Literature Report

Regio- and Enantioselective Bromocyclization of Difluoroalkenes as a Strategy to Generate Difluoromethylated Stereocenters

Reporter: Mu-Wang Chen
Checker: Xiang Li
Date: 2020-08-17

Miller, E.; Kim, S.; Toste, F. D.; et al.
J. Am. Chem. Soc. **2020**, *142*, 8946−8952.

CV of Prof. F. Dean Toste

Background:

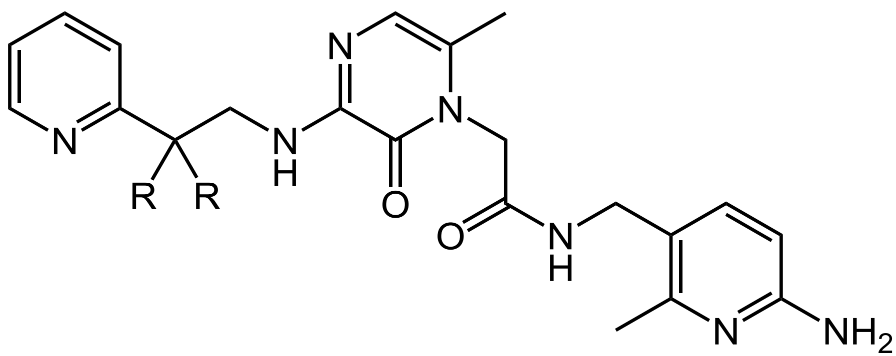
- **1993 &1995** University of Toronto;
- **1995-2000** Ph.D., Stanford University;
- **2001-2002** Postdoctoral fellow, Caltech;
- **2002- now** Professor, University of California, Berkeley.

Research:

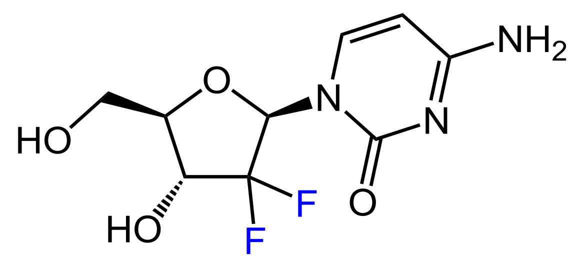
Research in my group is primarily aimed toward the development of catalysts and catalytic reactions and methods for organic synthesis. Ultimately, we are interested in using these methods to address problems in the synthesis of complex molecules possessing interesting structural, biological and physical properties.

Contents

Drugs Containing a Difluoroalkyl Group

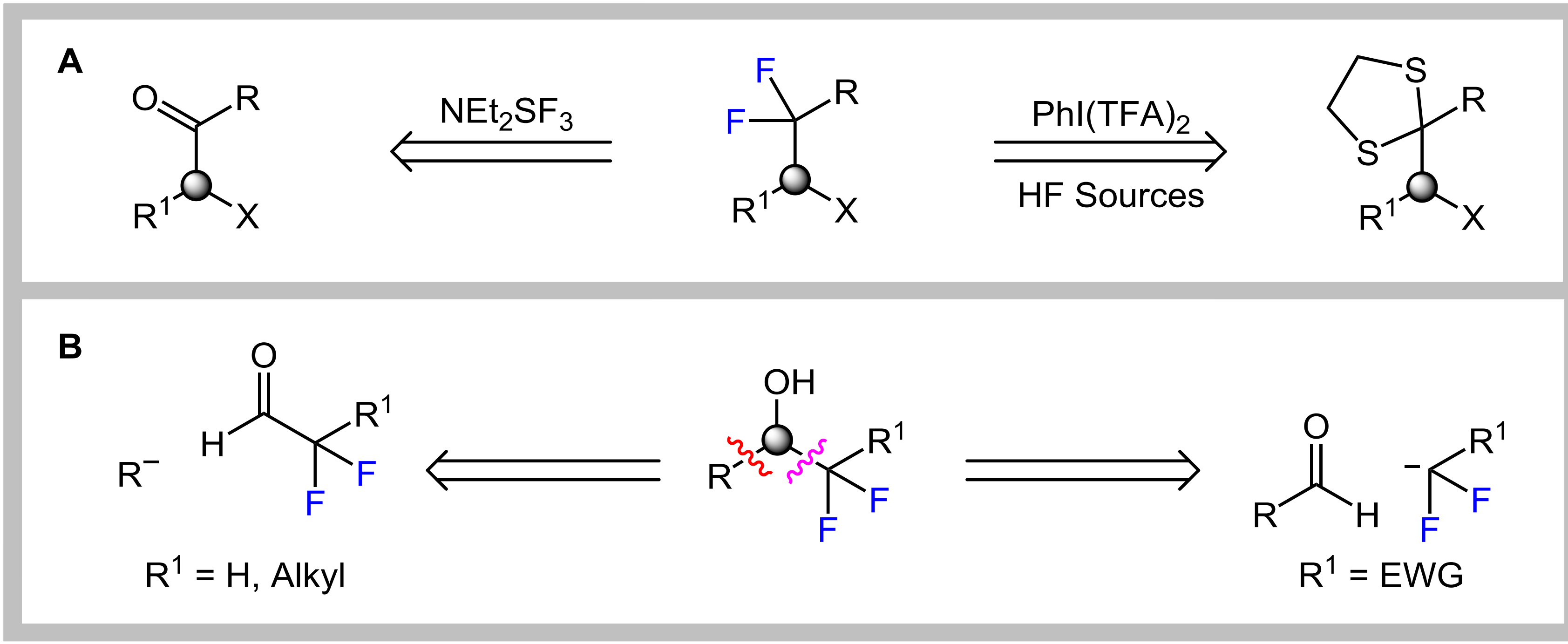


R = H, **Thrombin K_1 (IC_{50} = 0.27)**
R = F, **Thrombin K_1 (IC_{50} = 0.042)**



Gemcitabine
for the treatment of cancer

Incorporation of the Difluoromethylene Group



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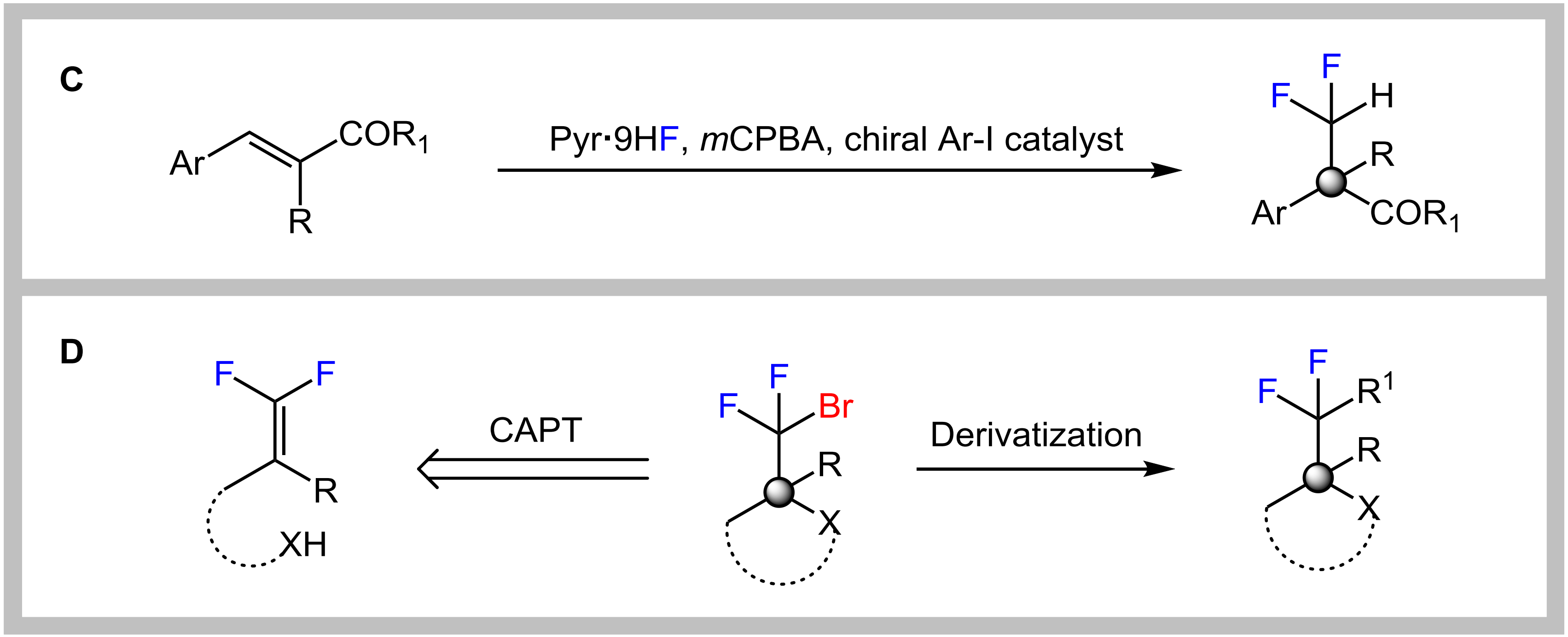
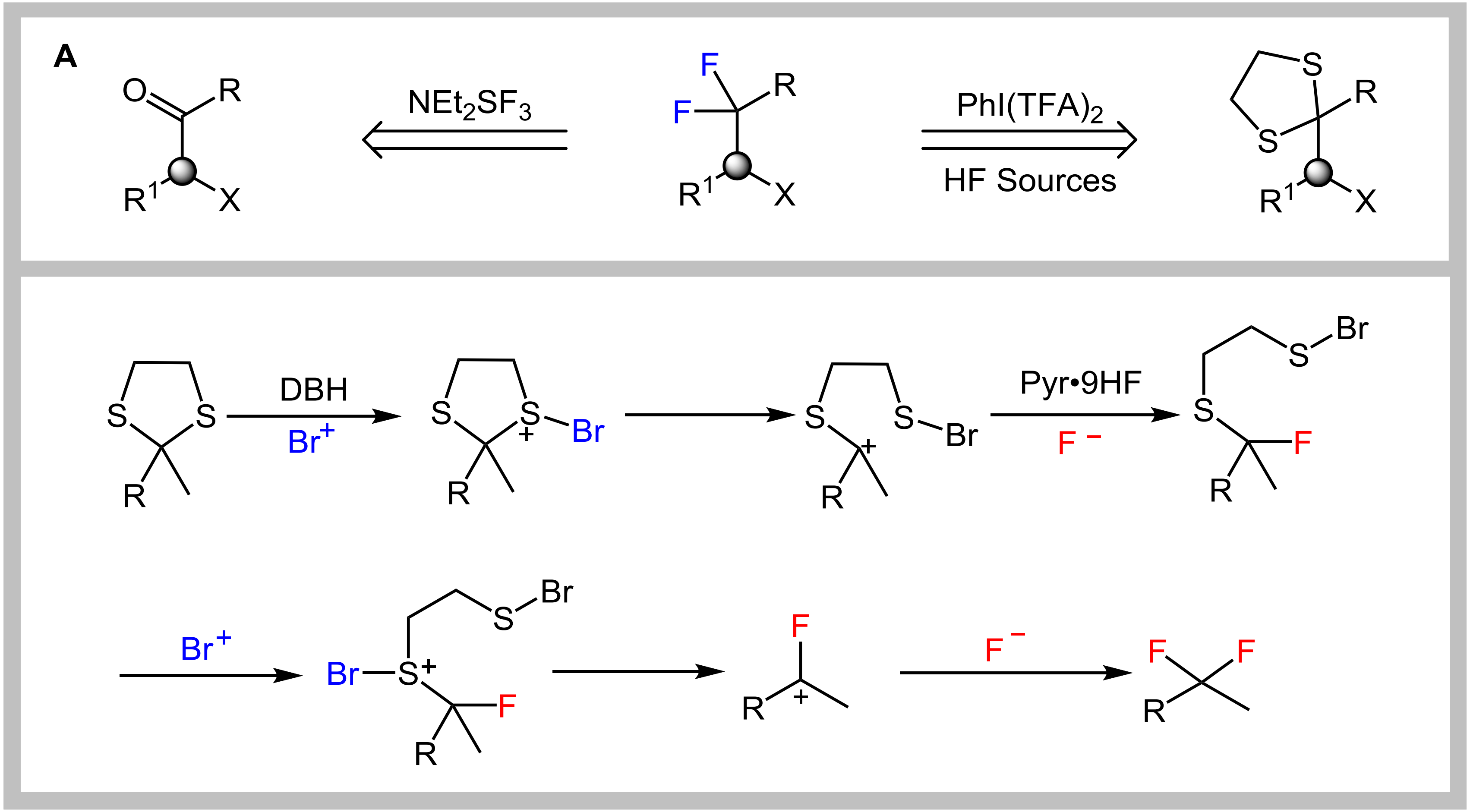
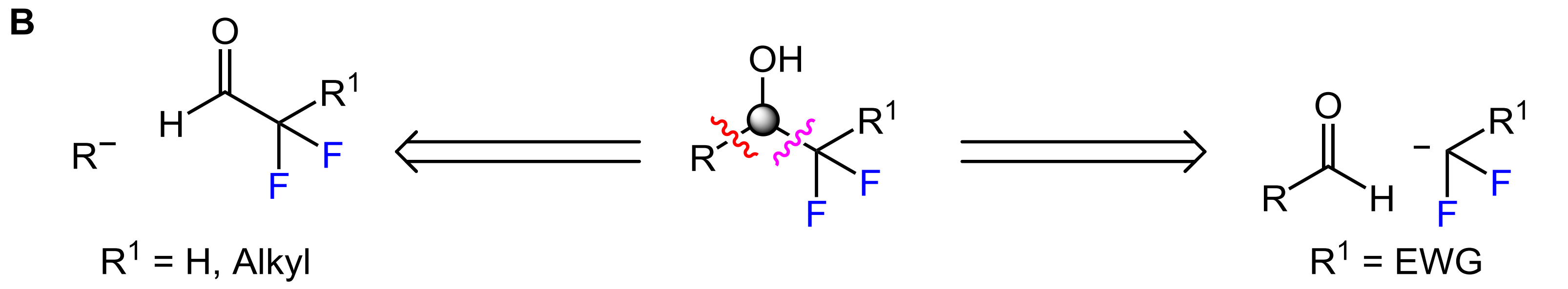


