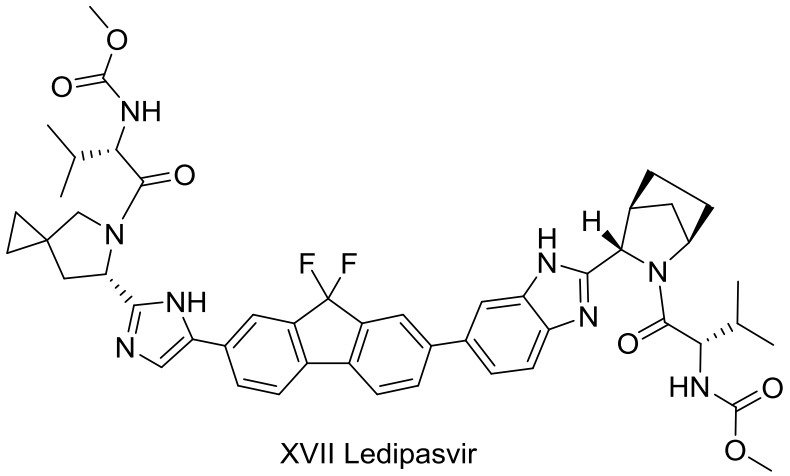
Total Synthesis of Ledipasvir (Harvoni®)

J. Med. Chem. **2014**, *57*, 2033-2046.
Bioorg. Med. Chem. **2016**, *24*, 1937-1980.

- Ledipasvir is a potent NS5A inhibitor that is approved for use in combination with sofosbuvir, a nucleotide inhibitor of viral polymerase, for the treatment of chronic hepatitis C virus (HCV) genotype 1 infection

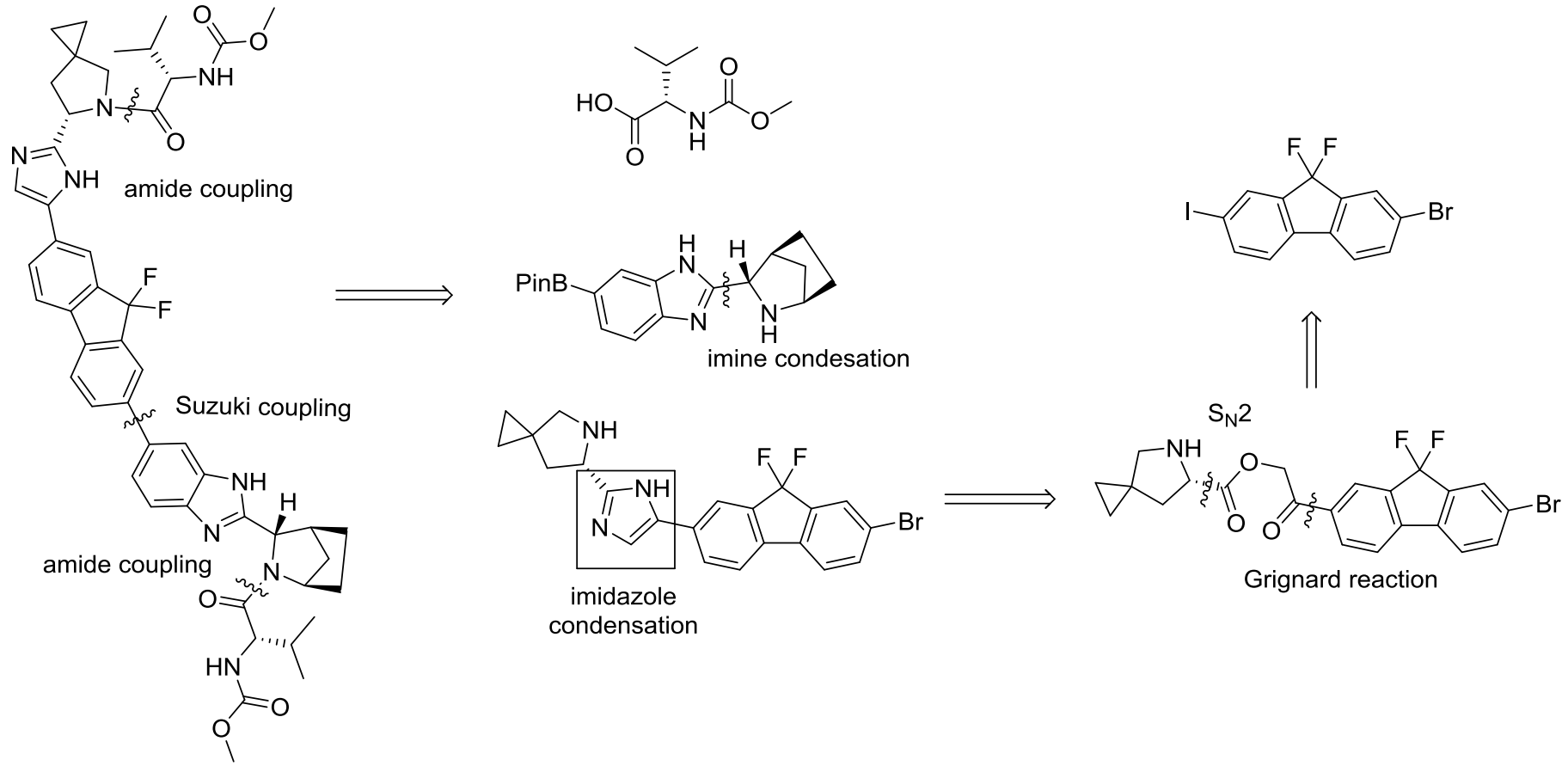
- The combination was discovered and developed at Gilead Sciences and is marketed as the fixed combination with brand name of Harvoni®.

