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Boronic acid catalysis

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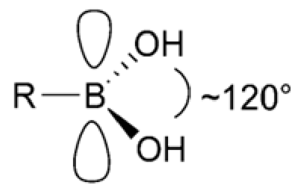
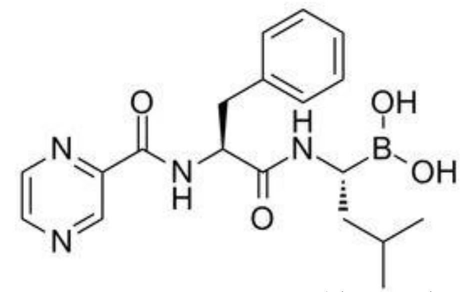
1. Background

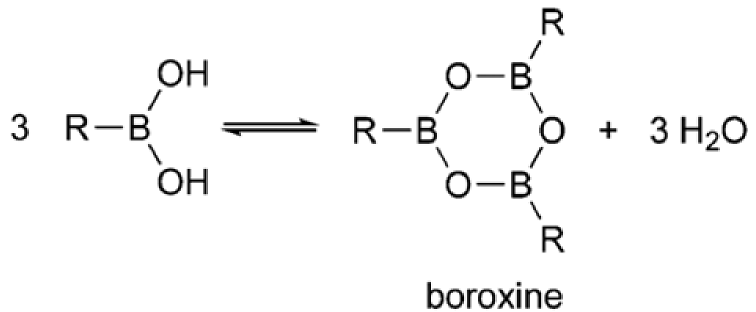
1) Boronic acids

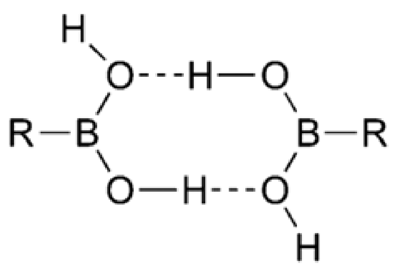


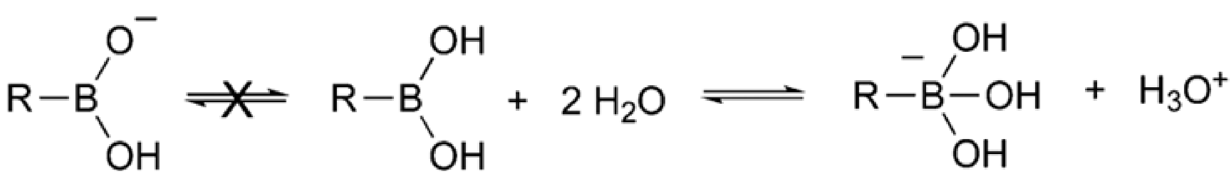
Human invention
Safe, green and chemically stable
Vacant p orbital (Lewis acidity)
pK_a: 5–9



Bortezomib (硼替佐米)
FDA approved in 2008
Multiple myeloma (多发性骨髓瘤)







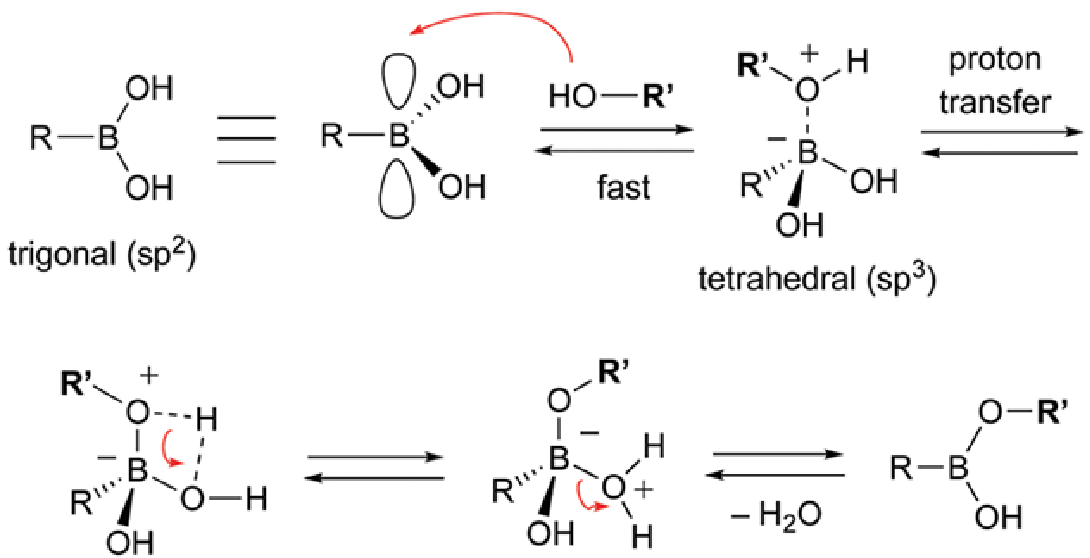
not Brønsted acids   Lewis acids

2) B–O bond exchange

Reversible exchange of -OH

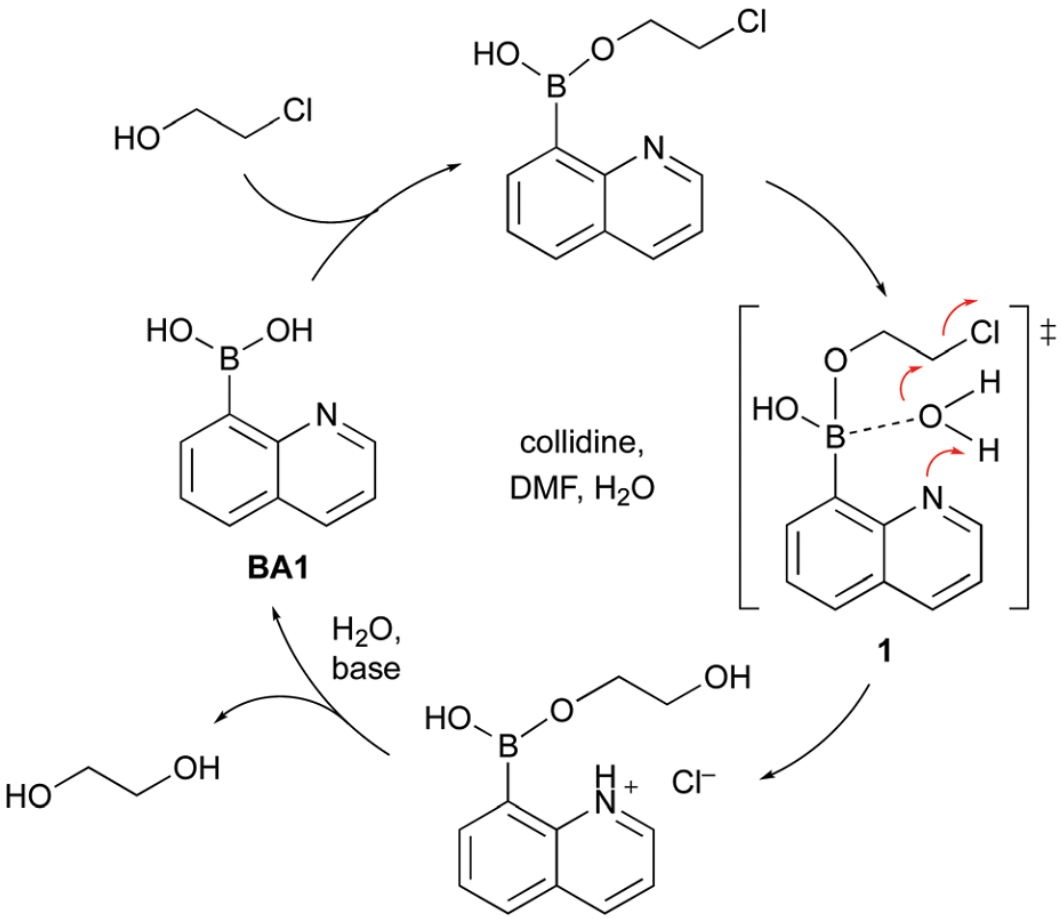
$$B{-}OH + HOR \rightleftharpoons B{-}OR + H_2O$$

Associative mechanism



3) First catalysis of boronic acids

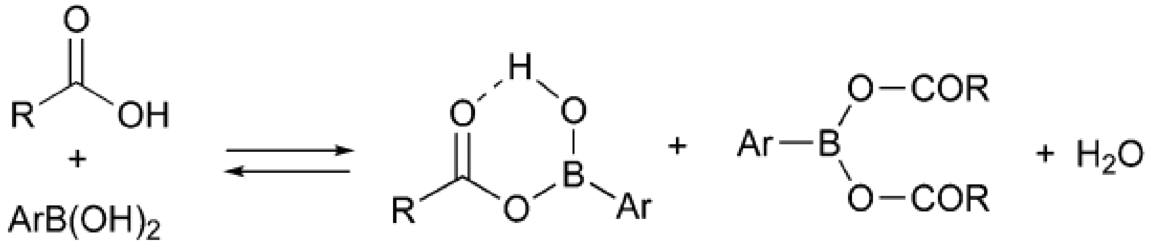
Letsinger (1963)



2. Electrophilic activation

1) Carboxylic acids

Acylboronates:



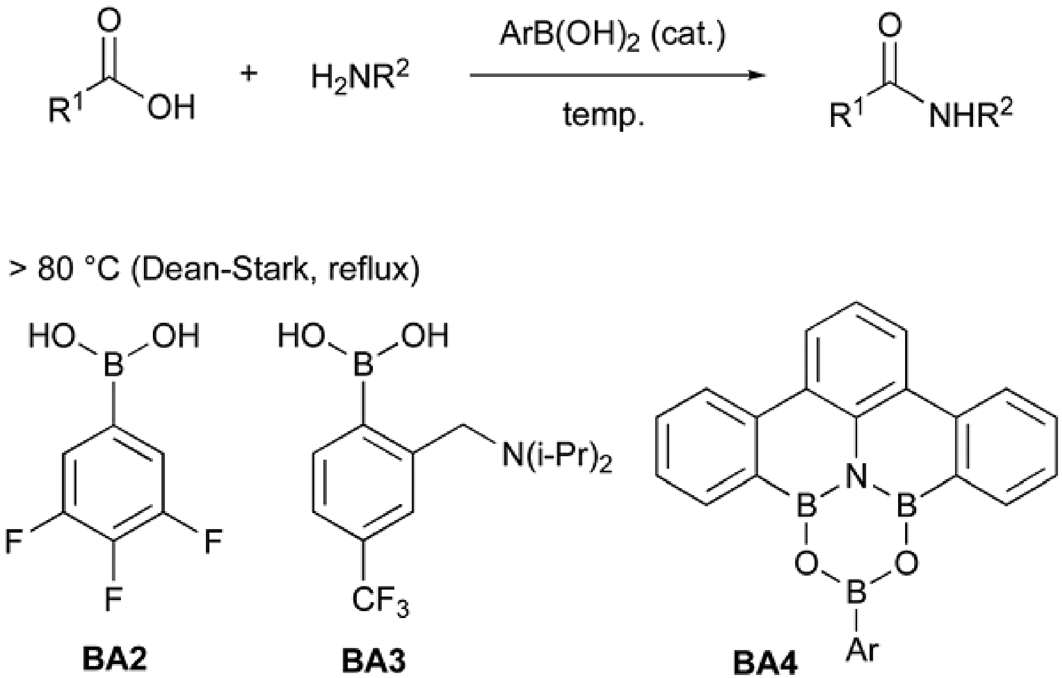
2 3

i) Direct amidation

ii) Esterification

iii) Anhydride formation

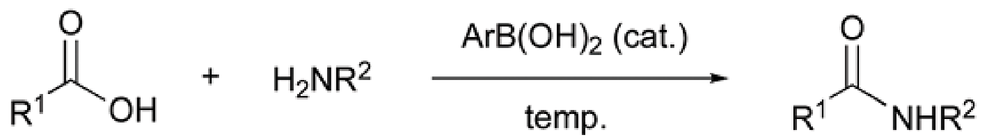
i) Direct amidation



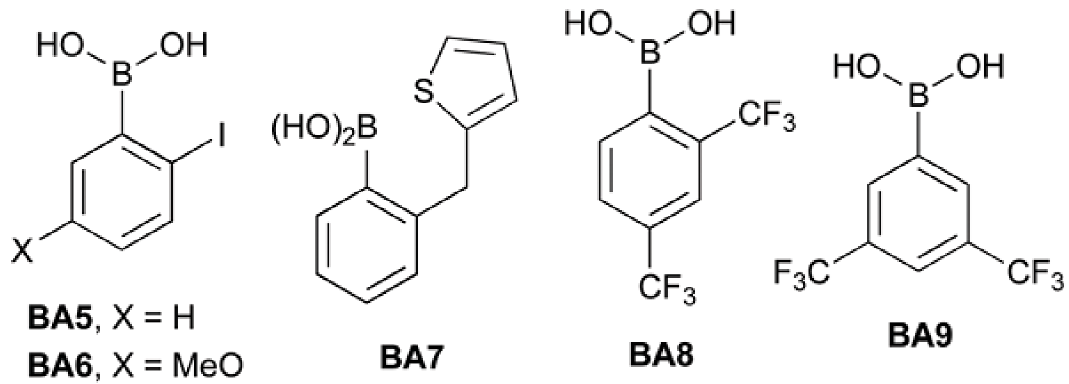
Yamamoto (1996)