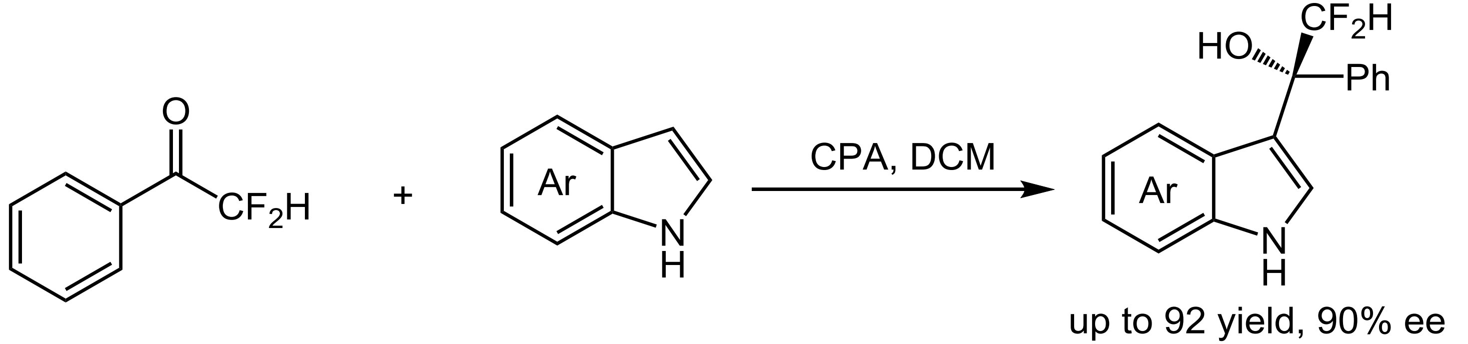
Incorporation of the Difluoromethylene Group



Tozer, M. J.; et al. *Tetrahedron* **1996**, *52*, 8619

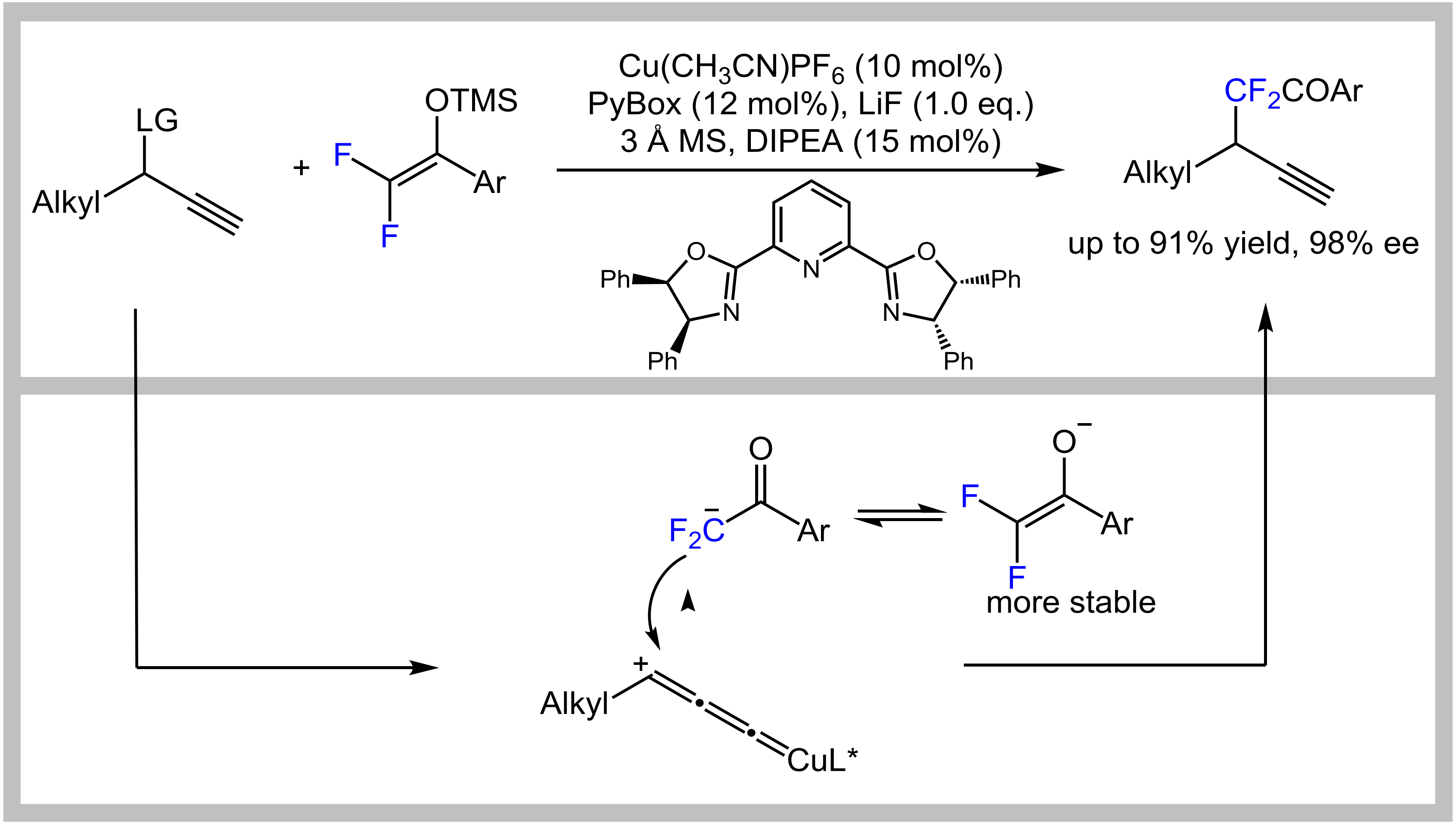
Incorporation of the Difluoromethylene Group





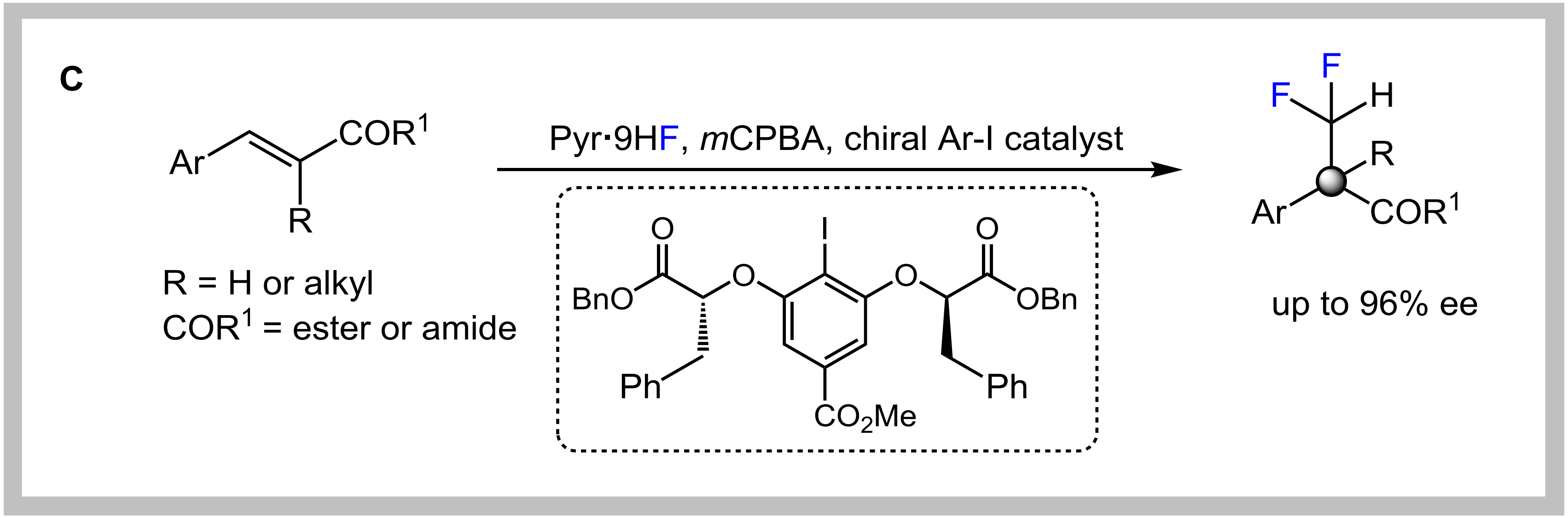
Ma, J.-A..; et al. *Chem.Commun* **2009**, 2356

Incorporation of the Difluoromethylene Group



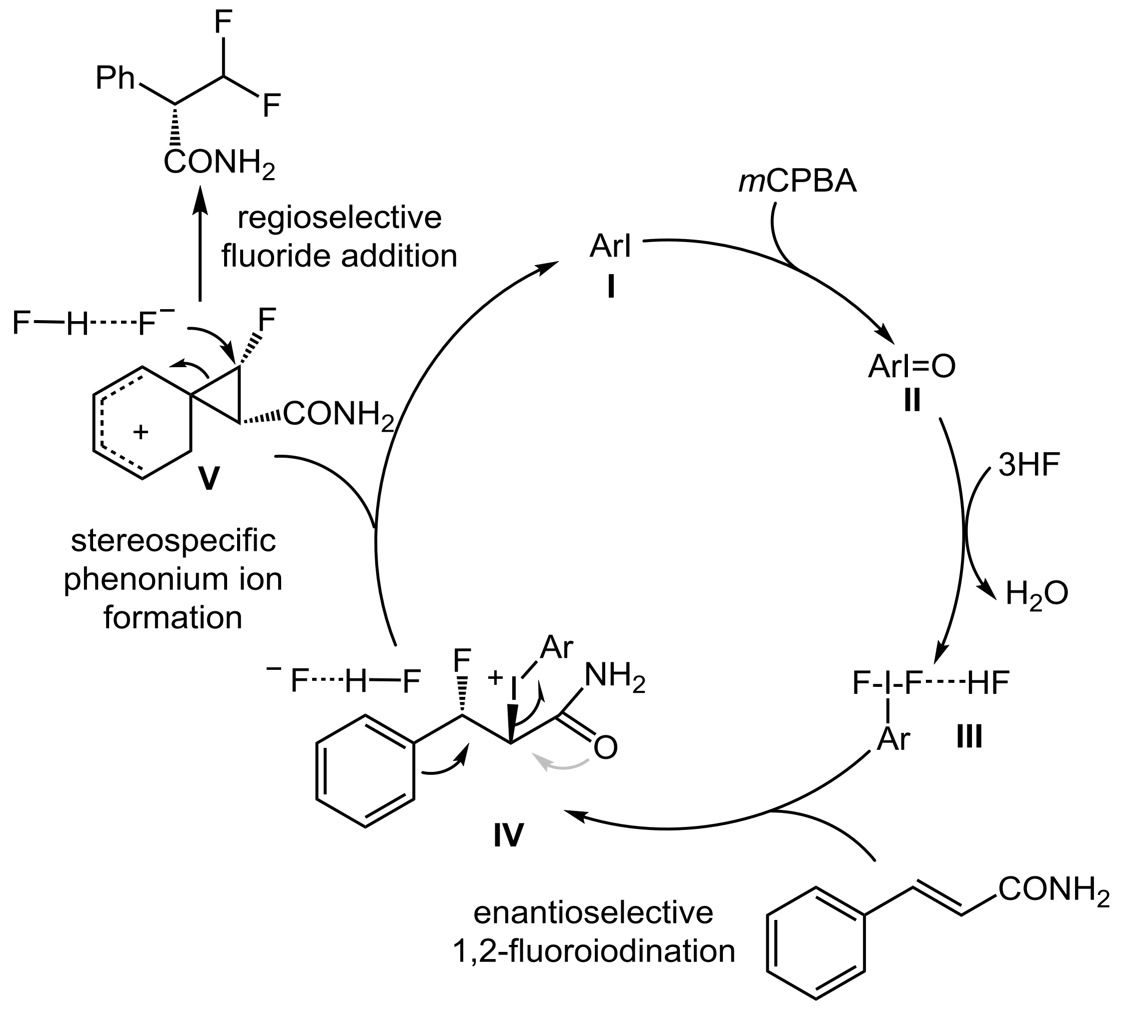
Zhang, X.; et al. *Chem.* **2019**, *5*, 2987