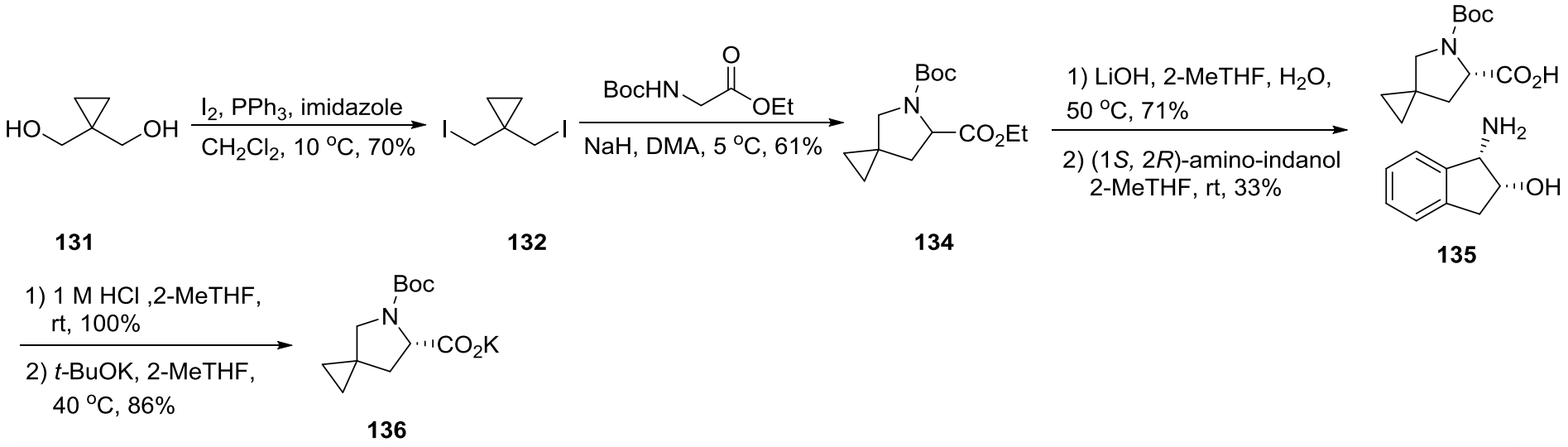


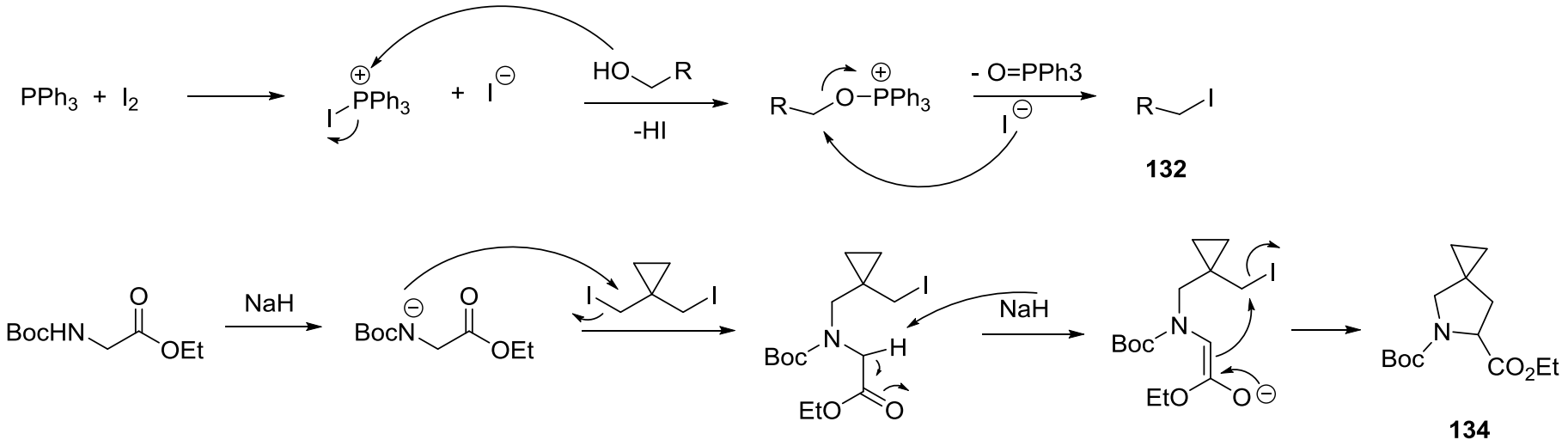
XVII Ledipasvir

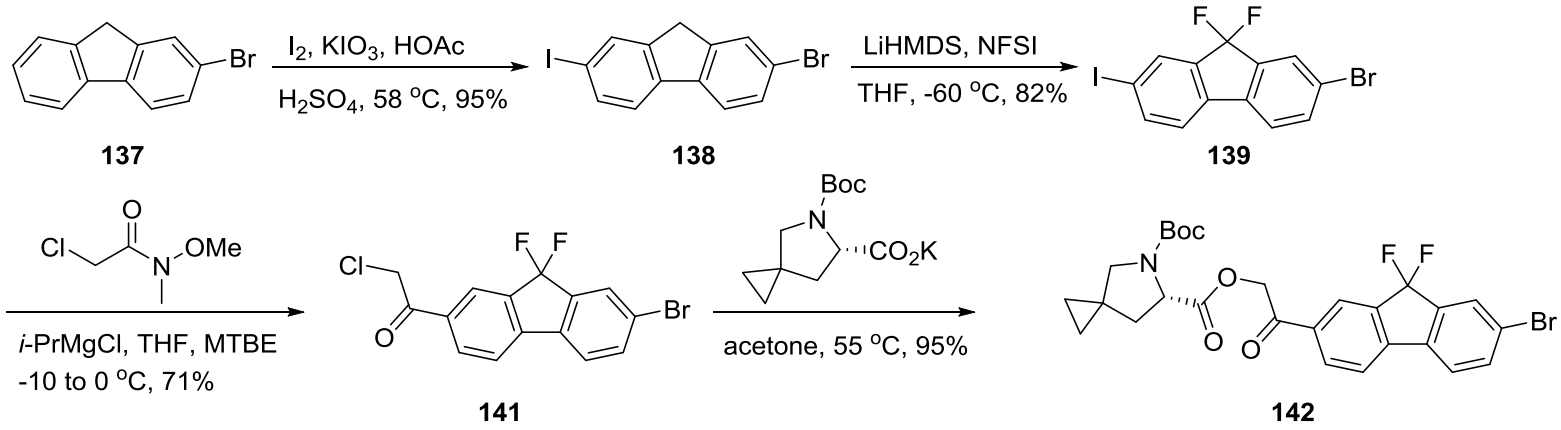
Presented by Yuanzhe Zhang, Liu group.