Whiting (2008)

Shibasaki (2017)



rt – 50 °C (4A molecular sieves)



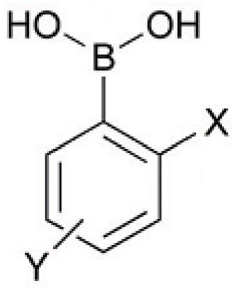
Hall (2008, 2012)

Blanchet (2015)

Ishihara (2018)

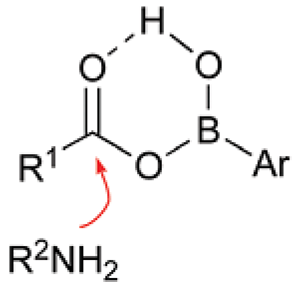
Ishihara (2016)

Proposed mechanism



preference to form dimeric species **4**

enhanced Lewis acidity of the boron atom



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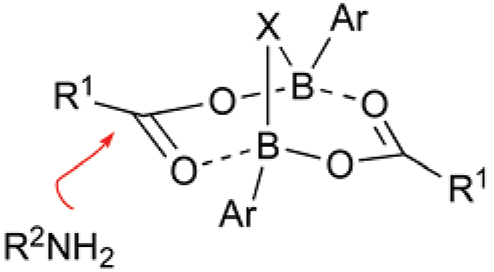
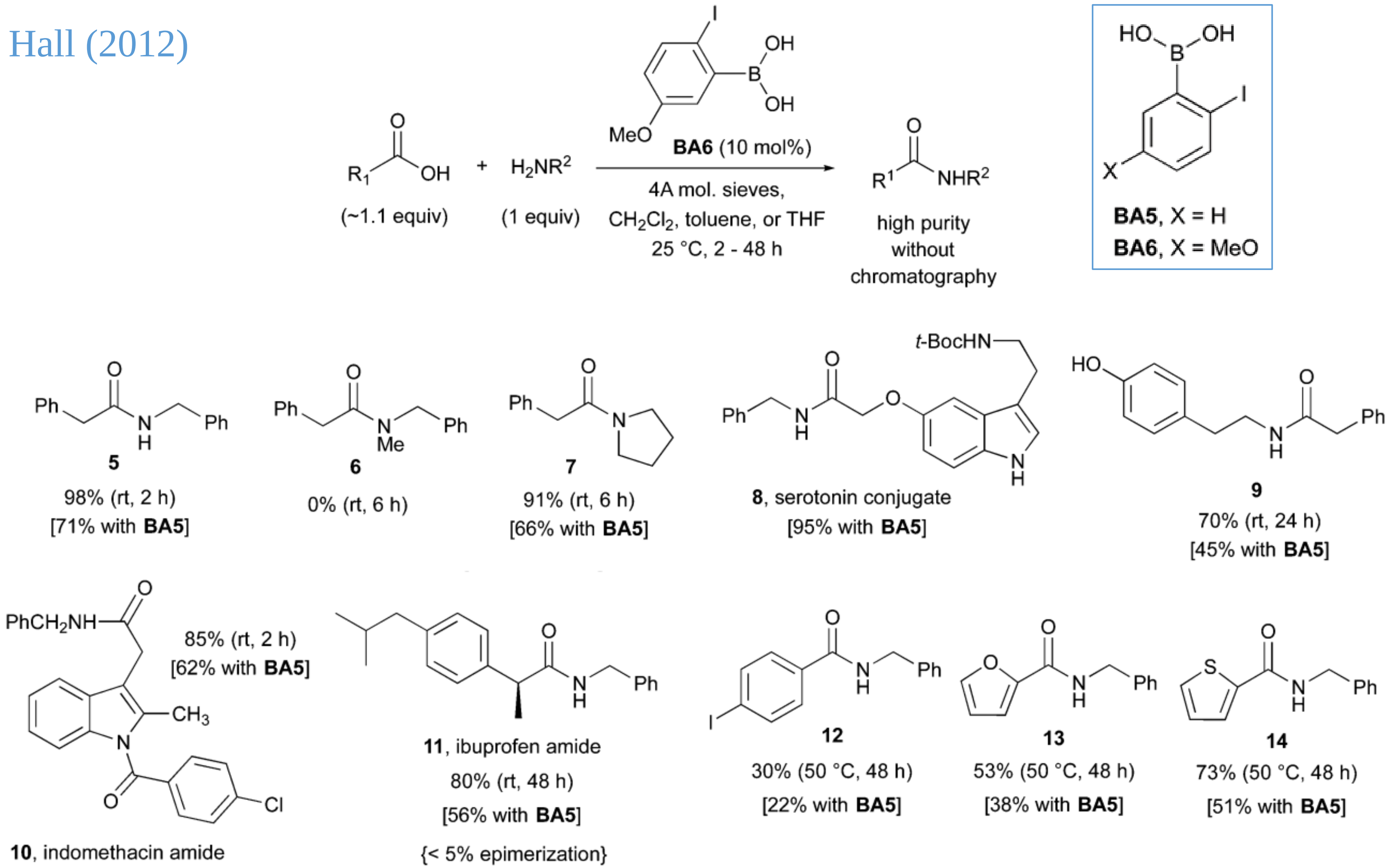
Whiting and Sheppard (2018)



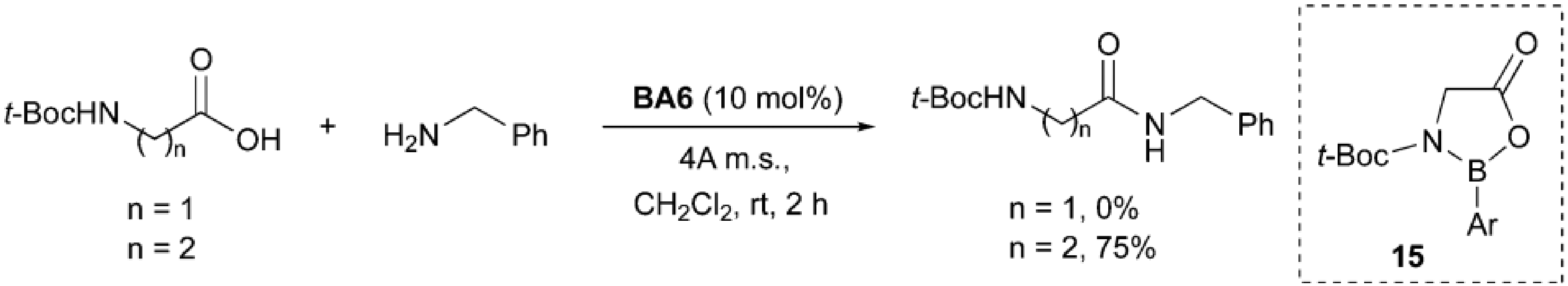
4, X = O or NHR^2

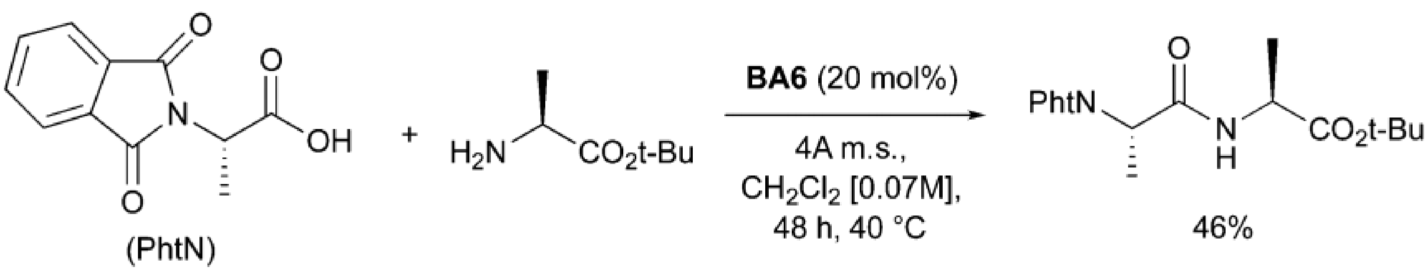
Hall (2012)



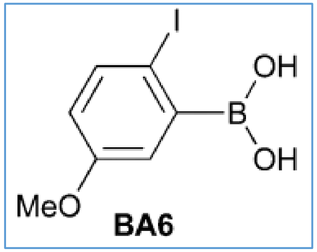
Aromatic amines are unreactive (not shown) and aromatic carboxylic acids were found to require a higher reaction temperature to afford low yields after 48 hours.

Hall (2015)

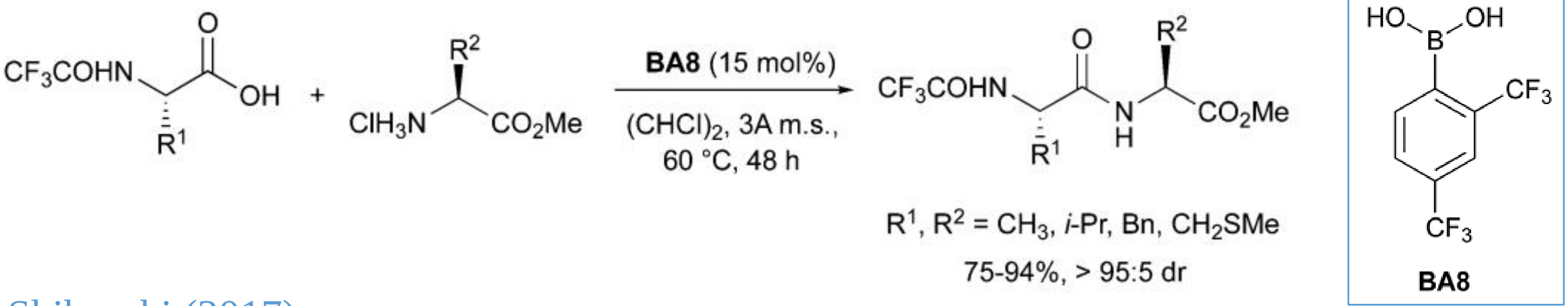




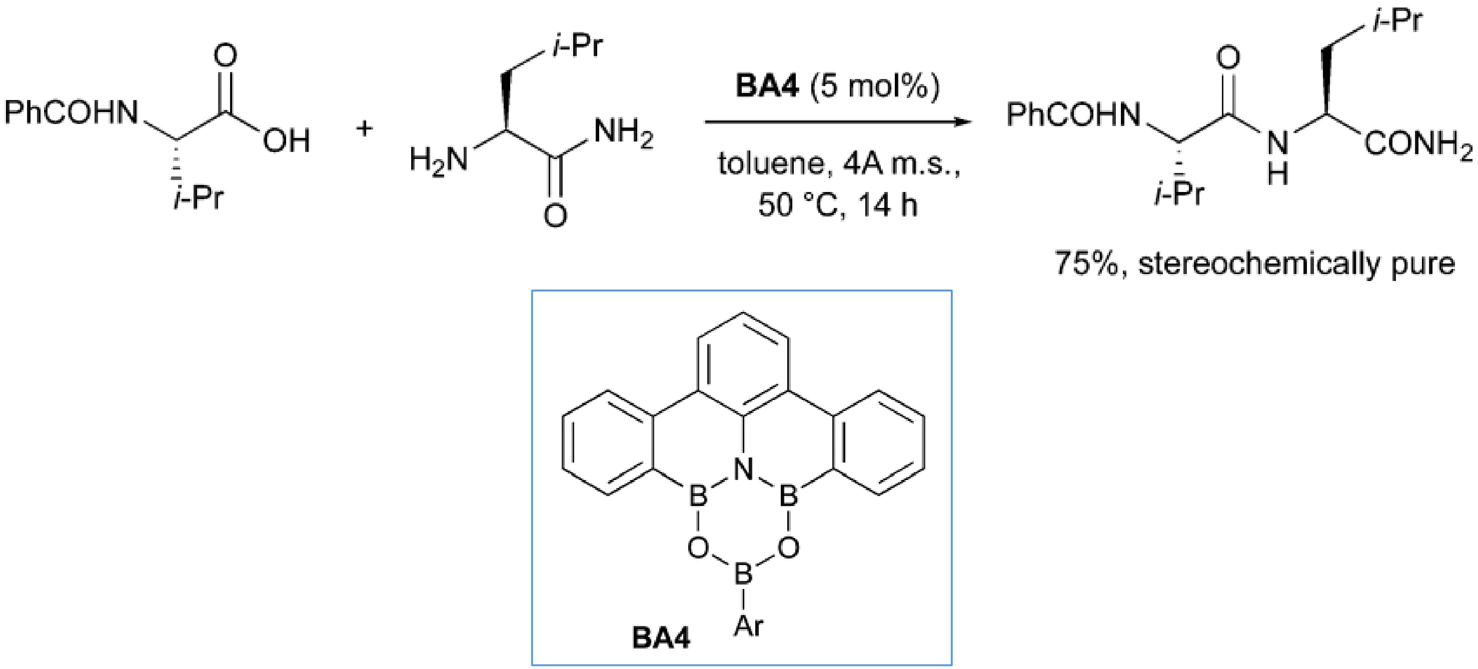
Alpha-aminoacids have proven to be very challenging substrates in boronic acid catalyzed amidations.



