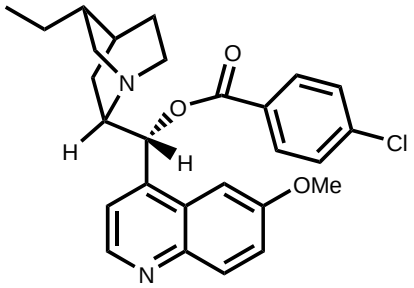


2. Catalysts:









The prevalence of fluorine atoms in pharmaceutical agents has driven the development of new methods for the enantioselective introduction of fluorine into small molecules that may constitute basic building blocks for elaboration into biologically relevant molecules. In this context, the chiral *β*-fluoroamine motif is one of remarkable utility; the presence of a *β*-fluorine is well established to lower the pKa of the amine nitrogen, impacting binding, metabolism, and other pharmacological Properties. Nevertheless, there are few direct methods for the asymmetric synthesis of *β*-fluoroamines. Those that do exist often proceed through processes in which introduction of the fluorine is not itself asymmetric or through *α*-fluorocarbonyl compounds generated by enantioselective fluorination of ketones and aldehydes. Organocatalysis has provided a number of elegant protocols for this asymmetric *α*-fluorination reaction, including cinchona alkaloid-mediated transformations and those based on enamine catalysis. We noted that the latter highly successful organocatalyic methods proceed via *α*-fluoroimine intermediates that are subsequently hydrolyzed for the necessary release of the secondary amine catalyst. We speculated that a methodology, distinct from enamine catalysis, in which an enantioenriched α-fluoroimine could be isolated would be highly versatile. These products could be elaborated through a number of well-precedented pathways to a wide variety of enantioenriched *β*-fluoroamines.

In summary, we have extended our concept of anionic phase-transfer catalysis to encompass the enantioselective fluorination of cyclic enamides. The scope of this transformation is broad, and we have demonstrated the effectiveness of the reaction on five-, six-, and seven-membered rings as well as heterocyclic rings. Our future work will focus on gaining insight into the factors controlling the selectivity and, more generally, opening new avenues for this mode of catalysis.