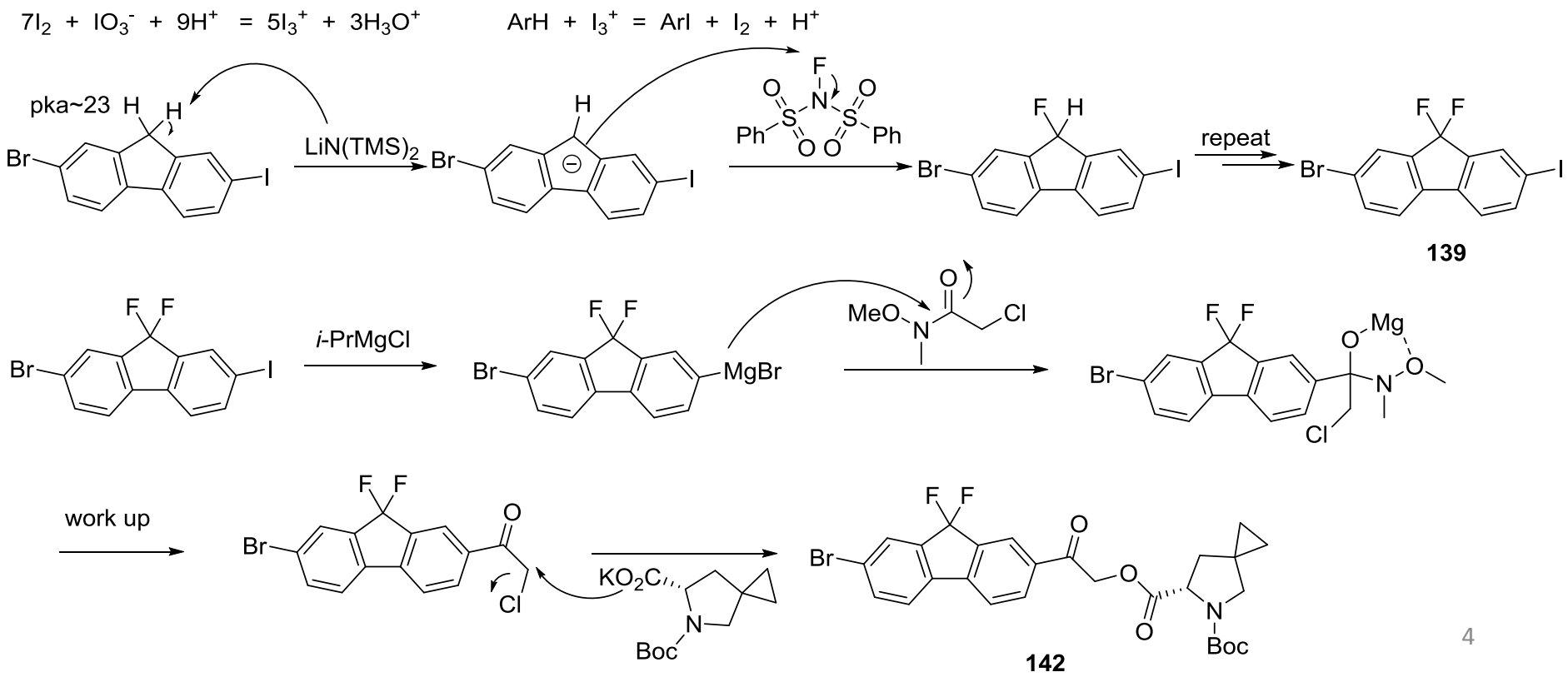
Retro-synthetic Analysis

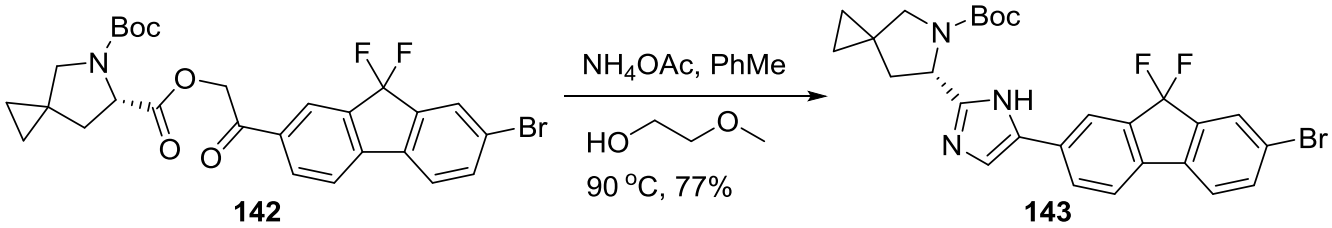


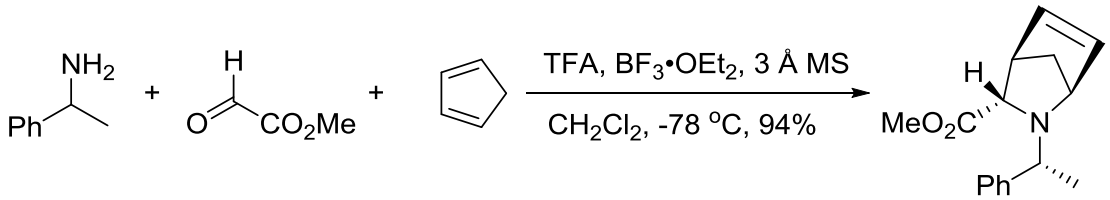

HO
OH
I2, PPh3, imidazole
CH2Cl2, 10 °C, 70%
I
I
BocHN
O
OEt
NaH, DMA, 5 °C, 61%
Boc
N
CO2Et
1) LiOH, 2-MeTHF, H2O,
50 °C, 71%
2) (1S, 2R)-amino-indanol
2-MeTHF, rt, 33%
Boc
N
CO2H
NH2
OH
131
132
134
135
1) 1 M HCl ,2-MeTHF,
rt, 100%
2) t-BuOK, 2-MeTHF,
40 °C, 86%
Boc
N
CO2K
136


PPh3 + I2
PPh3
I
+ I
HO
R
-HI
R
O
PPh3
- O=PPh3
I
R
I
132
BocHN
O
OEt
NaH
BocN
O
OEt
I
I
Boc
N
H
EtO
O
NaH
Boc
N
I
I
EtO
O
Boc
N
CO2Et
134
Boc
N
O
OEt
OH
Boc
N
O
OEt
OH
Boc
N
CO2H
resolution