Ishihara (2018)

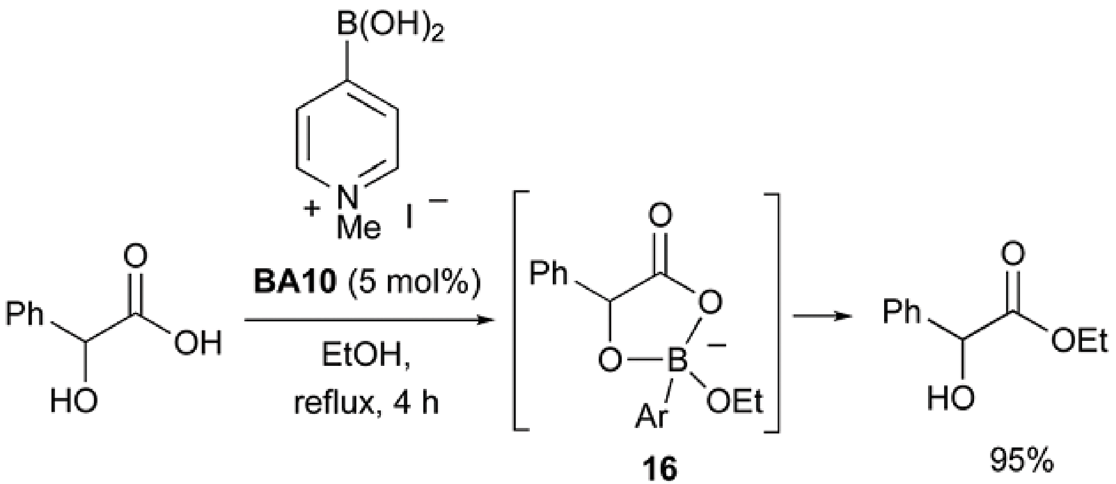


Shibasaki (2017)



ii) Esterification

Ishihara and Yamamoto (2005)

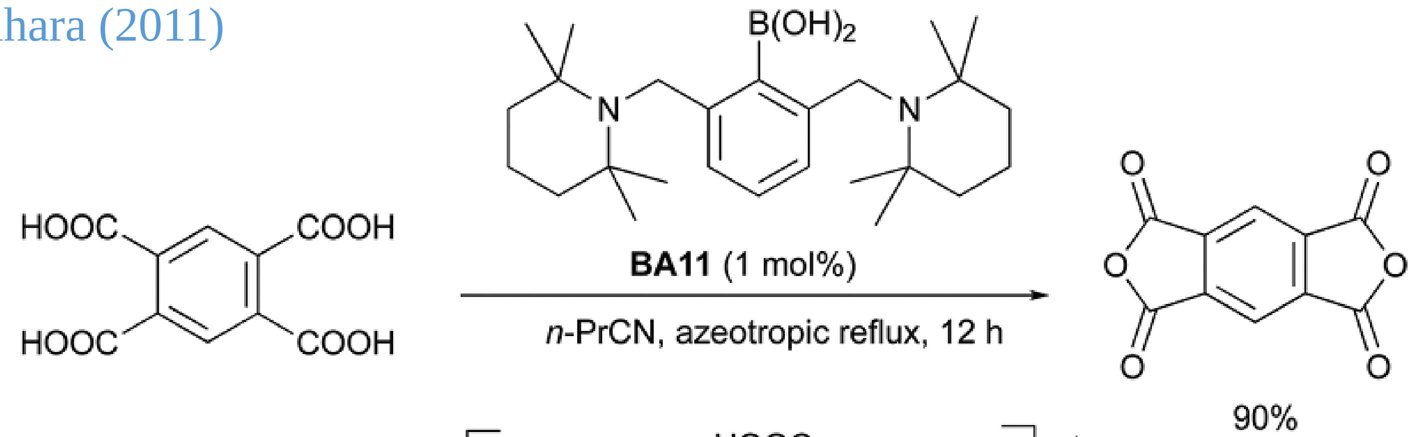


tetrahedral acyloxyborate intermediate

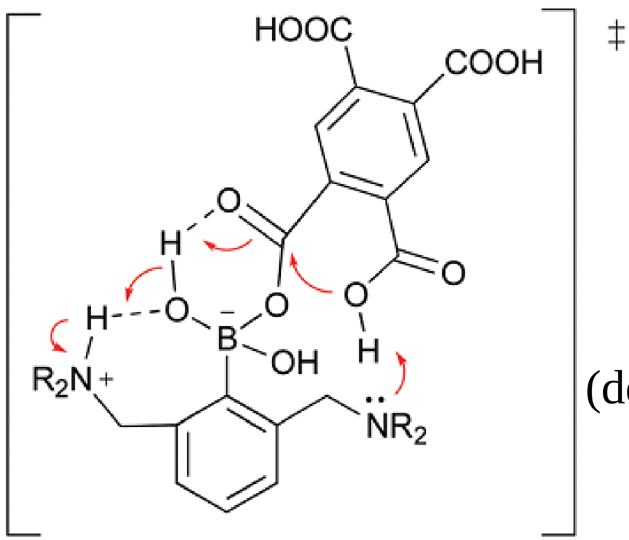
Hydroxy at the α- or β-position is essential.

iii) Anhydride formation

Ishihara (2011)



Brønsted acid
(activate the carbonyl group)



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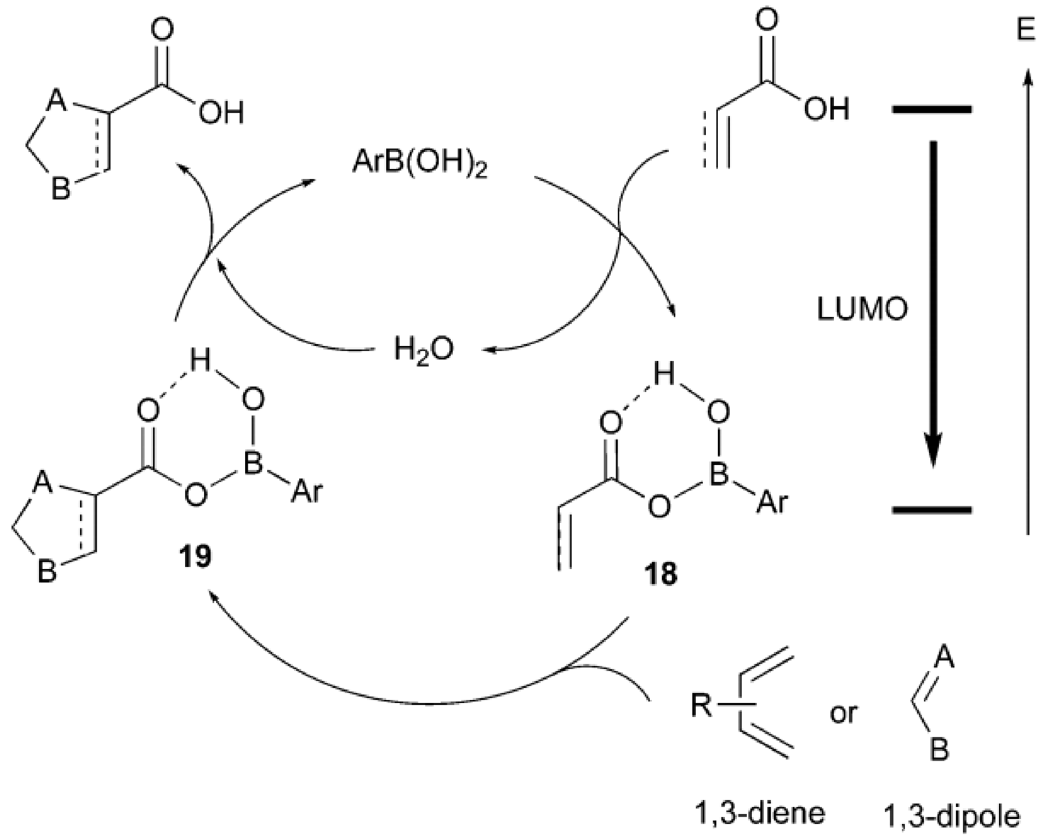
Brønsted base
(deprotonate carboxylic acid)

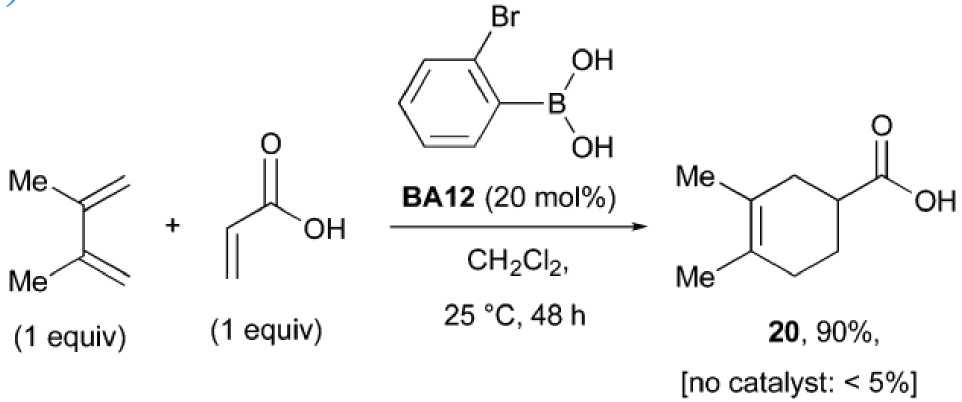
2) Unsaturated carboxylic acids

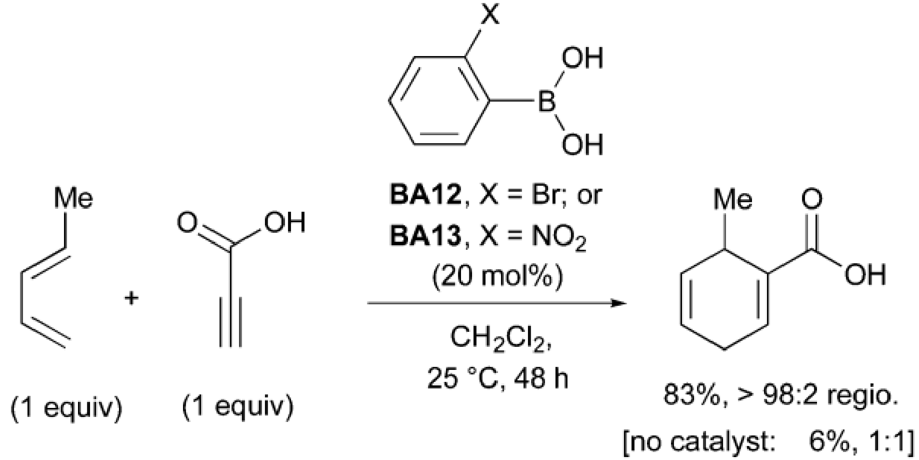


LUMO-lowering activation: i) Diels–Alder cycloadditions, ii) dipolar cycloadditions, iii) hetero-Michael additions.

Water is required for the catalyst turnover.

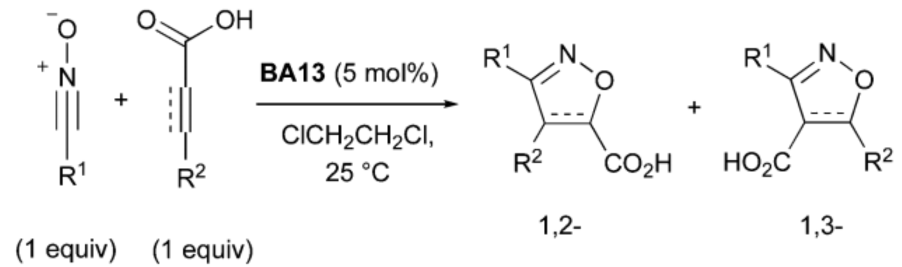
Hall (2008, 2010)

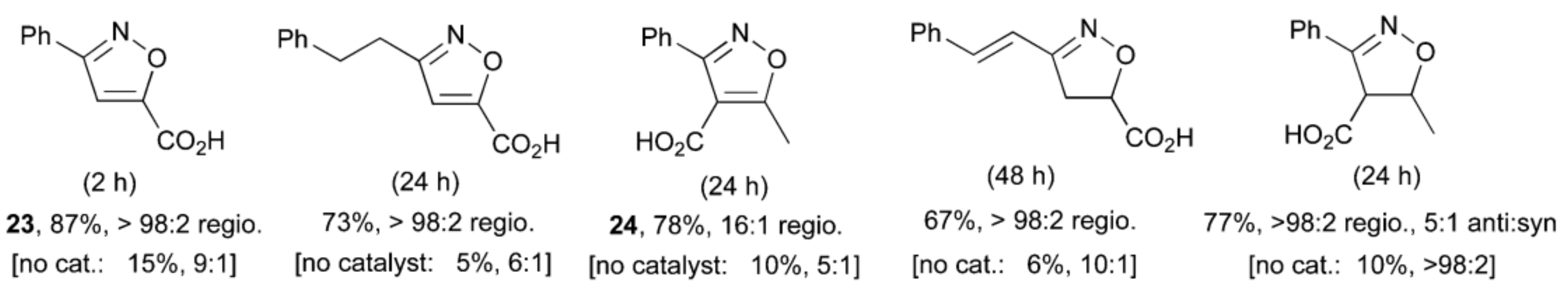


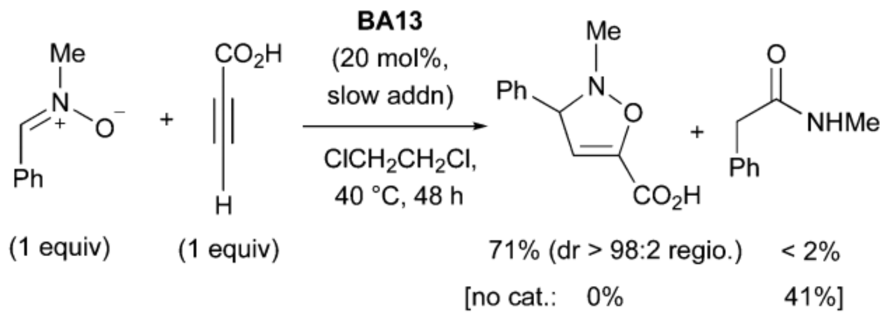


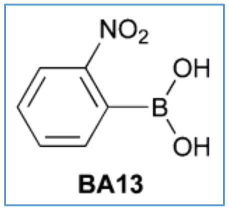
ii) Dipolar cycloadditions

Hall (2010)