Incorporation of the Difluoromethylene Group

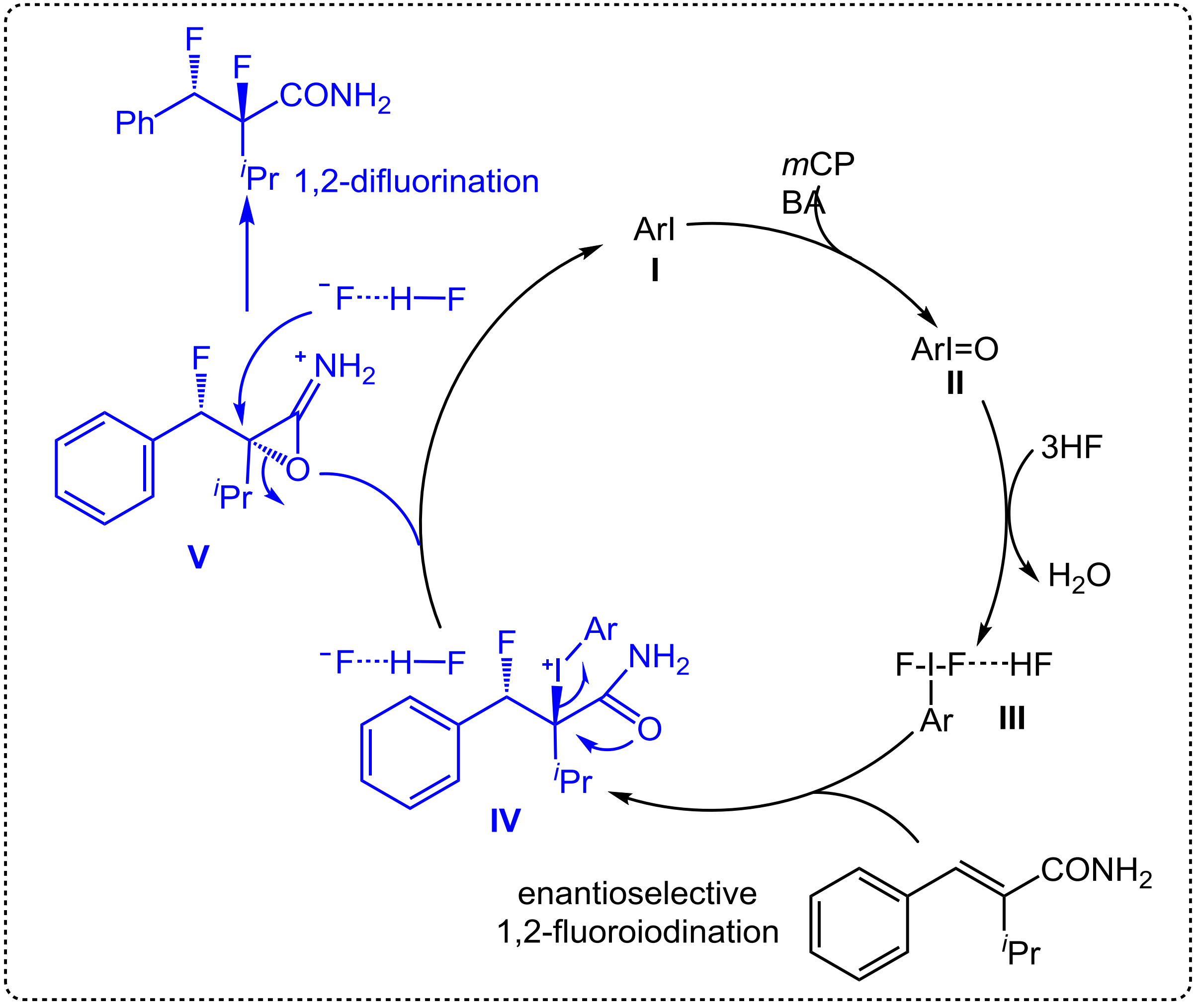


Jacobsen, E. N.; et al. *Science.* **2016**, *353*, 51

Proposed Mechanism

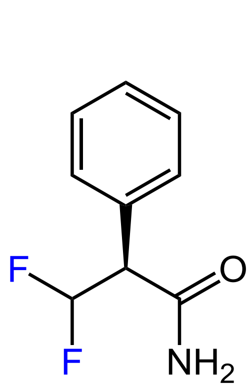


Proposed Mechanism

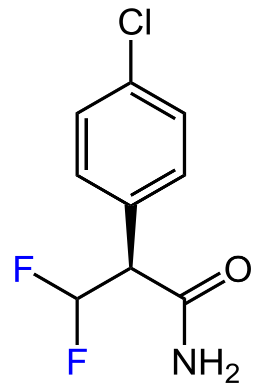


Jacobsen, E. N.; et al. *J. Am. Chem. Soc.* **2016**, *138*, 5000

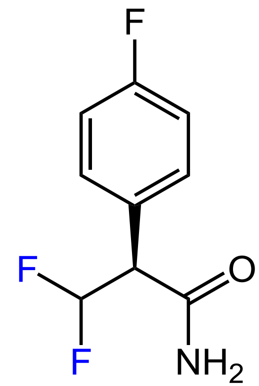
Substrate Scope



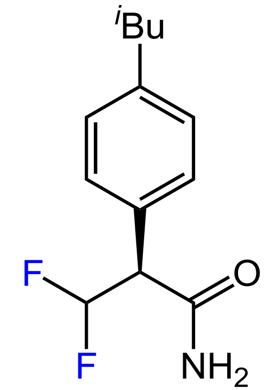
3a
67% yield, 92% ee



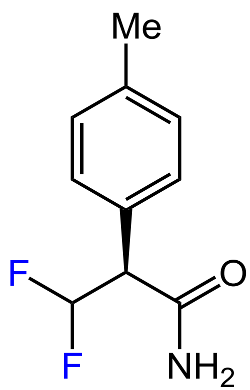
3b
63% yield, 92% ee



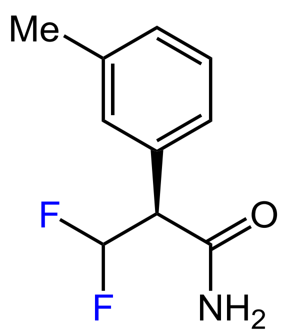
3c
76% yield, 91% ee



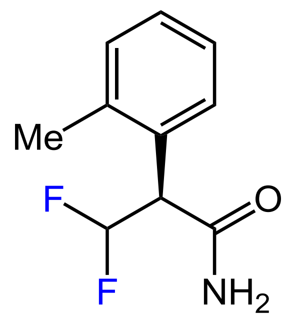
3d
80% yield, 83% ee



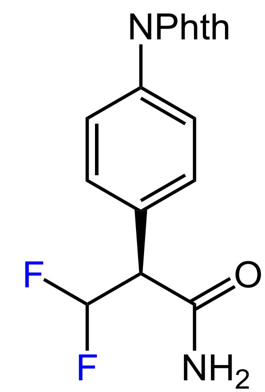
3e
83% yield, 84% ee



3f
73% yield, 94% ee

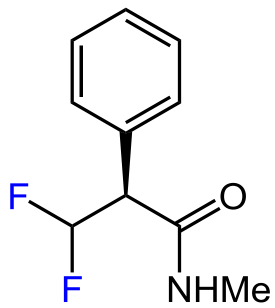


3g
67% yield, 82% ee

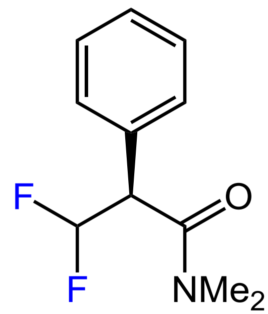


3h
76% yield, 94% ee

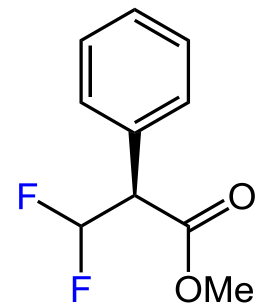
Substrate Scope



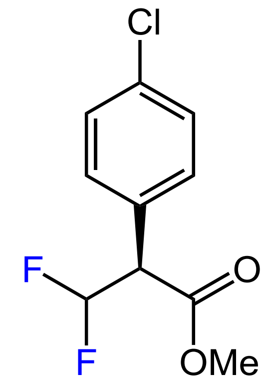
3i
67% yield, 90% ee



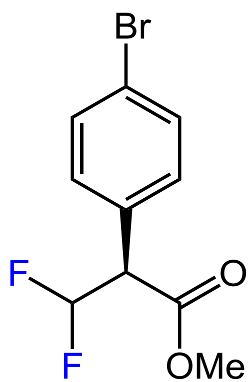
3j
28% yield, 96% ee



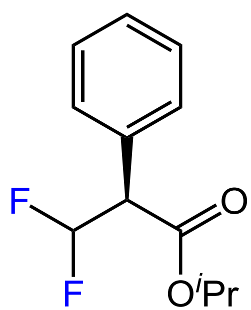
3k
49% yield, 84% ee



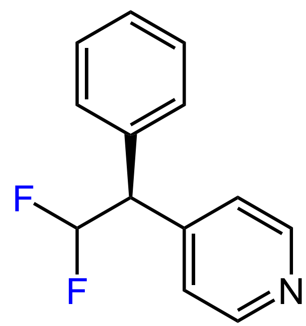
3l
62% yield, 87% ee



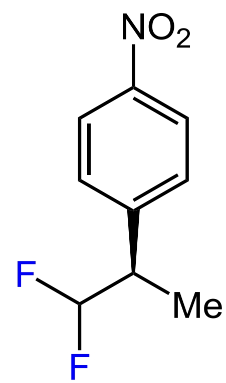
3m
45% yield, 87% ee



3n
63% yield, 85% ee

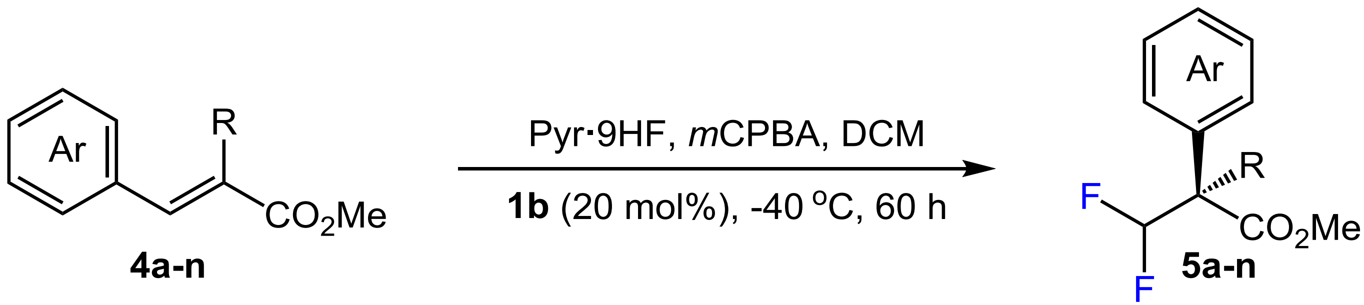


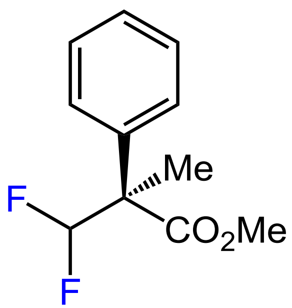
3o
74% yield, 71% ee



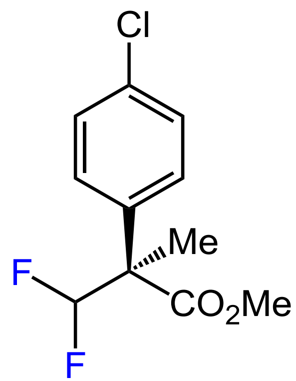
3p
52% yield, 74% ee

Substrate Scope

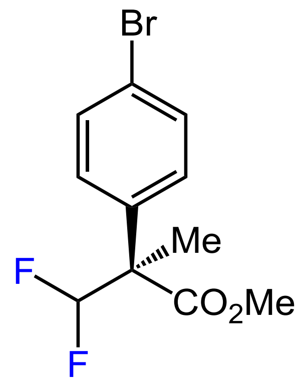




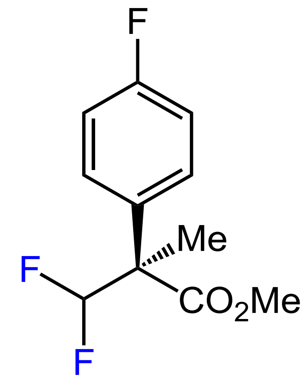
5a
74% yield, 94% ee



5b
70% yield, 96% ee

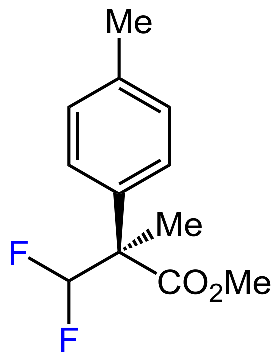


5c
76% yield, 96% ee

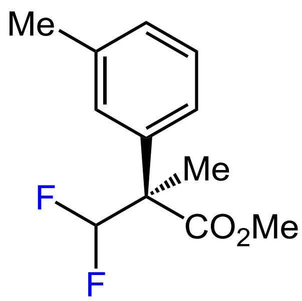


5d
71% yield, 95% ee

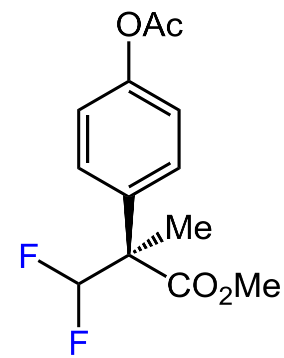
Substrate Scope



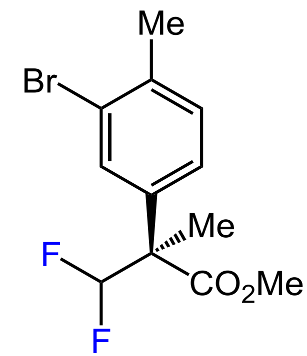
5e
54% yield, 94% ee



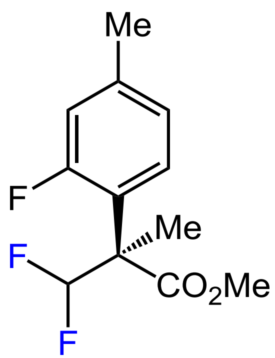
5f
59% yield, 97% ee



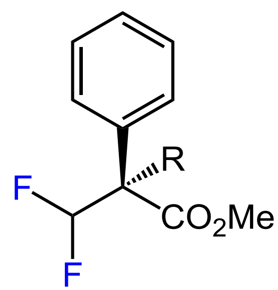
5g
63% yield, 95% ee



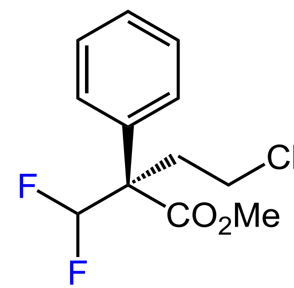
5h
78% yield, 97% ee



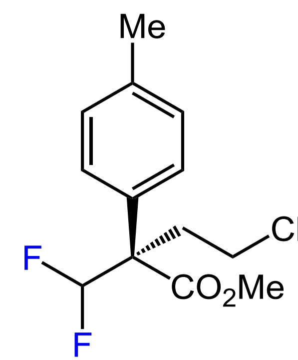
5i
71% yield, 90% ee



5j R = Et, 67% (96% ee)
5k R = *n*Bu, 60% (94% ee)
5l R = ^{i}Pent, 57% (93% ee)