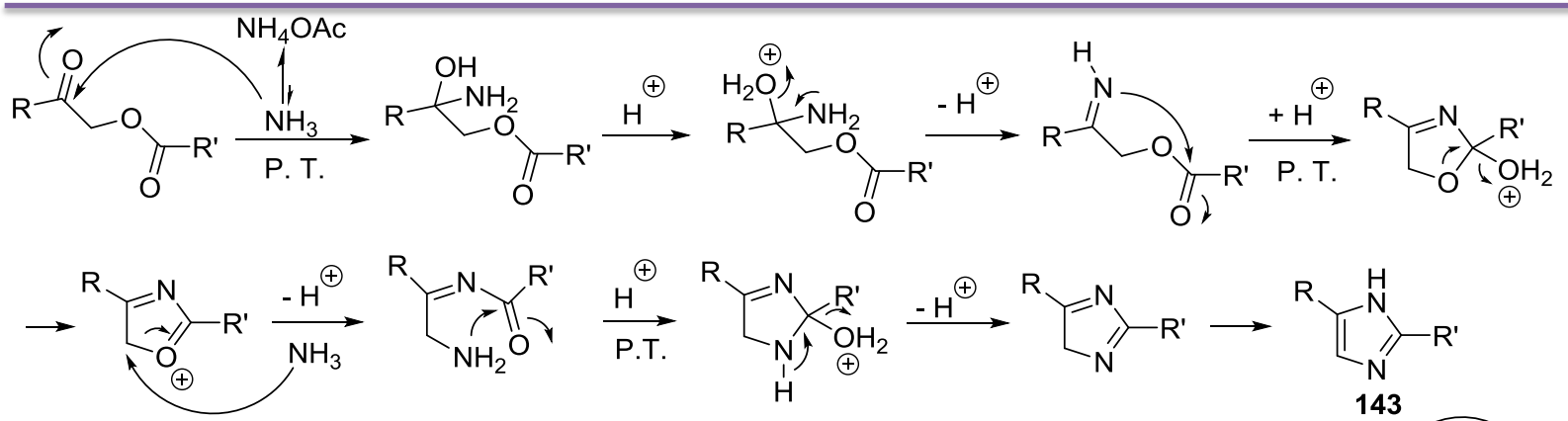

I2, KIO3, HOAc
H2SO4, 58 °C, 95%
LiHMDS, NFSI
THF, -60 °C, 82%
137
138
139
i-PrMgCl, THF, MTBE
-10 to 0 °C, 71%
141
acetone, 55 °C, 95%
142

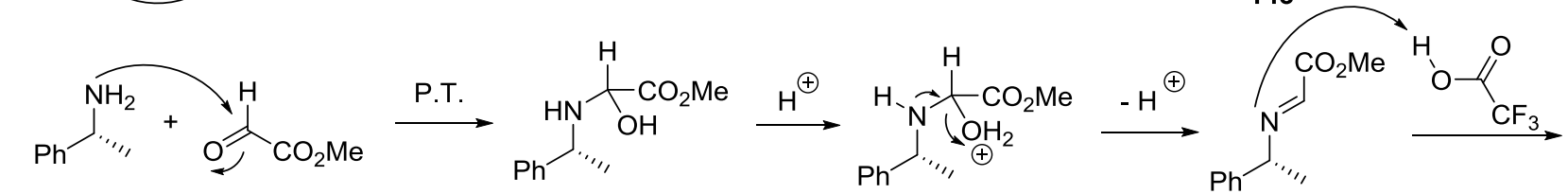

7I2 + IO3- + 9H+ = 5I3+ + 3H3O+
ArH + I3+ = ArI + I2 + H+
pka~23
LiN(TMS)2
repeat
139
i-PrMgCl
work up
142