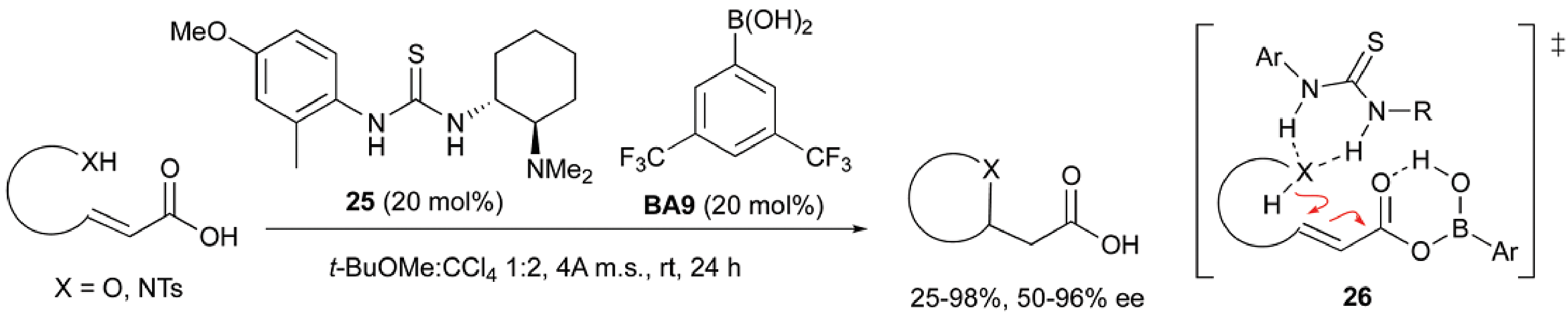


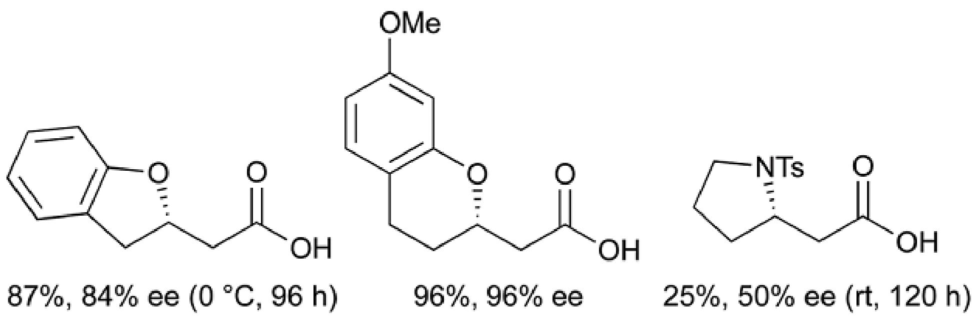




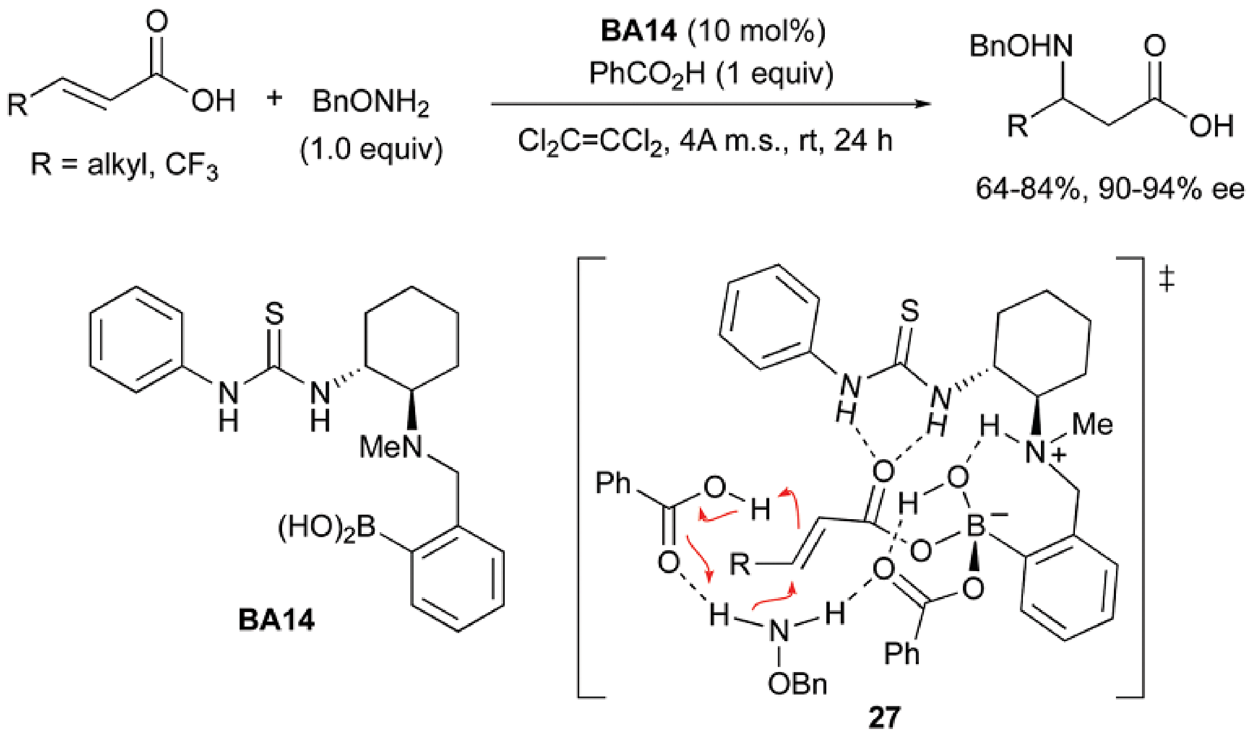
iii) Hetero-Michael additions

Takemoto (2008)



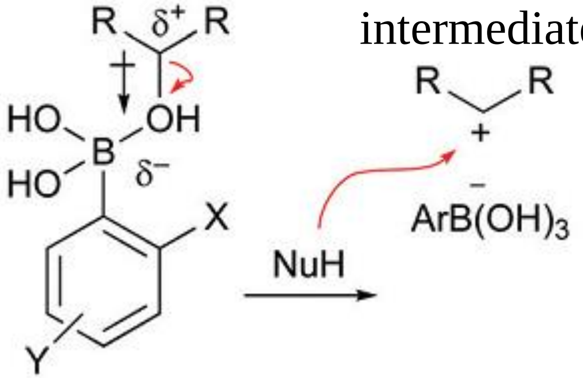


Takemoto (2016, 2018, 2019)



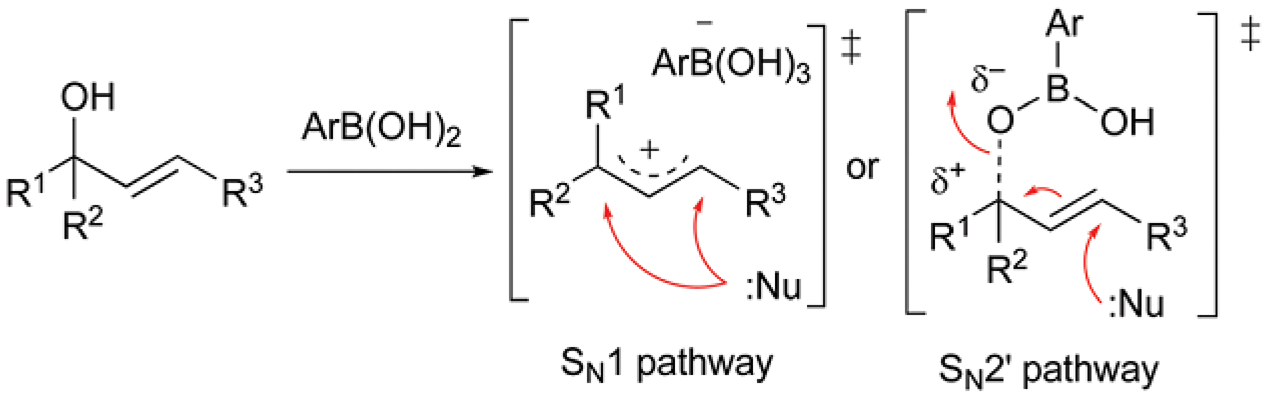
3) Alcohols

carbocation intermediate



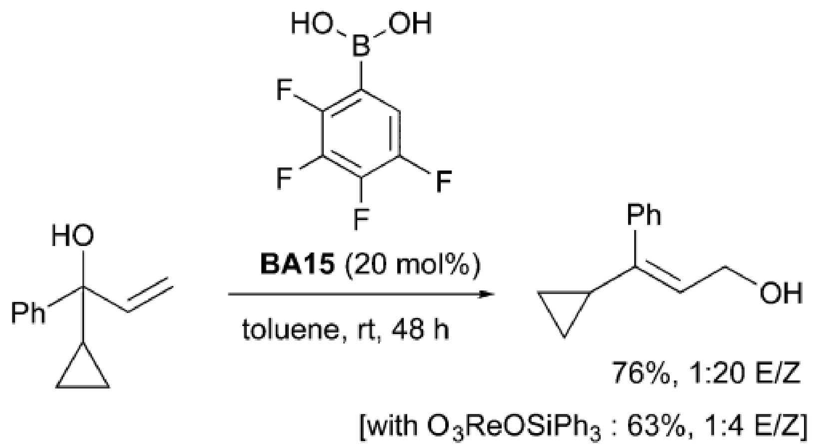
Electrophilic activation of alcohols:

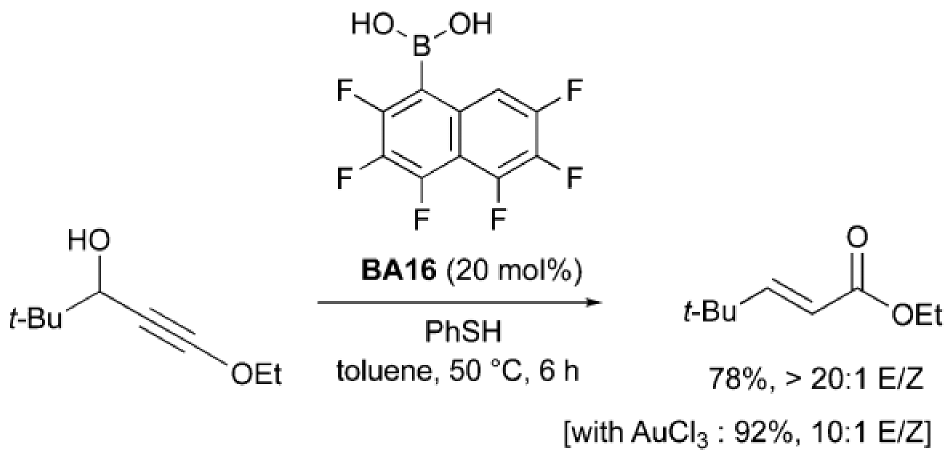
- i) Transposition of allylic and propargylic alcohols
- ii) X-H insertion / nucleophilic attack
- iii) Cyclization & cycloadditions



i) Transposition of allylic and propargylic alcohols

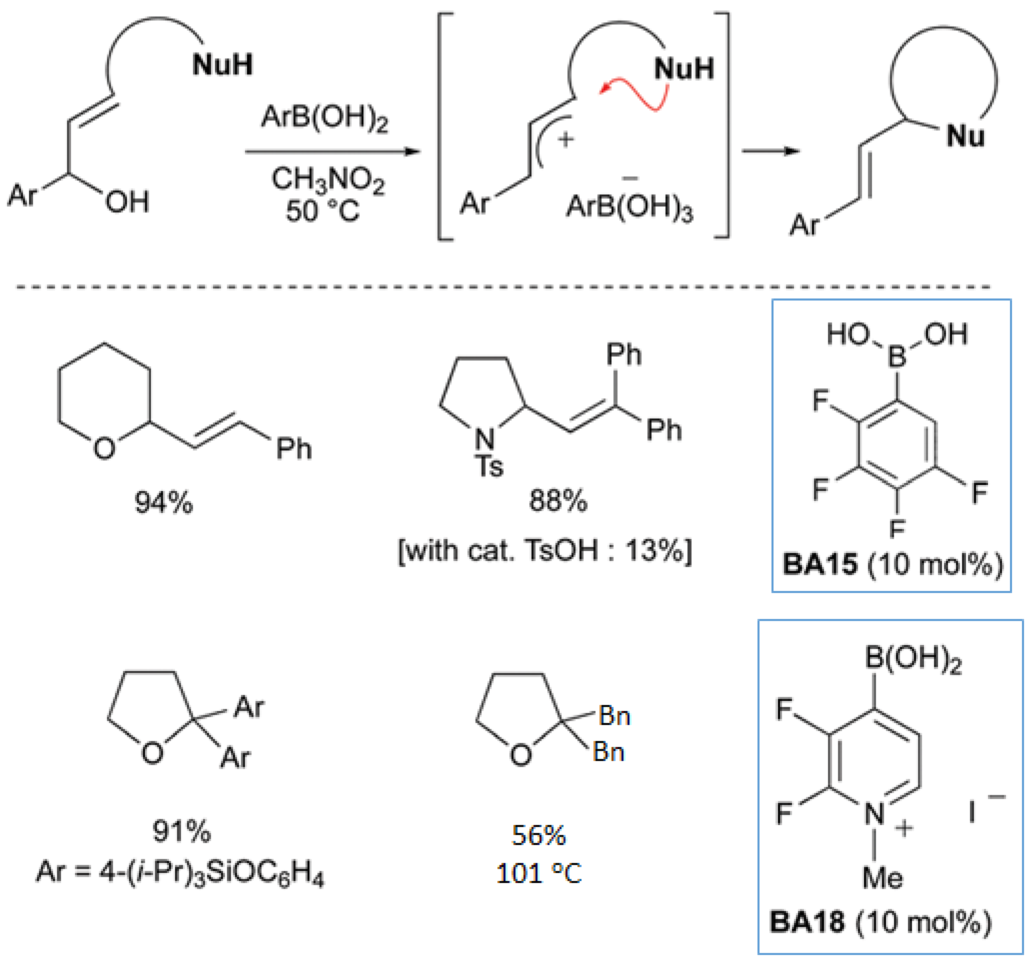
Hall (2011)