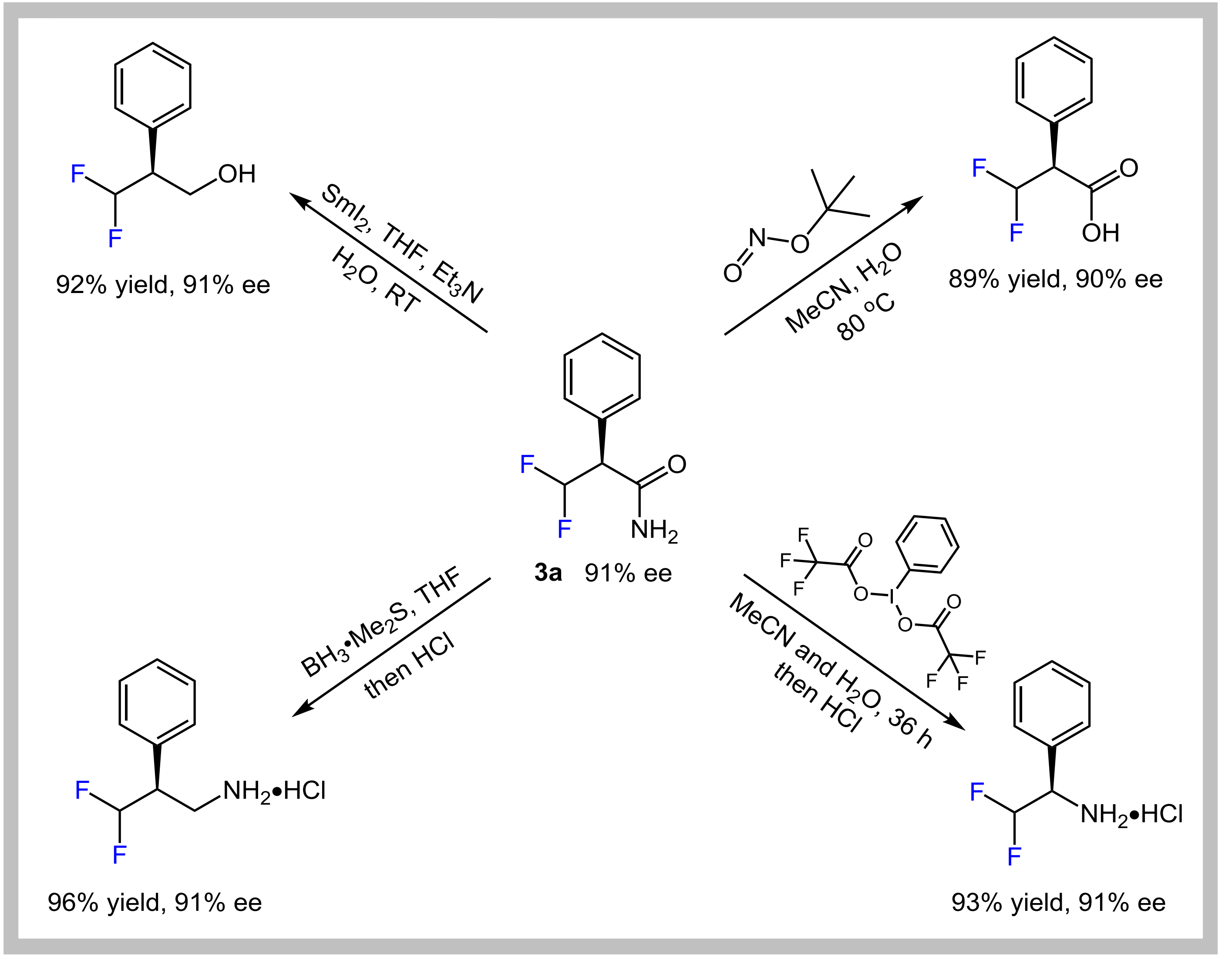


5m
76% yield, 96% ee

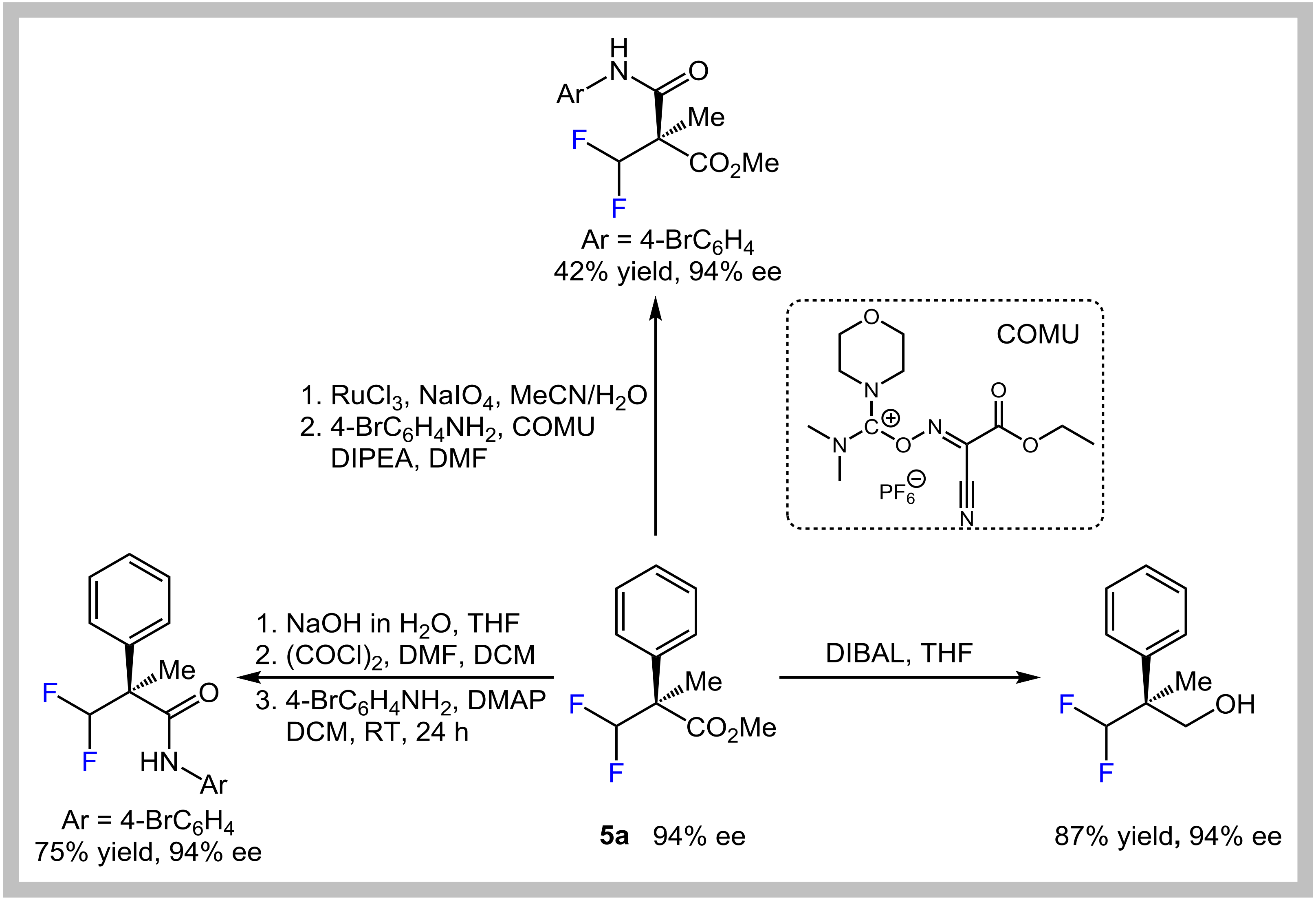


5n
71% yield, 95% ee

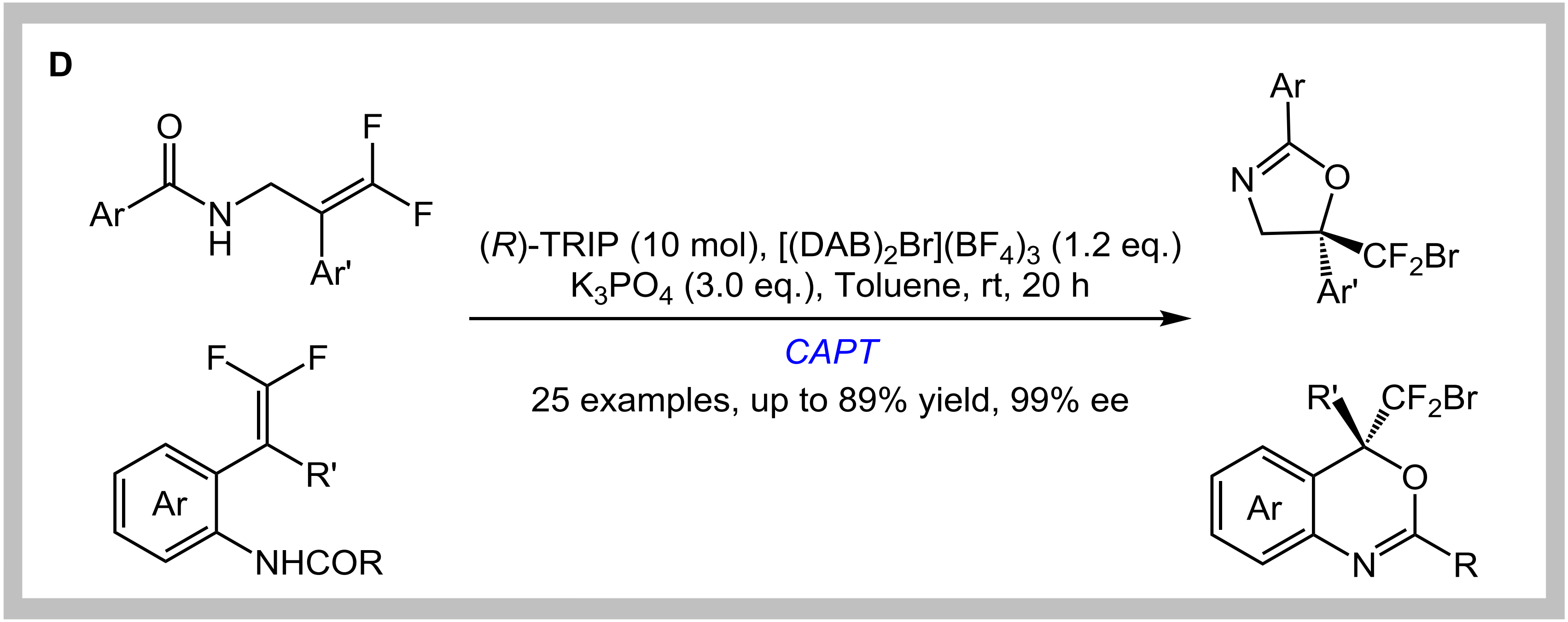
Transformations of Products



Transformations of Products



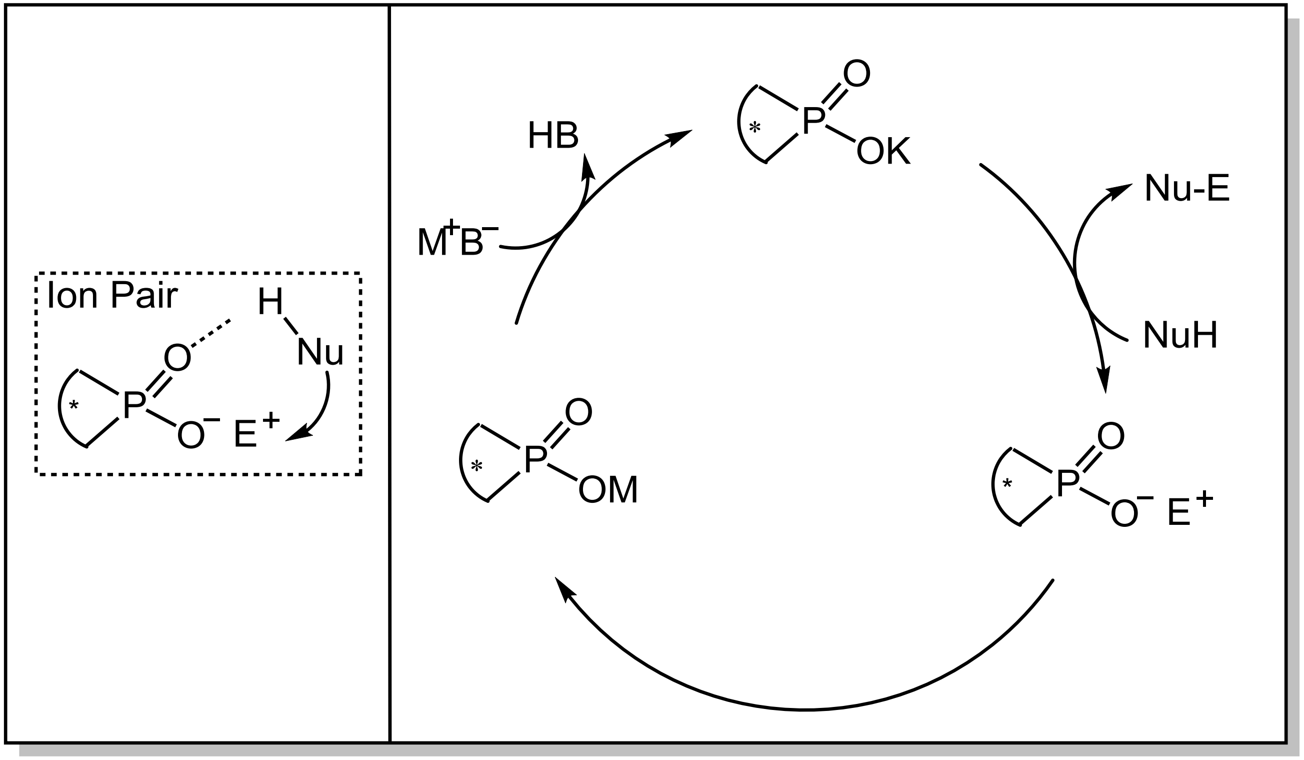
Incorporation of the Difluoromethylene Group



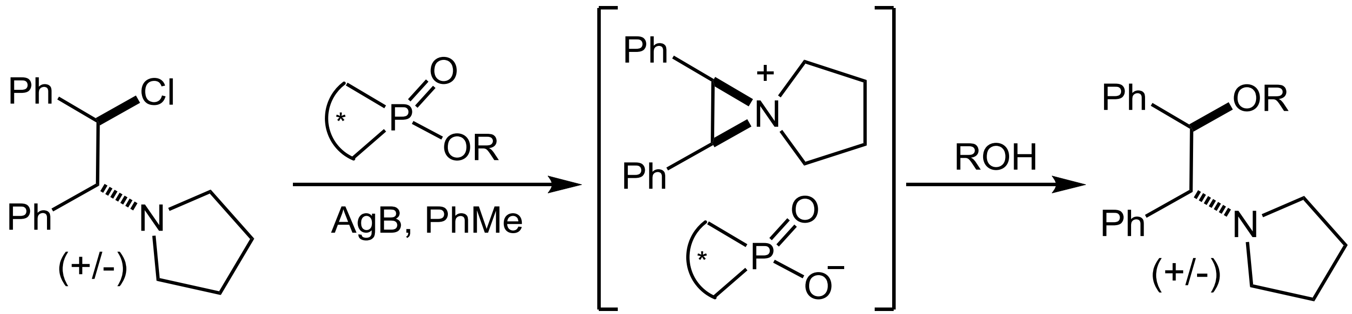
Toste, F. D.; et al. *J. Am. Chem. Soc.* **2020**, *142*, 8946

Chiral Anion Phase Transfer Catalysis

手性阴离子相转移催化剂，由F. Dean Toste提出的。 用手性膦酸的阴离子来做相转移催化剂。他总的思路是这样的：溶剂为两相溶剂，一份大极性，一份小极性。一些金属盐都存在在大极性溶剂中，而有机物在小极性溶剂中存在。手性相转移催化剂能将盐中阳离子，如卤素正离子带到小极性溶剂中，通过氢键作用实现手性催化。这样做的好处是，由于两相溶剂的存在，背景反应可以被大大抑制，对一些背景反应速率较快的反应也能实现手性催化。



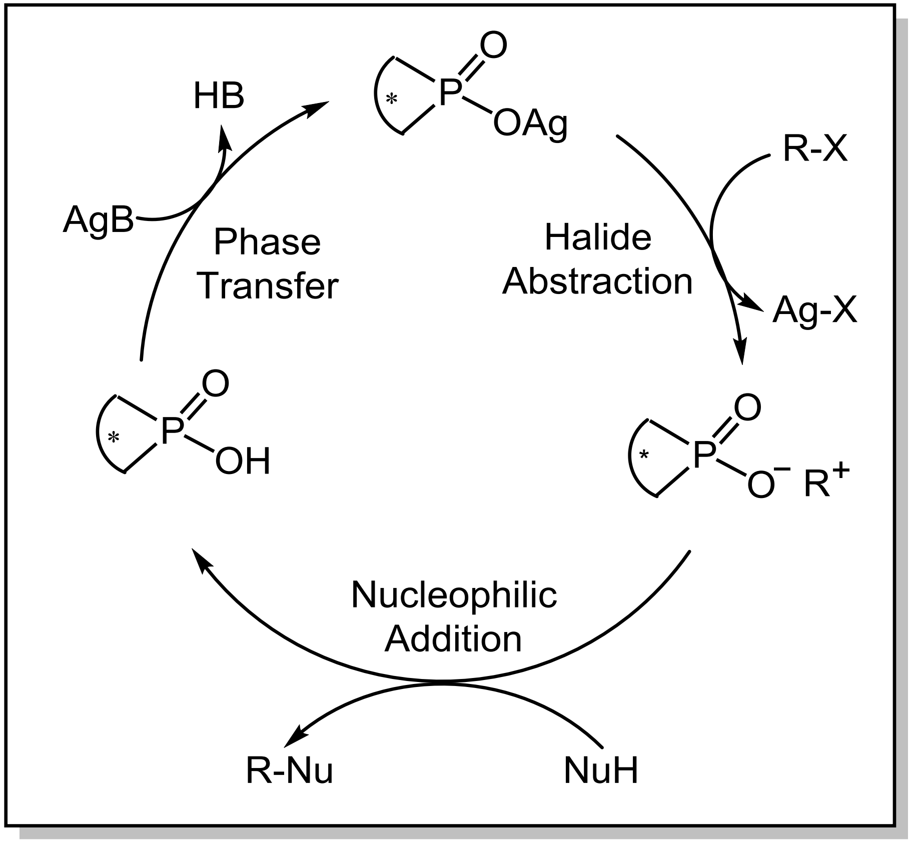
Chiral Anion Phase Transfer Catalysis



Entry	Cat. (R)	AgB	Additive	Yield (%)	Ee (%)
1	H	Ag_2CO_3	none	77	94
2	Ag	Ag_2CO_3	none	74	94
3	Ag	none	none	trace	ND
4	none	Ag_2CO_3	none	trace	ND
5	Ag	Ag_2CO_3	4Å MS	84	94