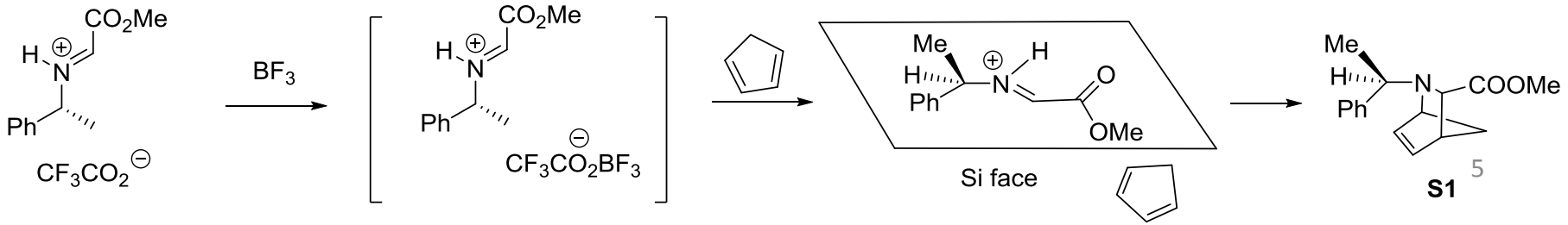

Boc
N
O
O
F F
Br
142
NH4OAc, PhMe
HO
O
90 °C, 77%
Boc
N
NH
N
F F
Br
143

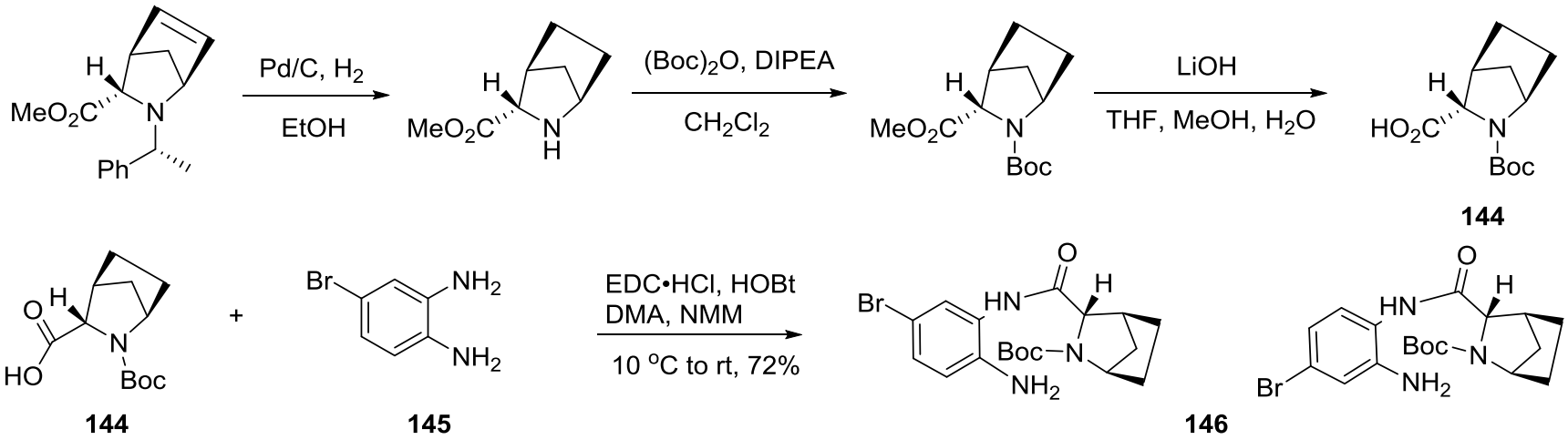

NH2
Ph
+
H
O
CO2Me
+
TFA, BF3•OEt2, 3 Å MS
CH2Cl2, -78 °C, 94%
H
MeO2C
N
Ph

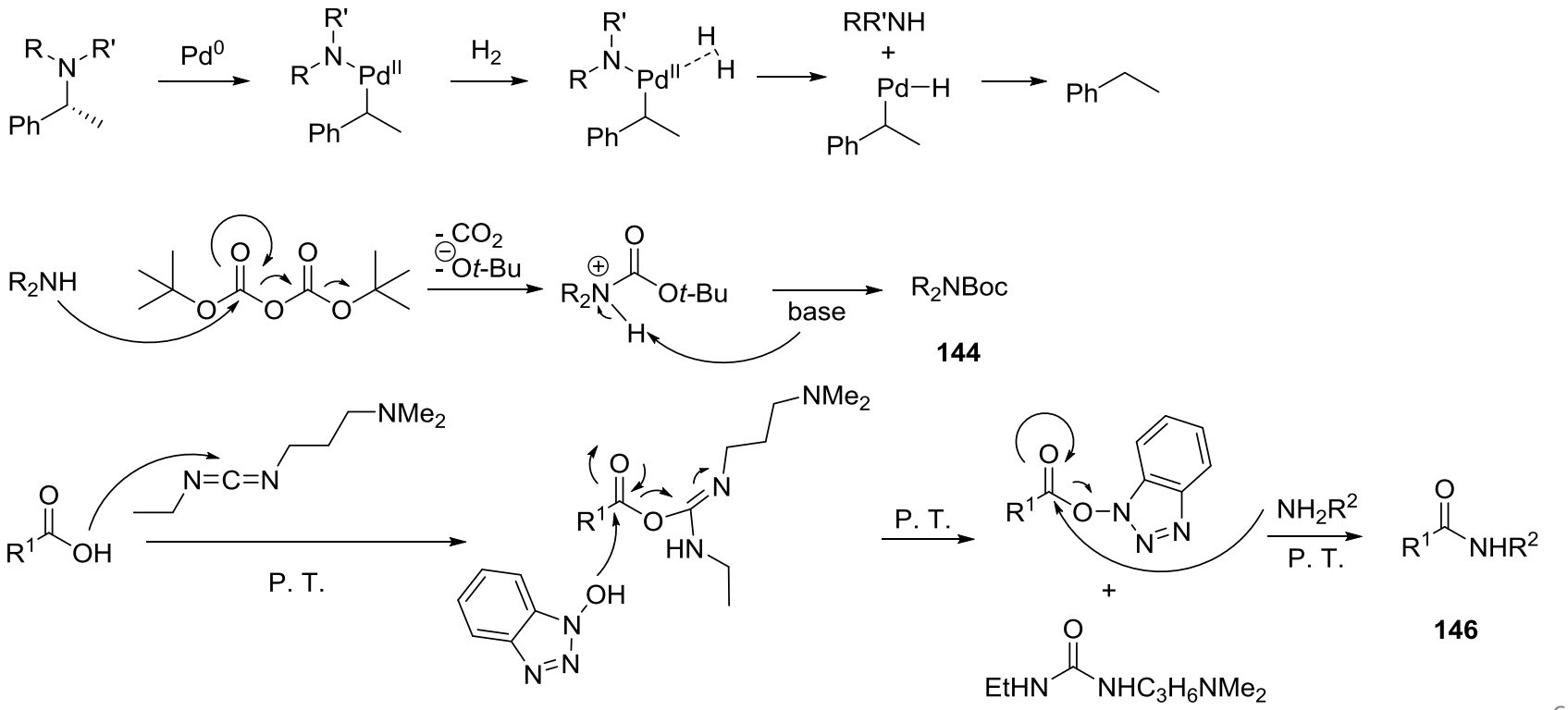
S1