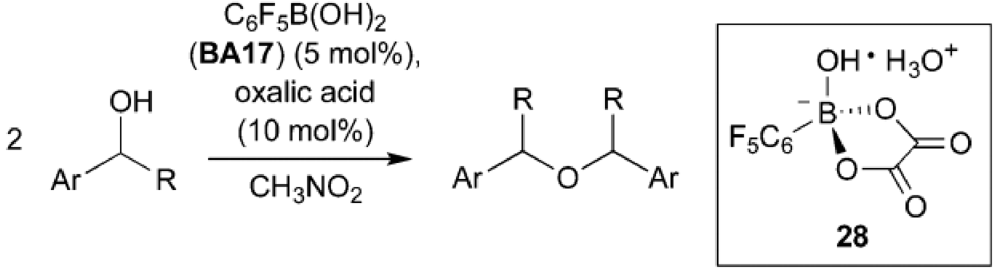


ii) X-H insertion / nucleophilic attack

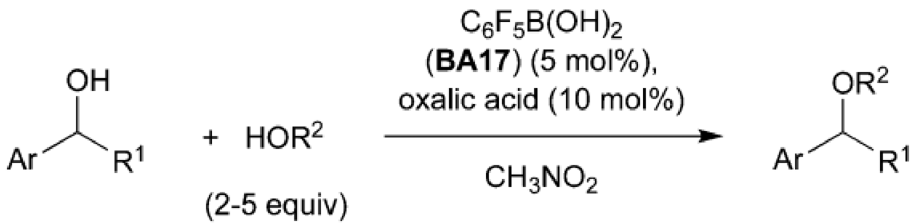
Hall (2012)



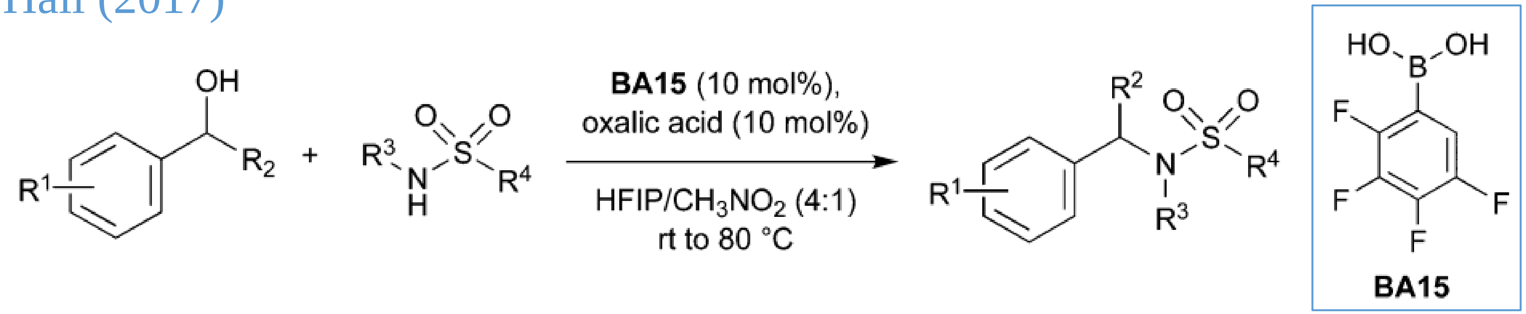
Moran (2015)



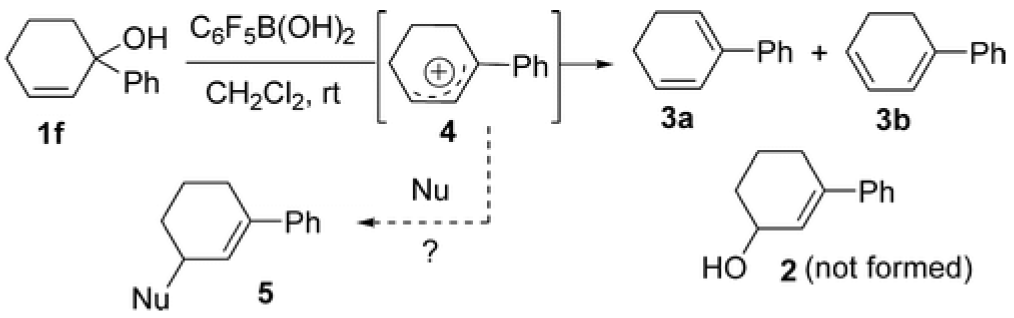
Taylor (2019)

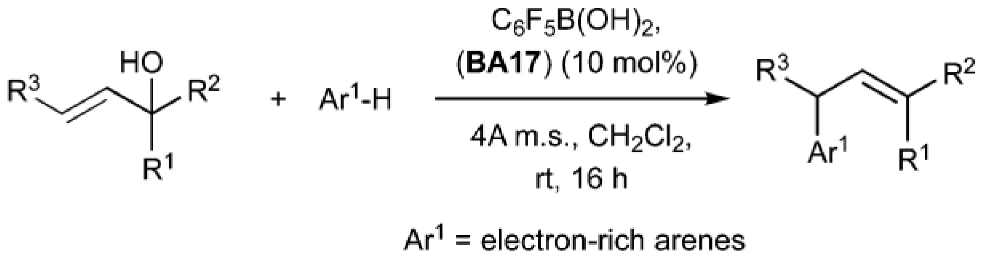


Hall (2017)

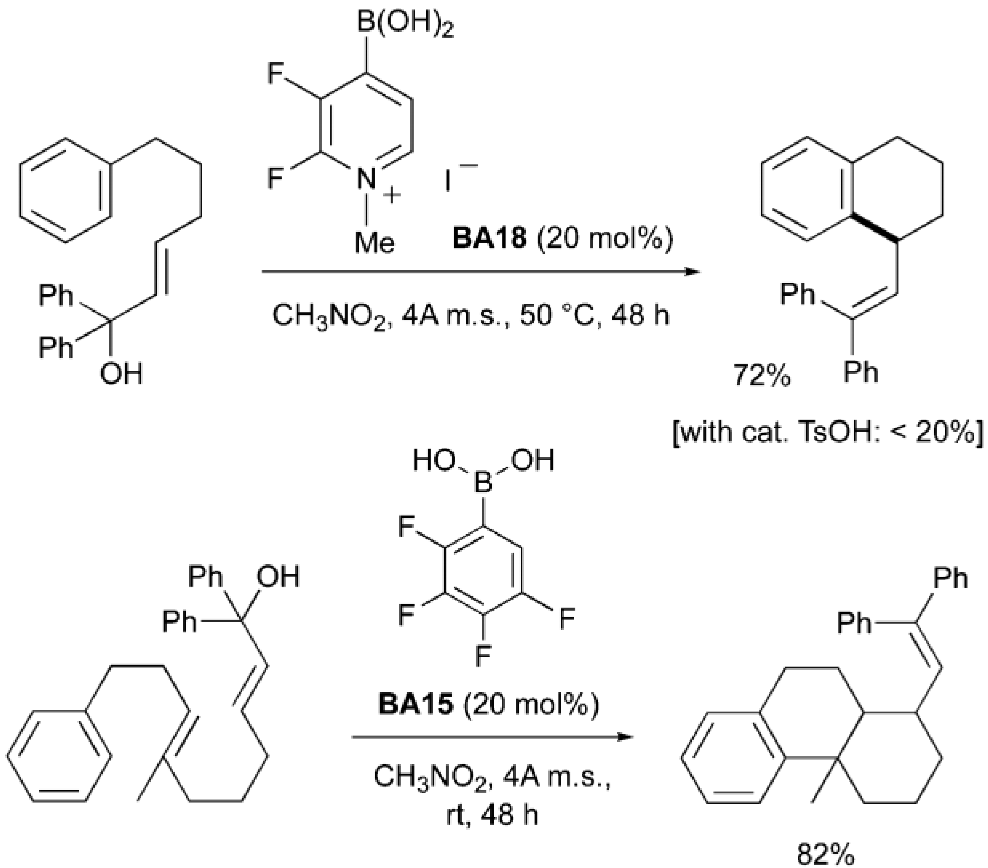


McCubbin (2010)

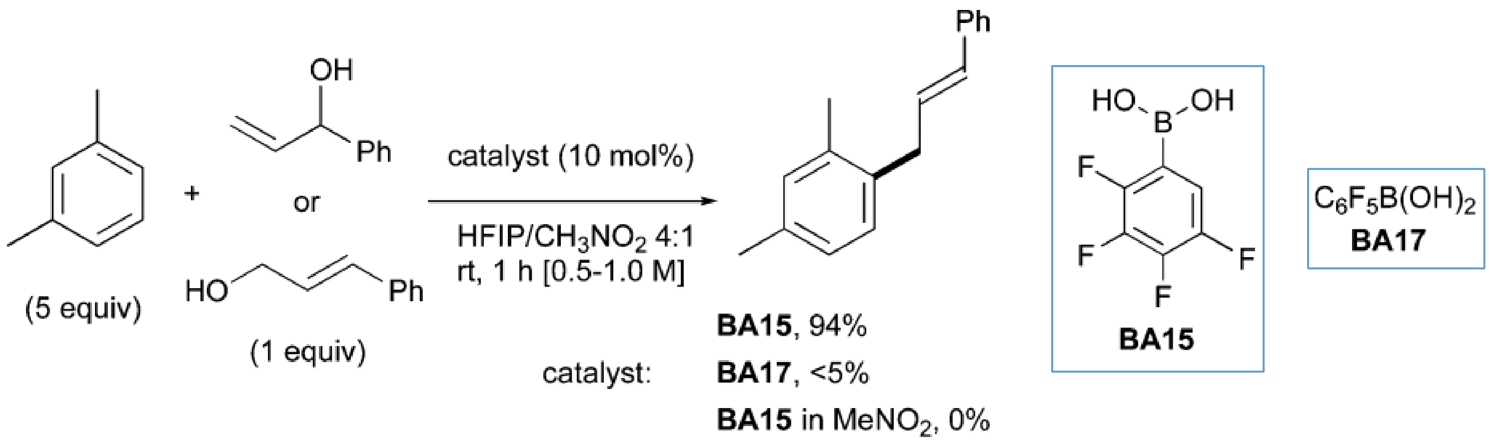


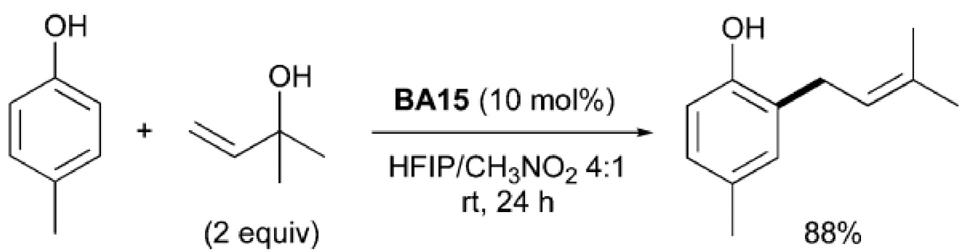


Hall (2012)