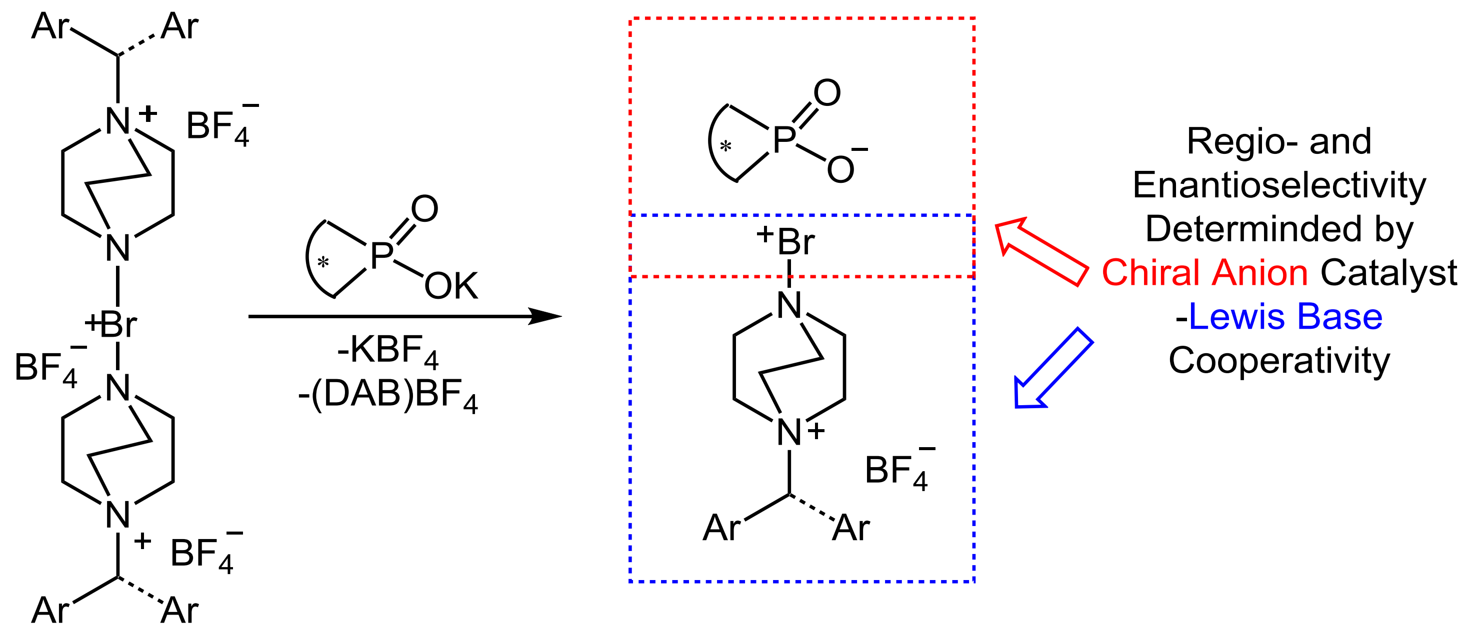
Toste, F. D.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 14984

Proposed Mechanism



Toste, F. D.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 14984

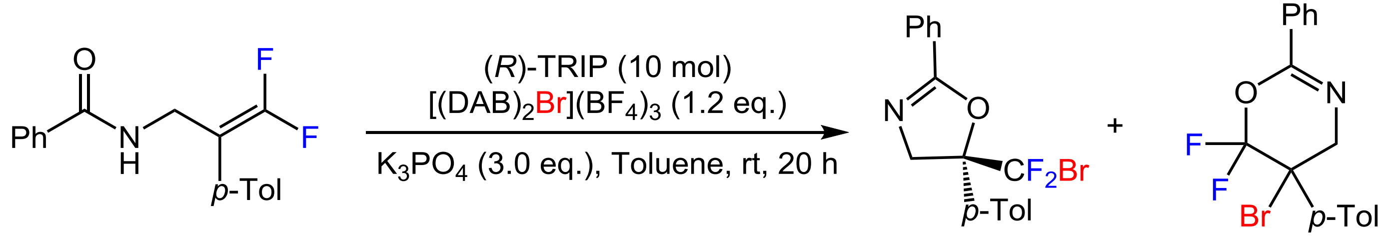
Chiral Anion Phase Transfer Catalysis



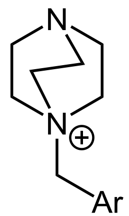
$[(DAB)_2Br](BF_4)_3$
(insoluble reagent)

$[(DAB)Br](TRIP)BF_4$
(soluble catalyst/reagent pair)

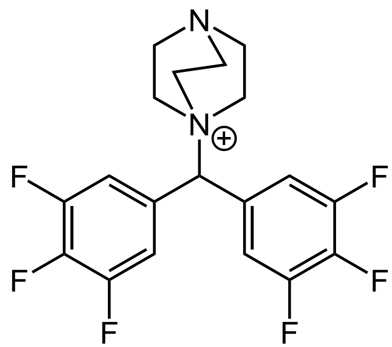
Optimization of Reaction Conditions



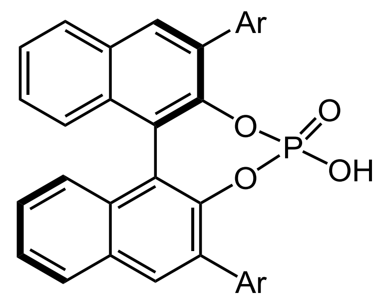
2a % yield (% ee) **2a'** % yield (% ee)



DAB[1] (Ar = Ph): 19(30); 25(49)
DAB[2] (Ar = 3,5-*t*Bu_2Ph): 20(0); 35(40)
DAB[3] (Ar = C_6Me_5): 23(-25); 40(69)
DAB[4] (Ar = C_6F_5): 26(77); 12(23)