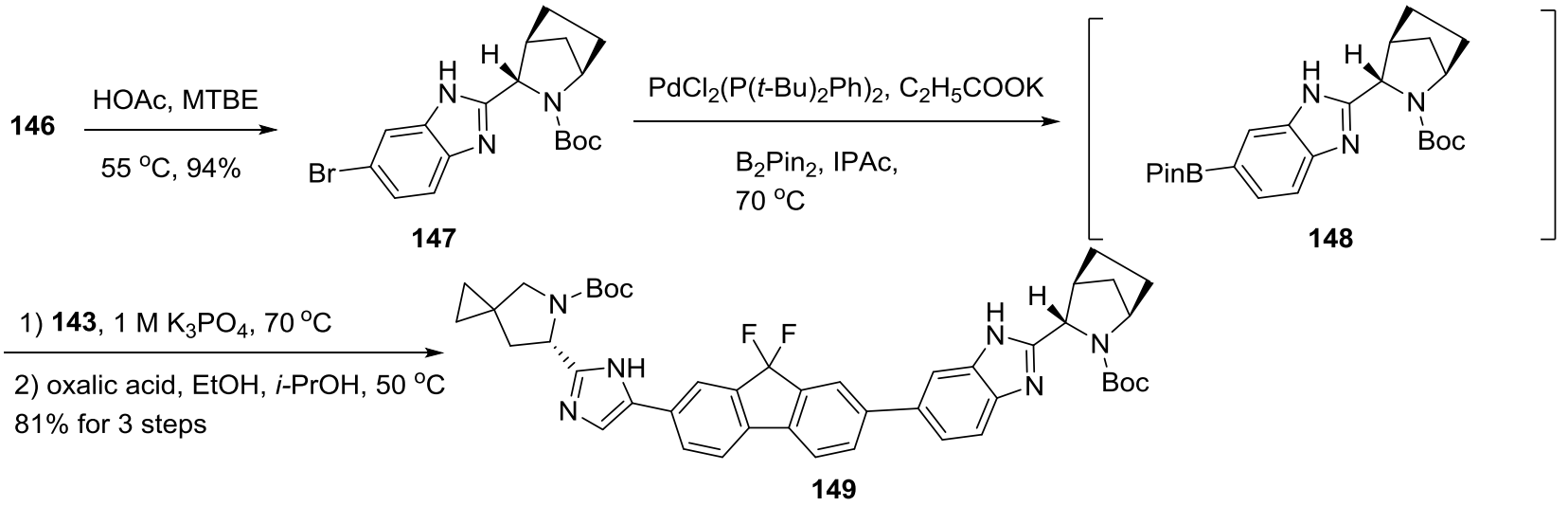

NH4OAc
NH3
P. T.
OH
NH2
H
H2O
- H
+ H
P. T.
OH2
- H
NH3
NH2
P.T.
OH2
- H
143

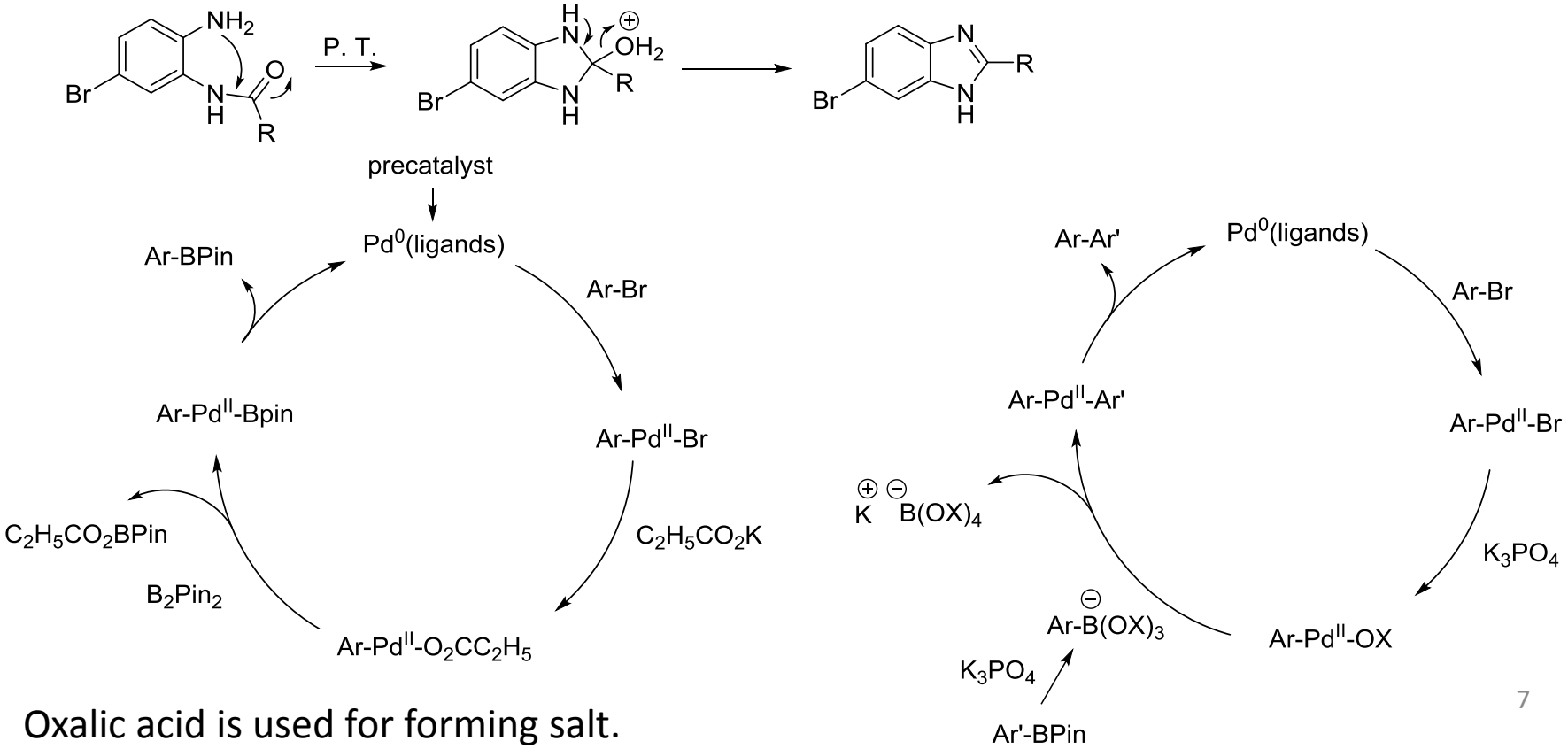

NH2
Ph
+
H
O
CO2Me
P.T.
HN
CO2Me
OH
Ph
H
N
CO2Me
OH2
Ph
- H
CO2Me
N
Ph
H
O
O
CF3


CO2Me
H
N
Ph
CF3CO2
BF3
CO2Me
H
N
Ph
CF3CO2BF3