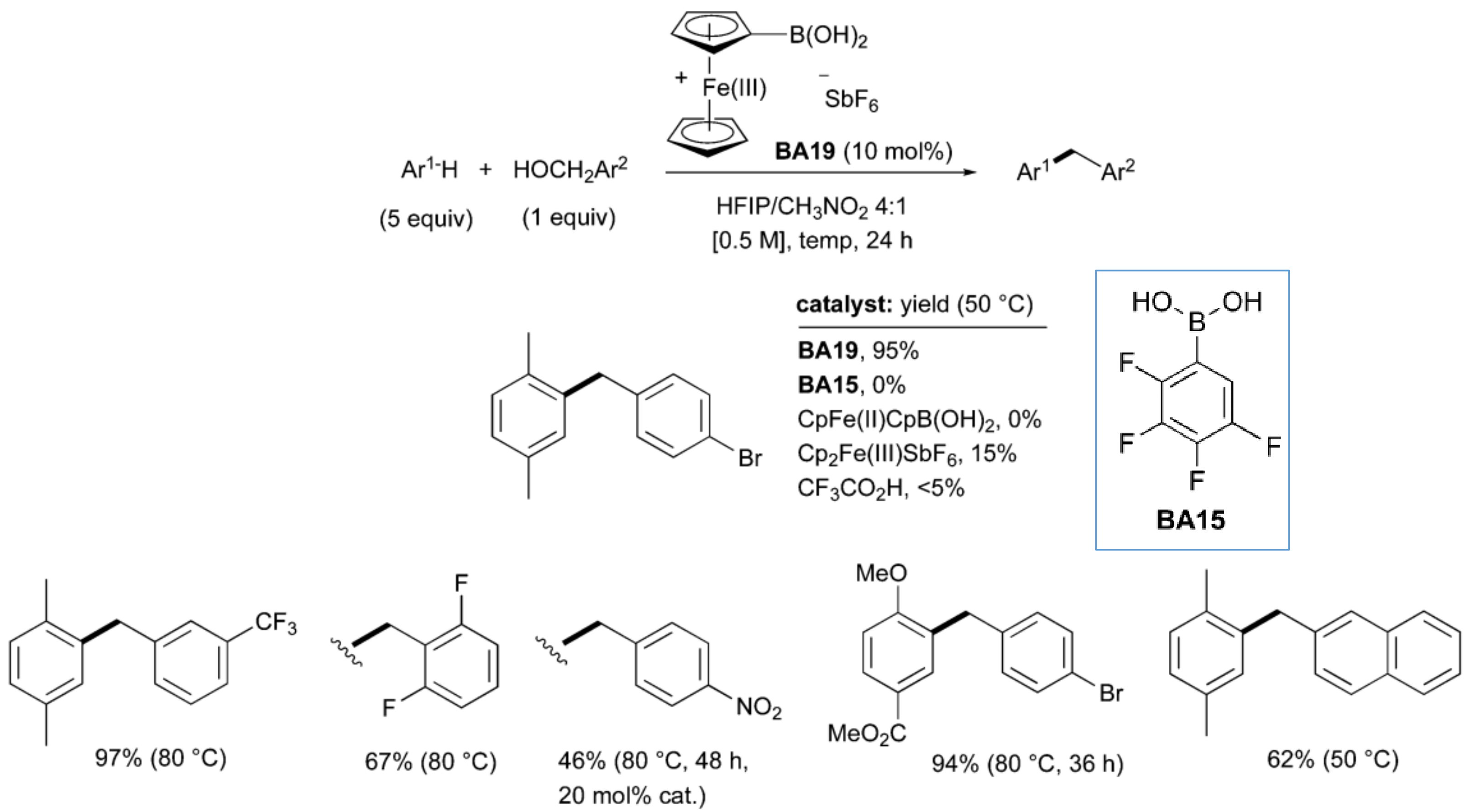

B(OH)2
F
F
N+
I−
Me
BA18 (20 mol%)
Ph
Ph
OH
CH3NO2, 4A m.s., 50 °C, 48 h
Ph
Ph
72%
[with cat. TsOH: < 20%]
HO
B
OH
F
F
F
F
Ph
OH
Ph
BA15 (20 mol%)
CH3NO2, 4A m.s.,
rt, 48 h
Ph
Ph
82%

Hall (2015)


OH
Ph
+
or
HO
Ph
(5 equiv)
(1 equiv)
catalyst (10 mol%)
HFIP/CH3NO2 4:1
rt, 1 h [0.5-1.0 M]
Ph
catalyst:
BA15, 94%
BA17, <5%
BA15 in MeNO2, 0%
HO
B
OH
F
F
F
F
F
BA15
C6F5B(OH)2
BA17

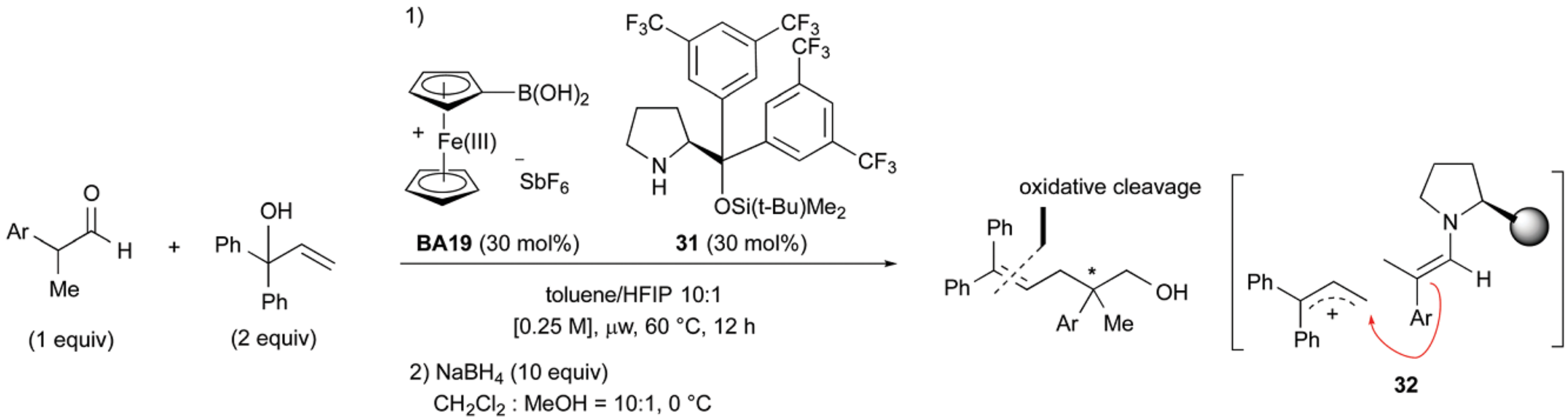

OH
+
OH
(2 equiv)
BA15 (10 mol%)
HFIP/CH3NO2 4:1
rt, 24 h
OH
88%

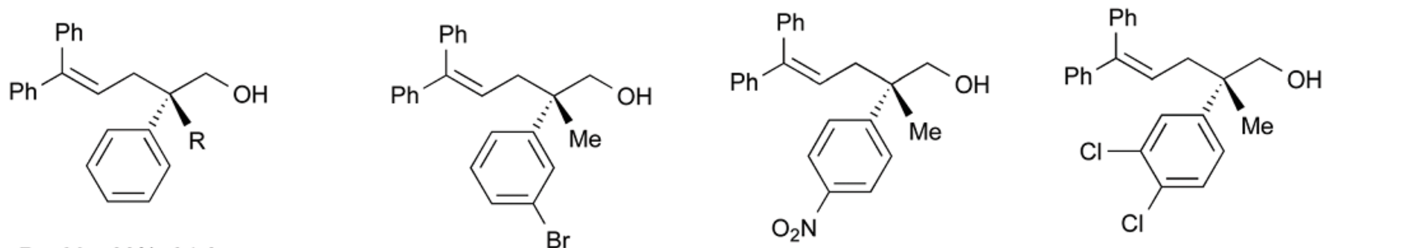
Hall (2015)



B(OH)$_2$
+
Fe(III)
$^-$SbF$_6$
BA19 (10 mol%)
Ar^1-H + HOCH$_2$Ar^2
(5 equiv) (1 equiv)
HFIP/CH$_3$NO$_2$ 4:1
[0.5 M], temp, 24 h
Ar^1 Ar^2
Br
catalyst: yield (50 °C)
BA19, 95%
BA15, 0%
CpFe(II)CpB(OH)$_2$, 0%
Cp$_2$Fe(III)SbF$_6$, 15%
CF$_3$CO$_2$H, <5%
HO B OH
F
F
F
F
BA15
CF$_3$
97% (80 °C)
F
F
67% (80 °C)
NO$_2$
46% (80 °C, 48 h, 20 mol% cat.)
MeO
MeO$_2$C
Br
94% (80 °C, 36 h)
62% (50 °C)

Hall (2016)





R = Me, 60%, 94:6 er
R = Et, 19%, 80:20 er

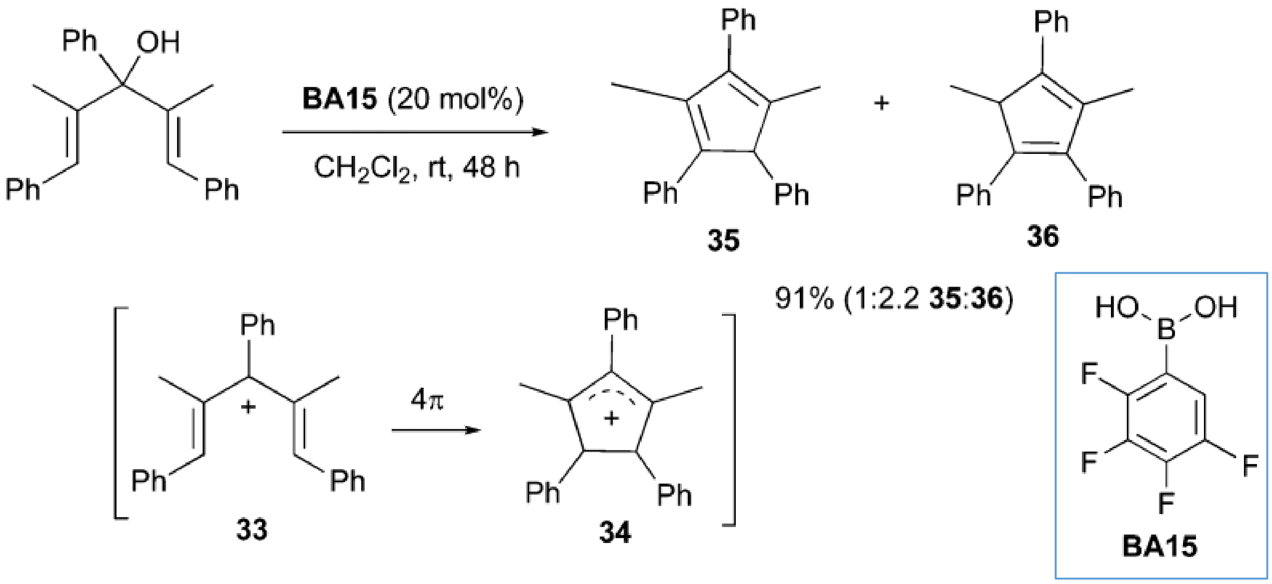
68%, 95.5:4.5 er

79%, 97:3 er

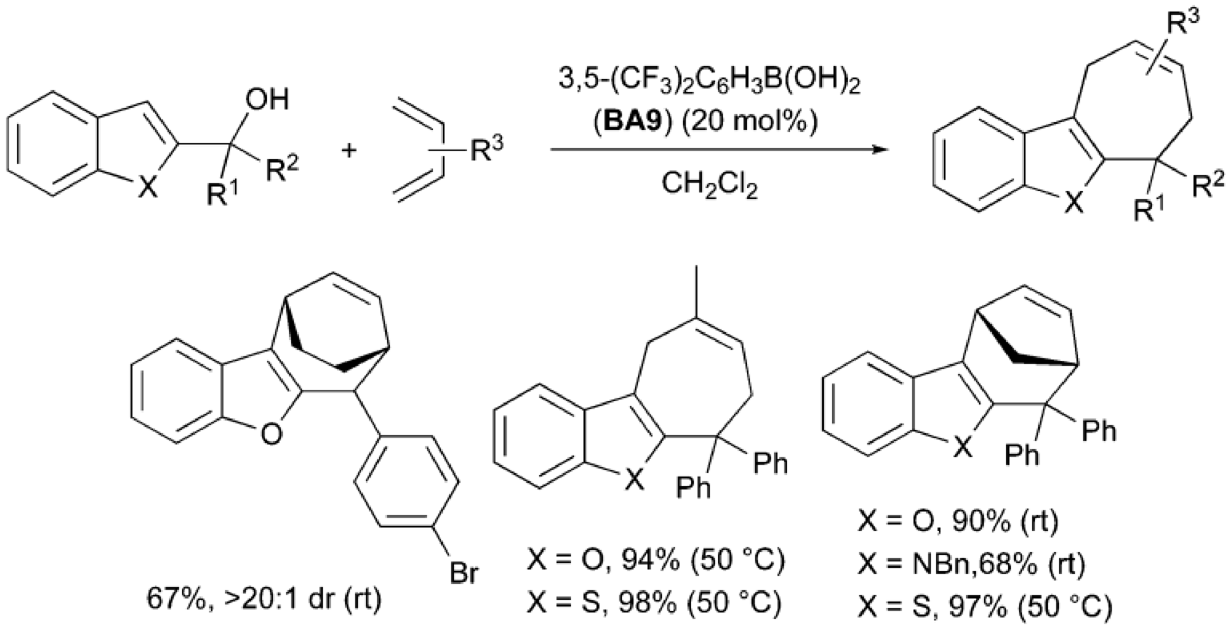
82%, 96.5:3.5 er
{gram-scale for a pharmaceutical intermediate: 67%}

iii) Cyclization & cycloadditions

Hall (2013)