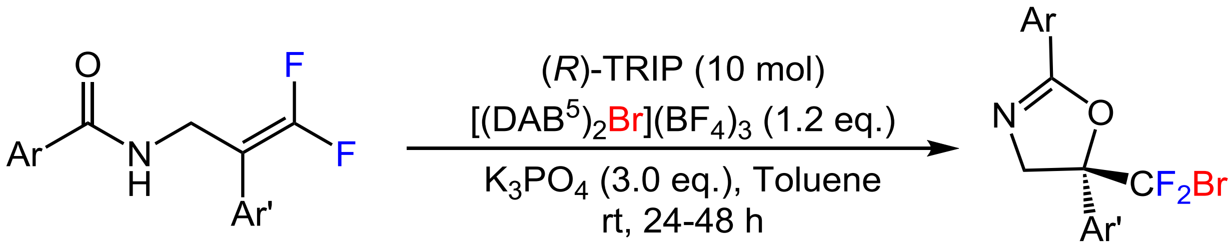


DAB[5]: 49(91); 12(-55)
DAB[5]: 75(90) 48h

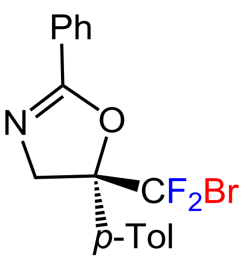


(*R*)-TRIP
Ar = 2,4,6-*i*Pr_3Ph

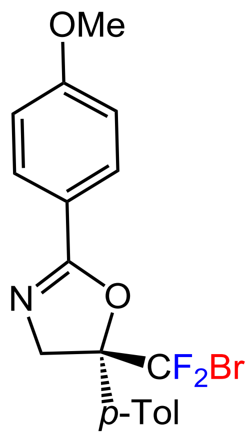
Substrate Scope



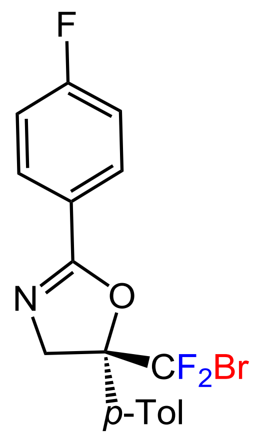
1a-l **2a-l**



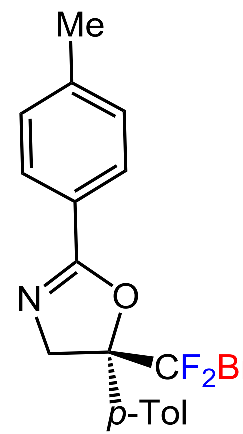
2a
75% yield, 90% ee



2b
63% yield, 89% ee

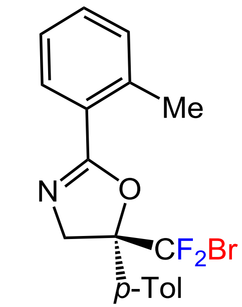


2c
68% yield, 90% ee

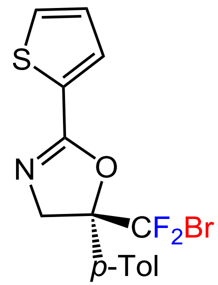


2d
58% yield, 90% ee

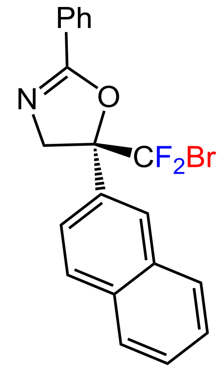
Substrate Scope



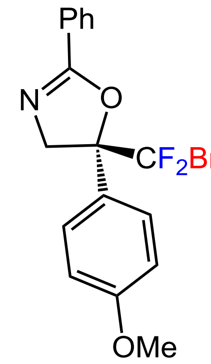
2e
53% yield, 92% ee



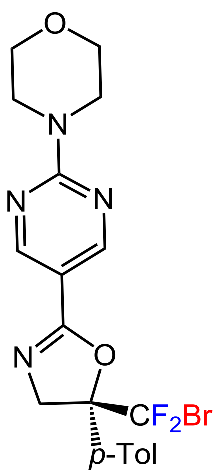
2f
69% yield, 92% ee



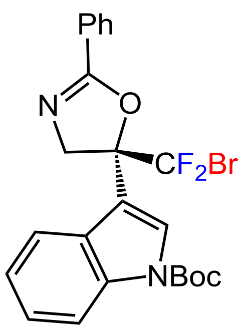
2g
37% yield, 90% ee



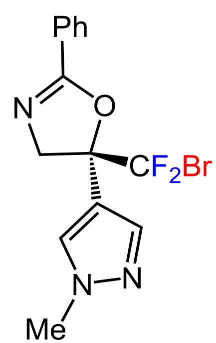
2h
79% yield, 83% ee



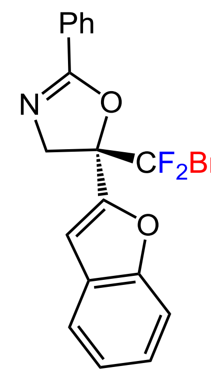
2i
62% yield, 84% ee



2j
62% yield, 76% ee

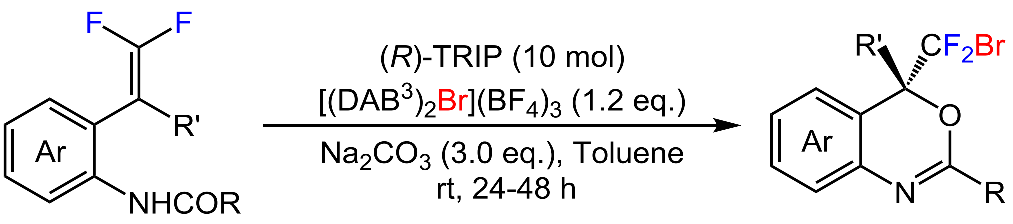


2k
68% yield, 60% ee

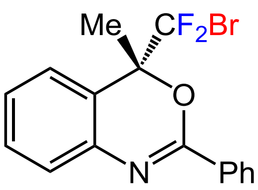


2l
36% yield, 82% ee

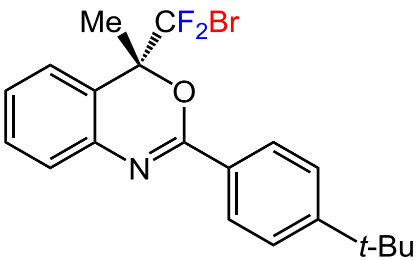
Substrate Scope



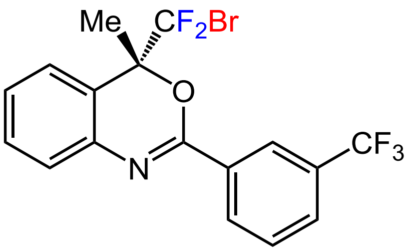
3a-l **4a-l**



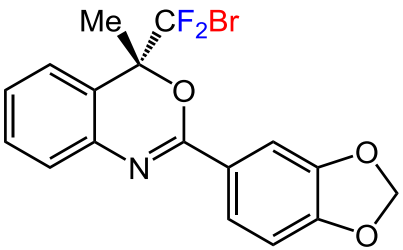
4a
80% yield, 96% ee



4b
89% yield, 98% ee

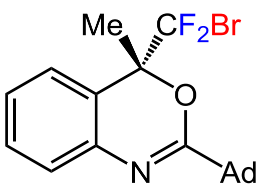


4c
75% yield, 94% ee

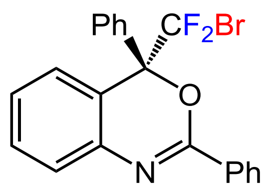


4d
85% yield, 95% ee

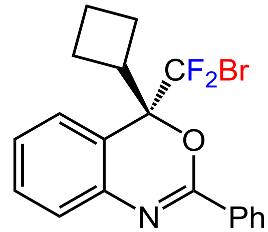
Substrate Scope



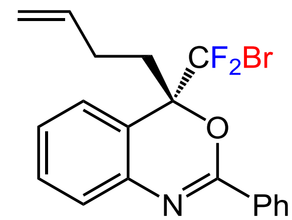
4e
68% yield, 69% ee



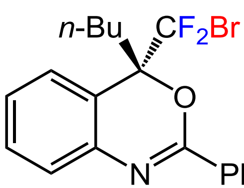
4f
73% yield, 93% ee



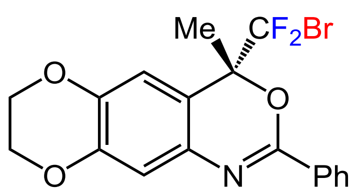
4g
75% yield, 94% ee



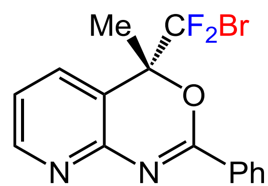
4h
79% yield, 93% ee



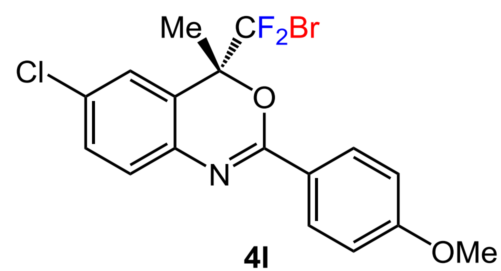