Me
H
Ph
N
H
O
OMe
Si face
Me
H
Ph
N
COOMe
S1

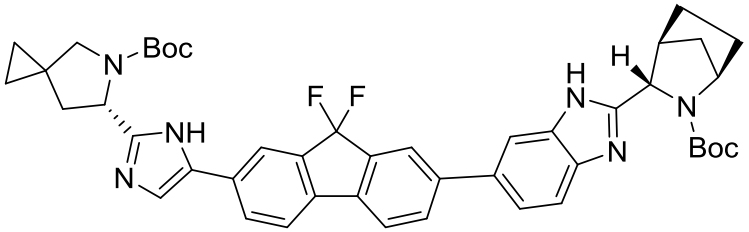

Pd/C, H2
EtOH
(Boc)2O, DIPEA
CH2Cl2
LiOH
THF, MeOH, H2O
144
EDC•HCl, HOBt
DMA, NMM
10 °C to rt, 72%
144
145
146


Pd0
H2
RR'NH
base
144
P. T.
P. T.
NH2R2
P. T.
146





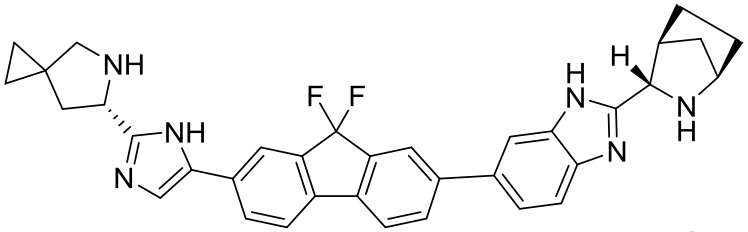