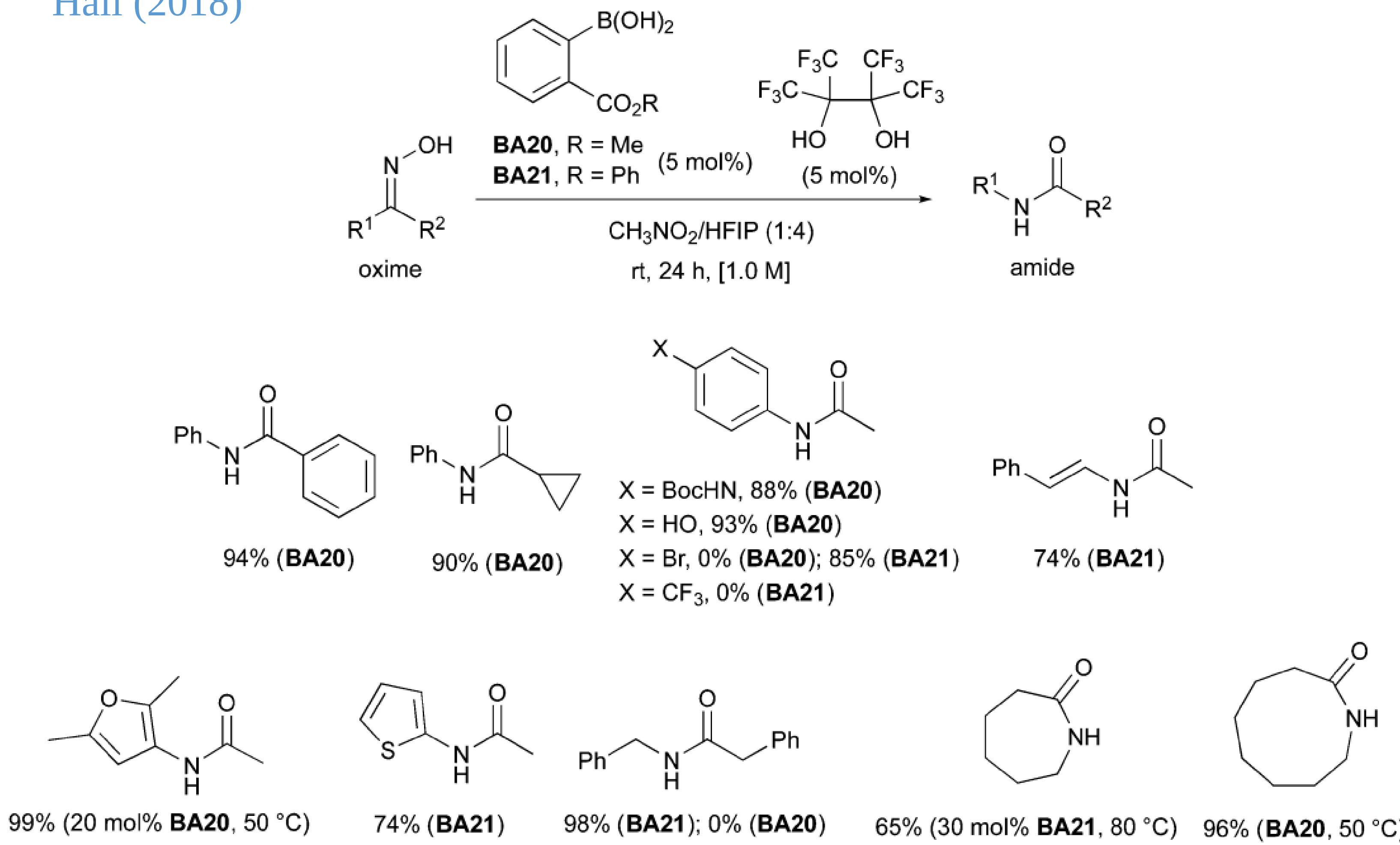


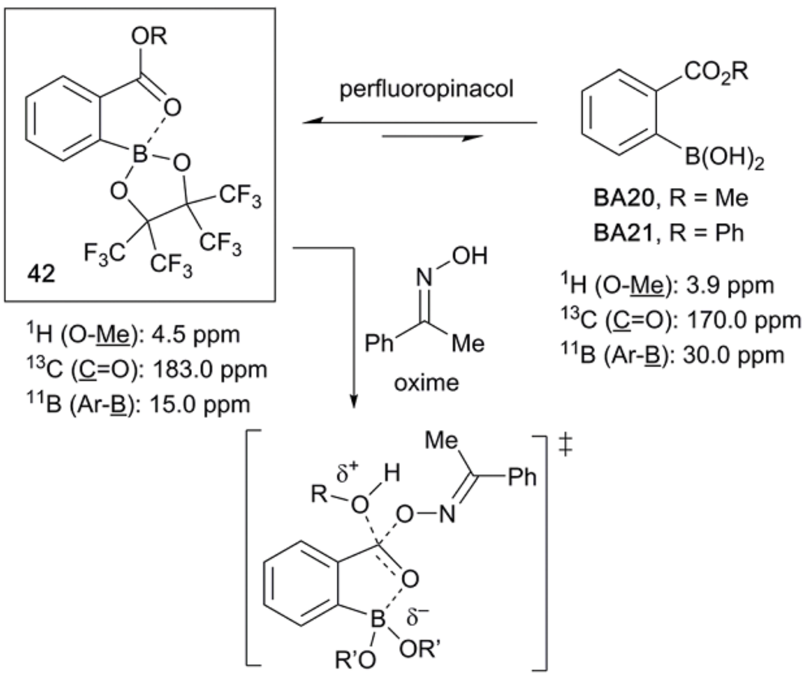
Zheng (2015)


OH
X
R1
R2
+
R3
3,5-(CF3)2C6H3B(OH)2
(BA9) (20 mol%)
CH2Cl2
R3
X
R1
R2
O
Br
67%, >20:1 dr (rt)
X
Ph
Ph
X = O, 94% (50 °C)
X = S, 98% (50 °C)
X
Ph
Ph
X = O, 90% (rt)
X = NBn,68% (rt)
X = S, 97% (50 °C)

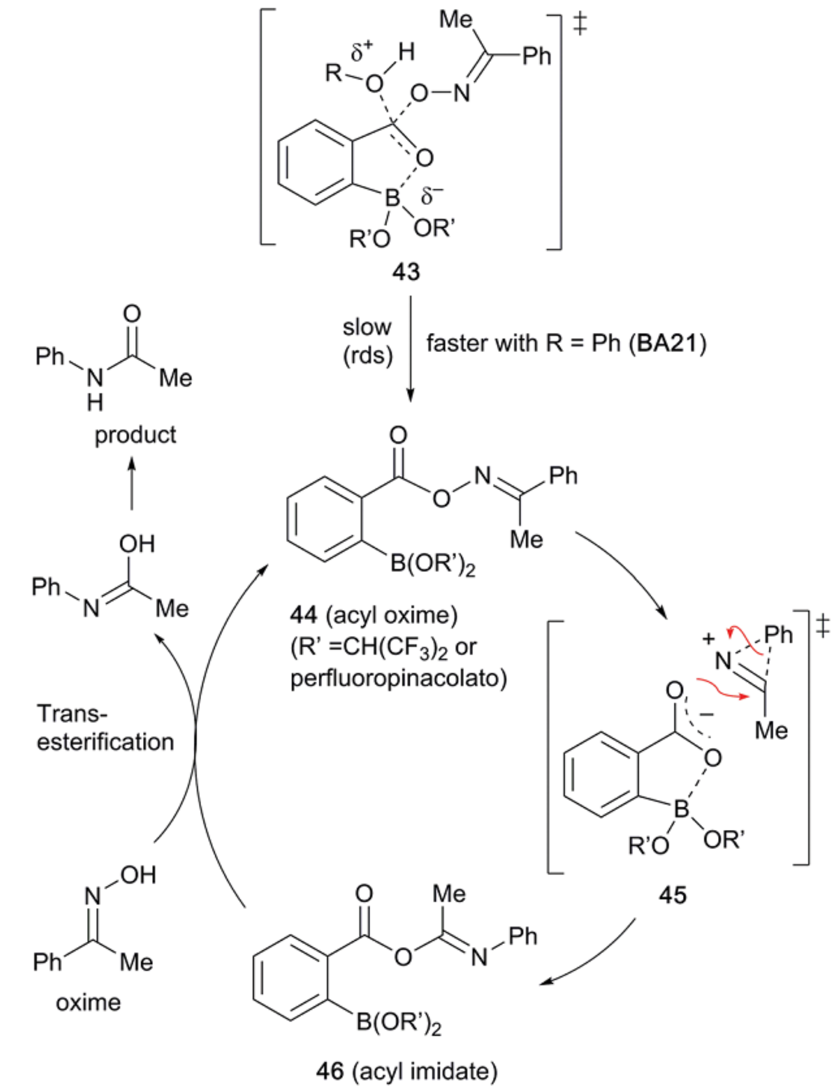
4) Oximes

Hall (2018)





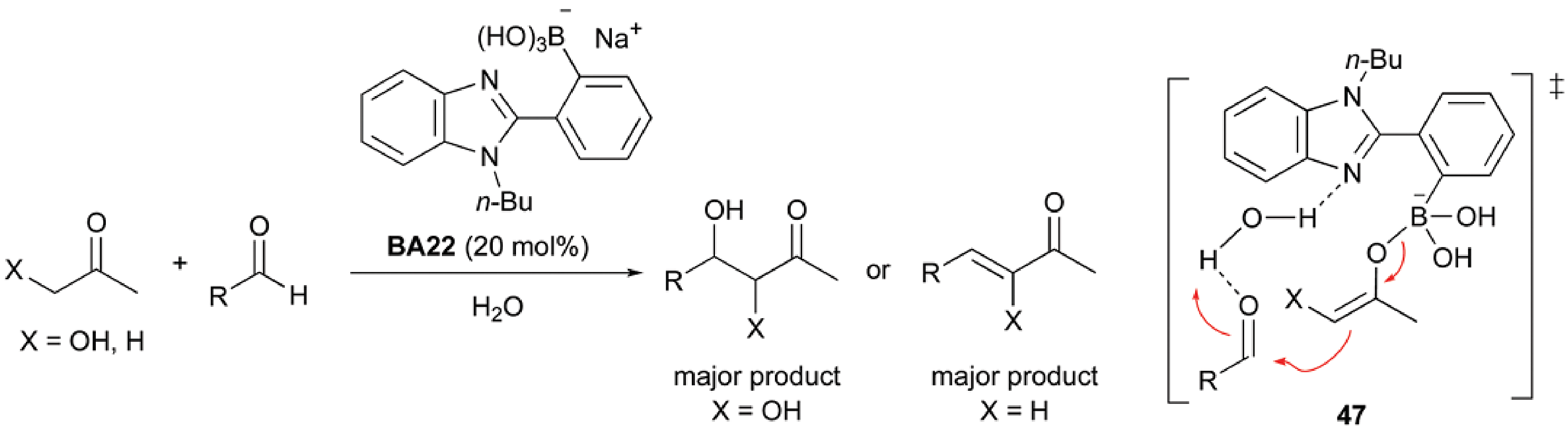
43, tetrahedral intermediate (R'O = perfluoropinacolato)

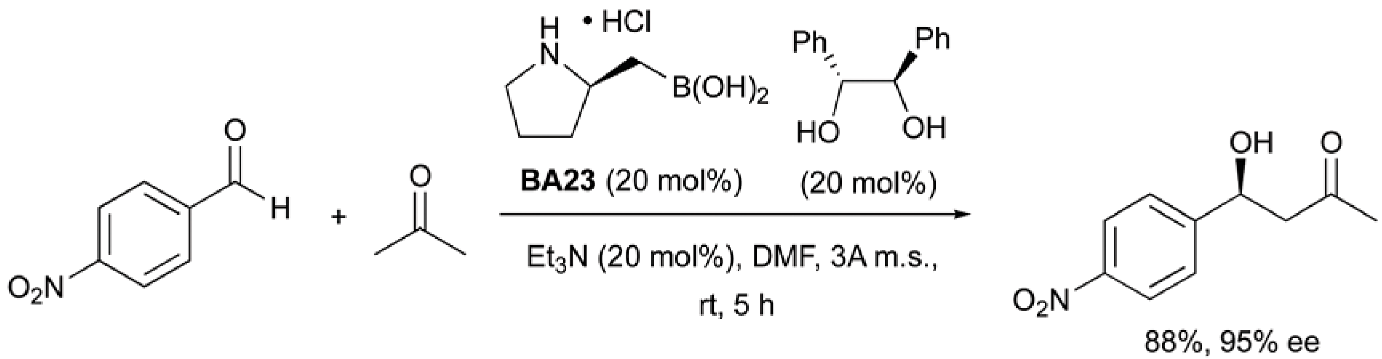


3. Nucleophilic activation

1) Carbonyl compounds

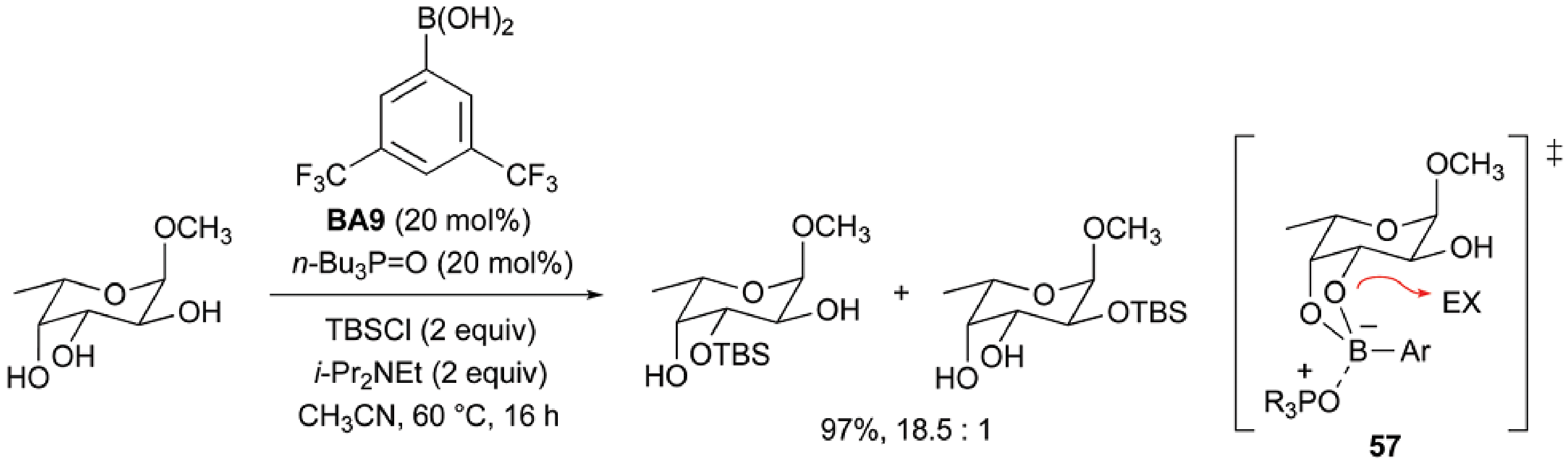
Whiting (2008, 2012)