4i
79% yield, 93% ee



4j
62% yield, 73% ee

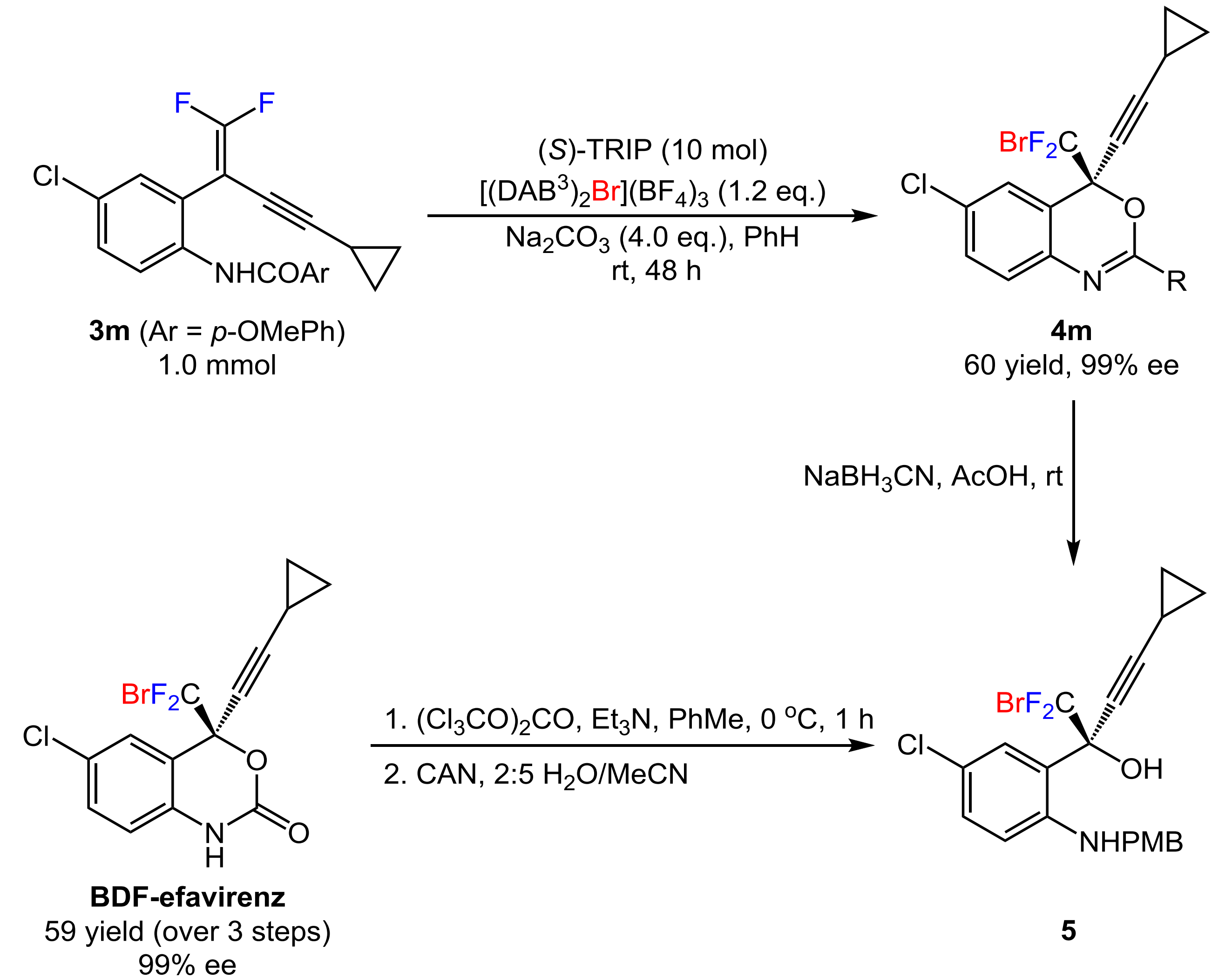


4k
41% yield, 61% ee

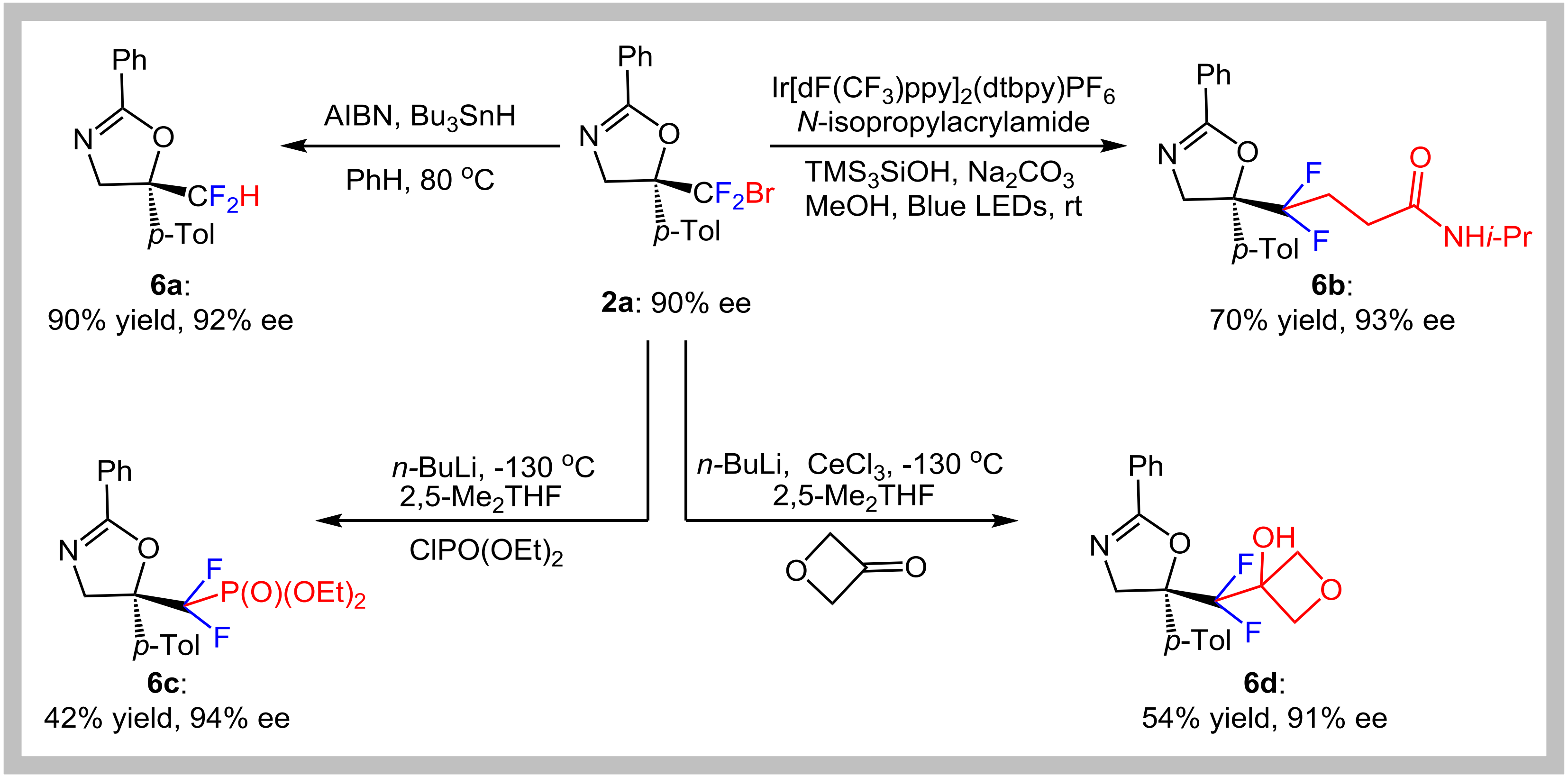


4l
79% yield, 93% ee

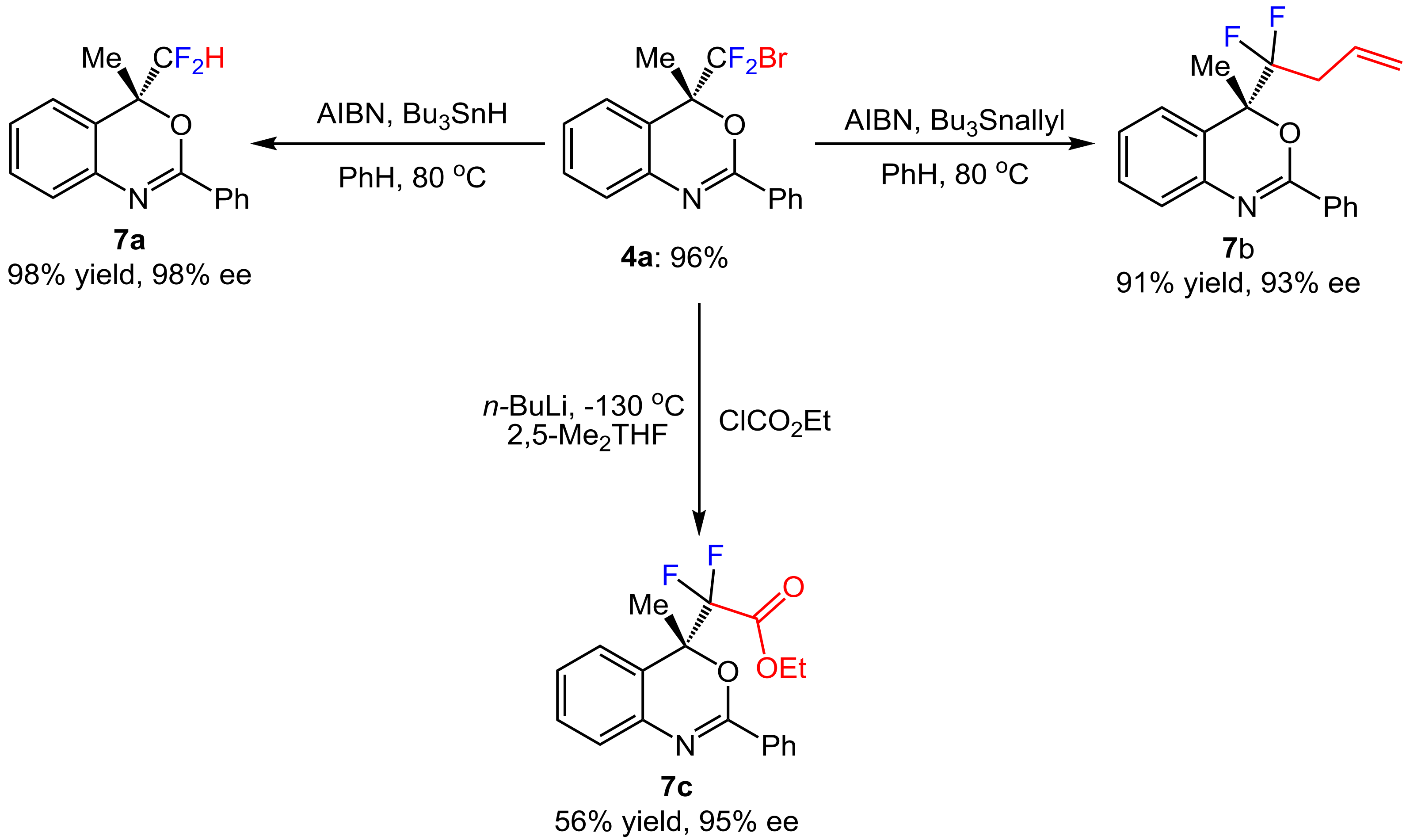
Synthesis of an Efavirenz Analogue



Transformations of Products



Transformations of Products



The First Paragraph

Writing Strategy

The importance of incorporation of fluorine atom into molecules

↓

Methods for synthesis of difluoromethylated compounds

The First Paragraph

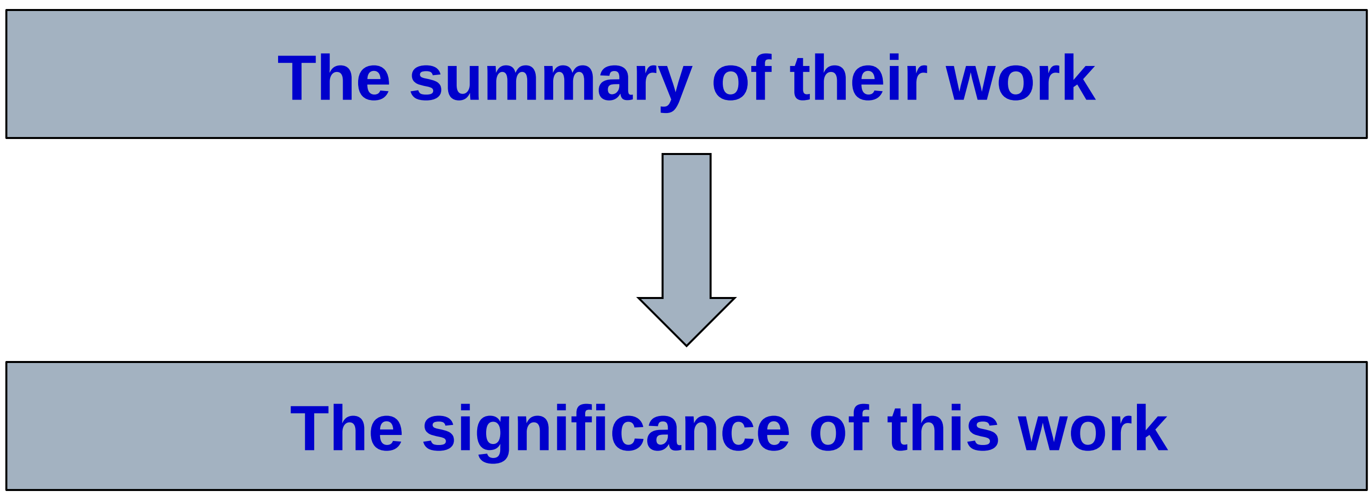
The difluoromethylene unit can confer a variety of unique pharmacological properties to drug molecules, in addition to the benefits typically associated with fluorinated functional groups, such as increased lipophilicity, oxidative stability, and modulated bioavailability. In a medicinal chemistry setting, the CF_2 moiety acts as a lipophilic mimic for polar functional groups, such as carbonyls and sulfonyls, and as a replacement for a single oxygen atom in phosphates, sulfates, and aryl ethers. Uniquely, the difluoromethyl group (RCF_2H) has been shown to be a lipophilic hydrogen bond donor because of the high polarization of the C−H bond, allowing it to act as a bioisostere of alcohols and thiols. Despite the immense potential for difluoromethylene groups to mimic structural motifs conventionally used for molecular recognition, a survey of fluorine containing pharmaceuticals reveals relatively few

The First Paragraph

difluoromethylene moieties. Traditional synthetic methods, such as difluorination of carbonyls or carbonyl surrogates, feature harsh, acidic conditions where heterocycles and acid sensitive functional groups are not well tolerated. More importantly, substitution at the α-position hinders reactivity and leads to carbocation rearrangement pathways, which precludes the applicability of these protocols to compounds with α-stereocenters.