Oxalic acid is used for forming salt.



149

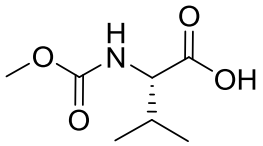
HCl, MeCN, 65 °C

80%



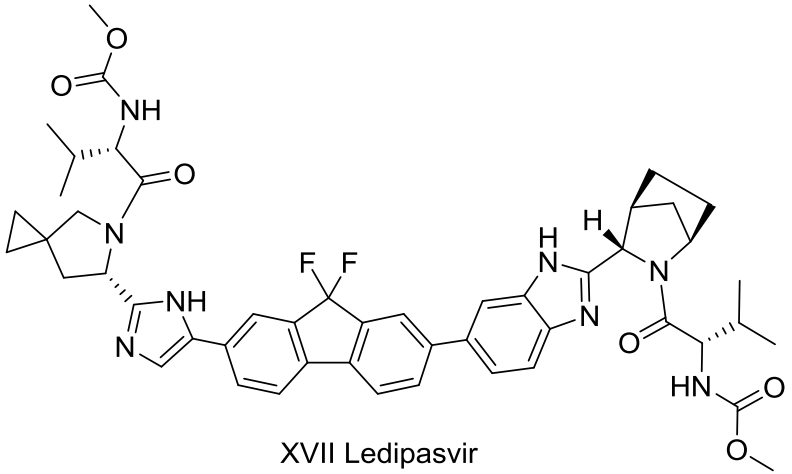
• 4HCl

150



EDC•HCl, HOBt, DMA, NMM

0 °C to rt, 73%



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