The Last Paragraph

Writing Strategy



The Last Paragraph

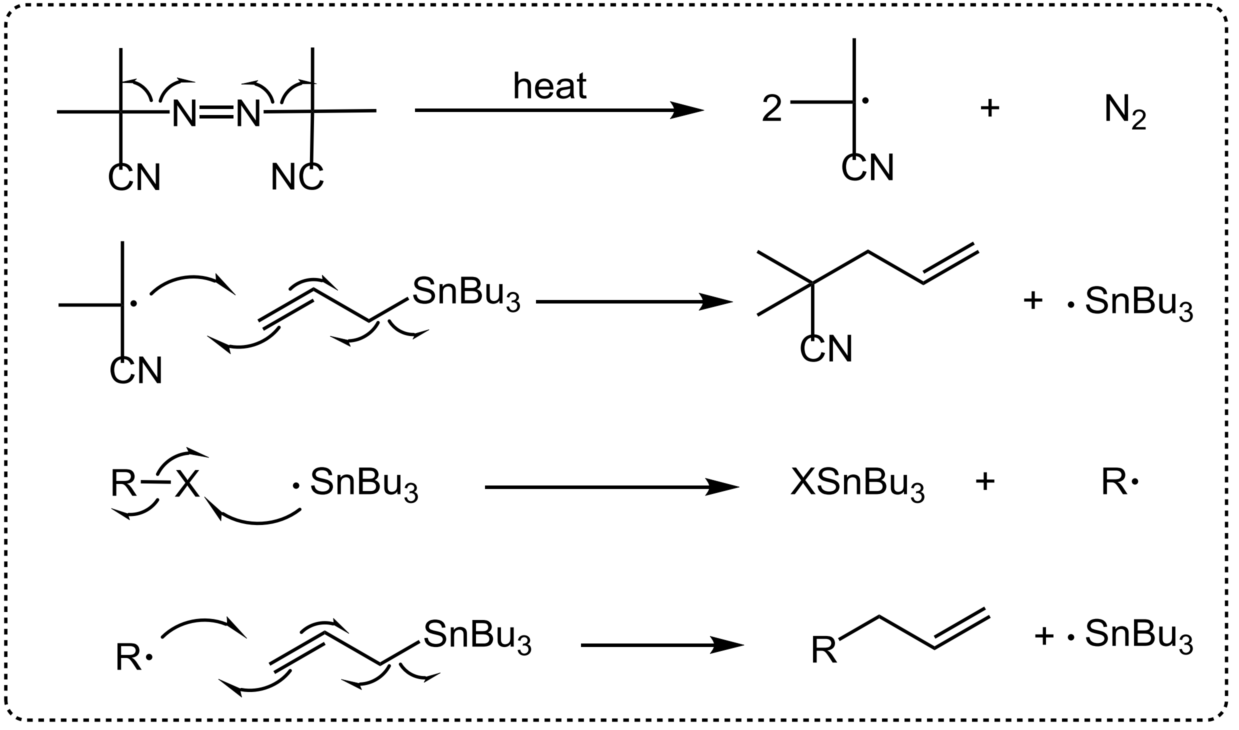
In summary, we have developed an approach for synthesizing bromodifluoromethyled stereocenters from difluoroalkenes via an enantioselective bromocyclization strategy. This transformation was facilitated by chiral anion phase-transfer catalysis and featured a strong dependence of the achiral brominating reagent on a variety of observed selectivities. Enantioenriched bromodifluoro-containing heterocycles, including an efavirenz analogue, were synthesized using this approach. Importantly, further derivatization of the bromodifluoromethyl group provides access to cyclic and acyclic compounds bearing difluoromethylene- and difluoromethyl containing tetrasubstituted stereocenters from a common precursor.

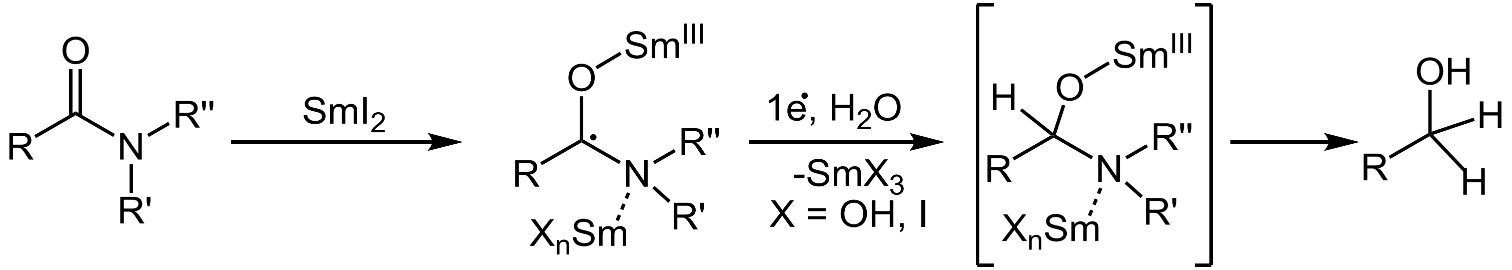
Representative Examples

We posited that the enantioselective bromocyclization of readily accessible difluoroalkene-containing compounds to the corresponding CF_2Br group would enable a general approach for accessing tetrasubstituted difluoromethylene-containing stereocenters. (提出课题设想的描写)

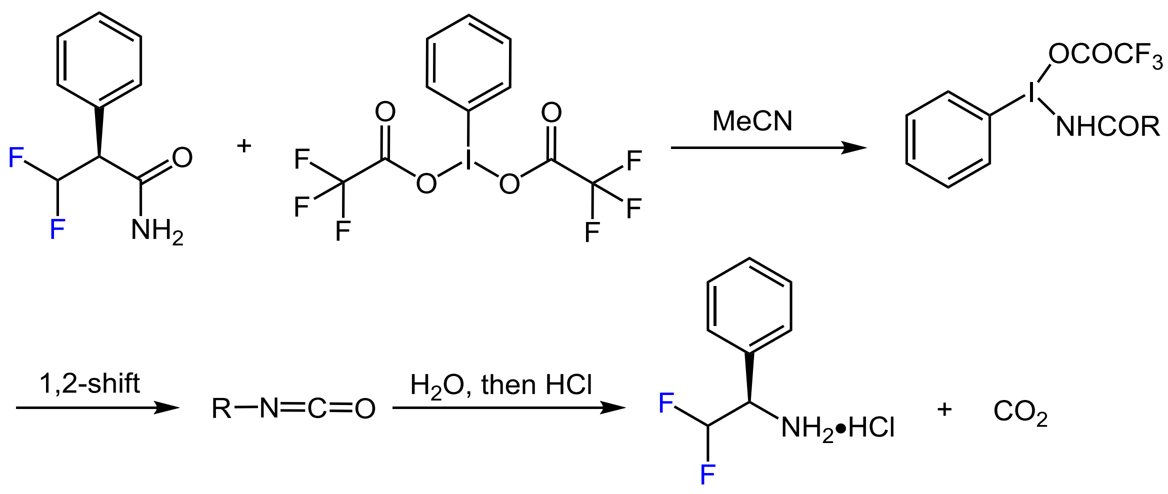
After slight adjustment of the reaction conditions, the bromocyclization of substrate **3m** to **4m** was achieved with a 60% isolated yield and 99% ee on a 1.0 mmol scale. (改变一点条件的描写）

Keck Radical Allylation





Carbinolamine


F
F
O
NH2
+
O
O
F
F
F
O
I
O
F
F
F
MeCN
OCOCF3
I
NHCOR
1,2-shift
R—N=C=O
H2O, then HCl
F
F
NH2•HCl
+
CO2