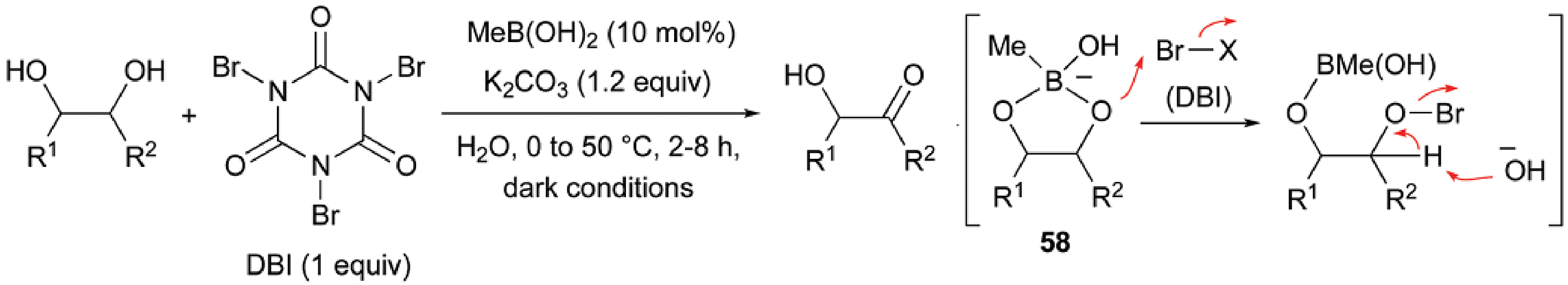


2) Diols and carbohydrates

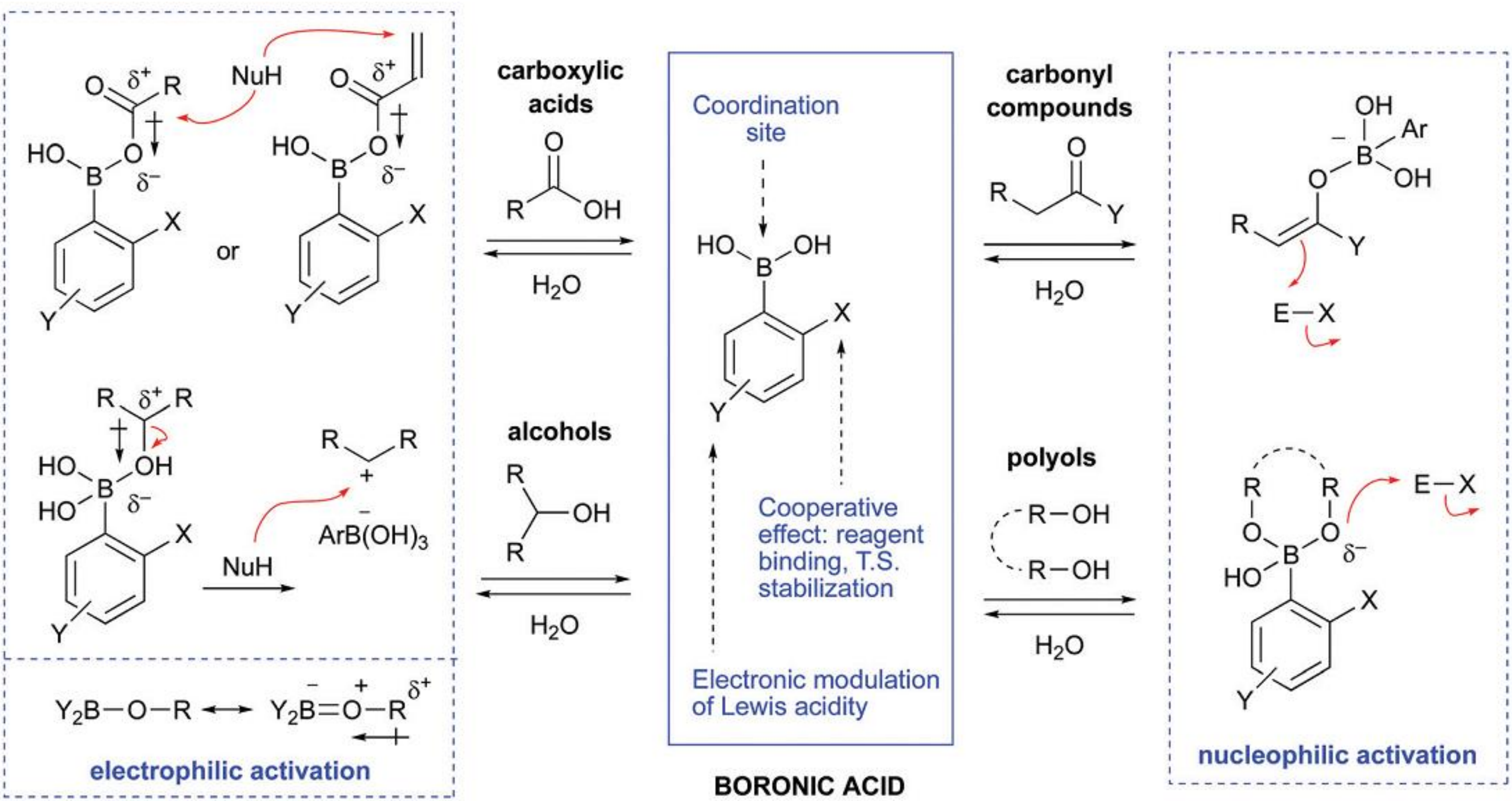
Taylor (2013)



Onomura (2014)

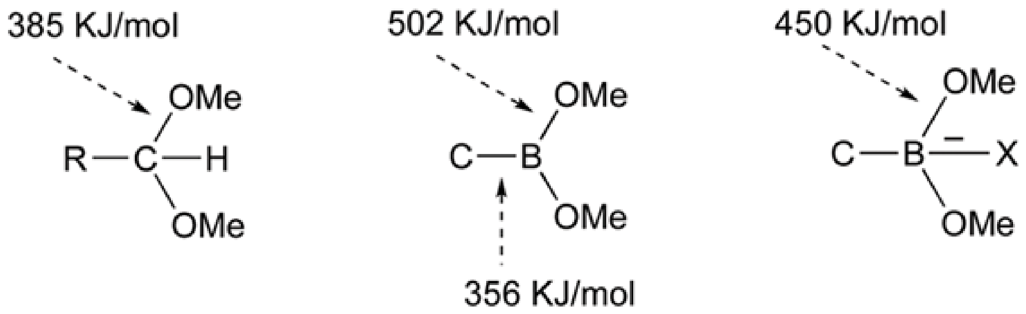


Summary


carboxylic acids
carbonyl compounds
alcohols
polyols
Coordination site
Cooperative effect: reagent binding, T.S. stabilization
Electronic modulation of Lewis acidity
BORONIC ACID
electrophilic activation
nucleophilic activation
or
NuH
ArB(OH)3
H2O

End
Thank You

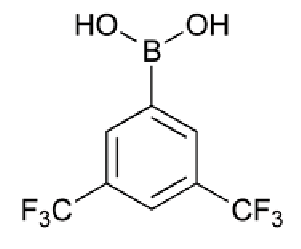
Bond enthalpies in comparable B–O and C–O compounds



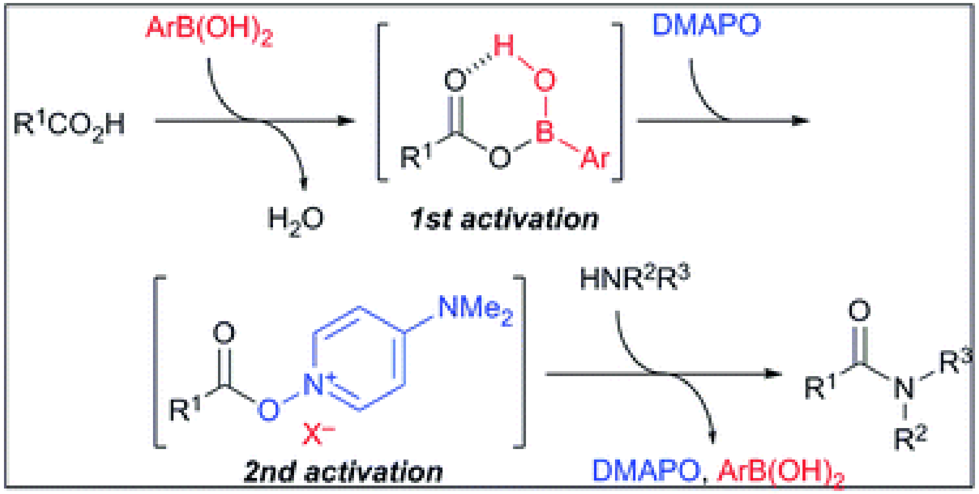
The facile exchange of B–O bonds of boronic acids is surprising considering the great strength of these covalent bonds. In spite of having bond enthalpies approximately 115 and 65 kJ/mol lower than sp^2 and sp^3 B–O bonds, respectively, the C–O bond of acetals is significantly less labile.

Direct amidation via **BA9** & DMNPO cooperative catalysis

Ishihara (2016)



BA9

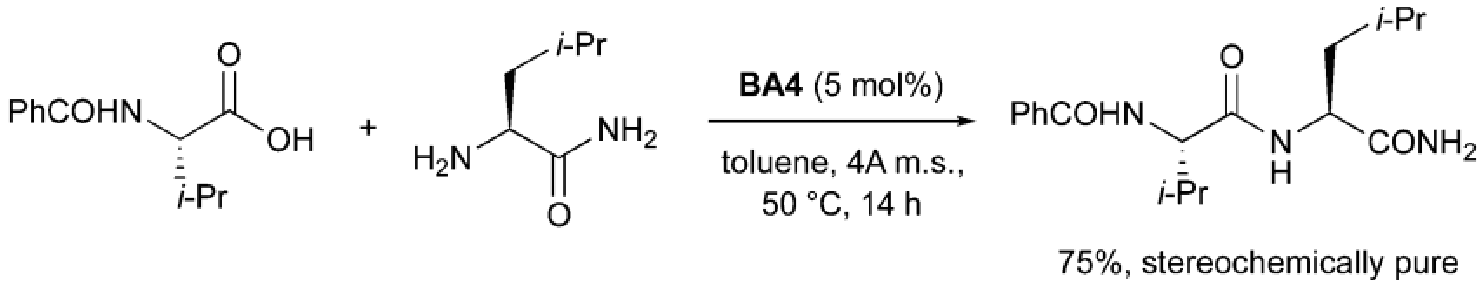


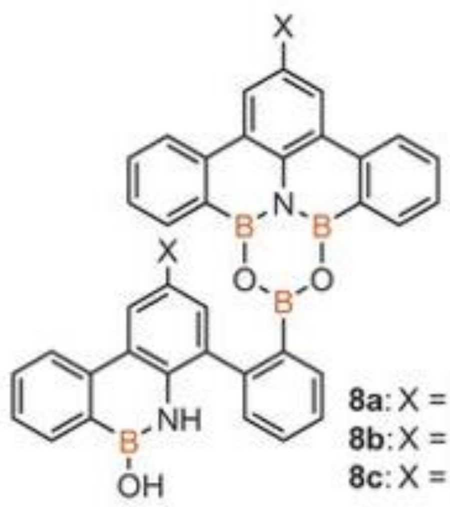
acyl N-oxide

Effective amidation of less reactive aromatic carboxylic acids and sterically hindered aliphatic α-branched carboxylic acids.

Synthesis of α-dipeptides using BAC

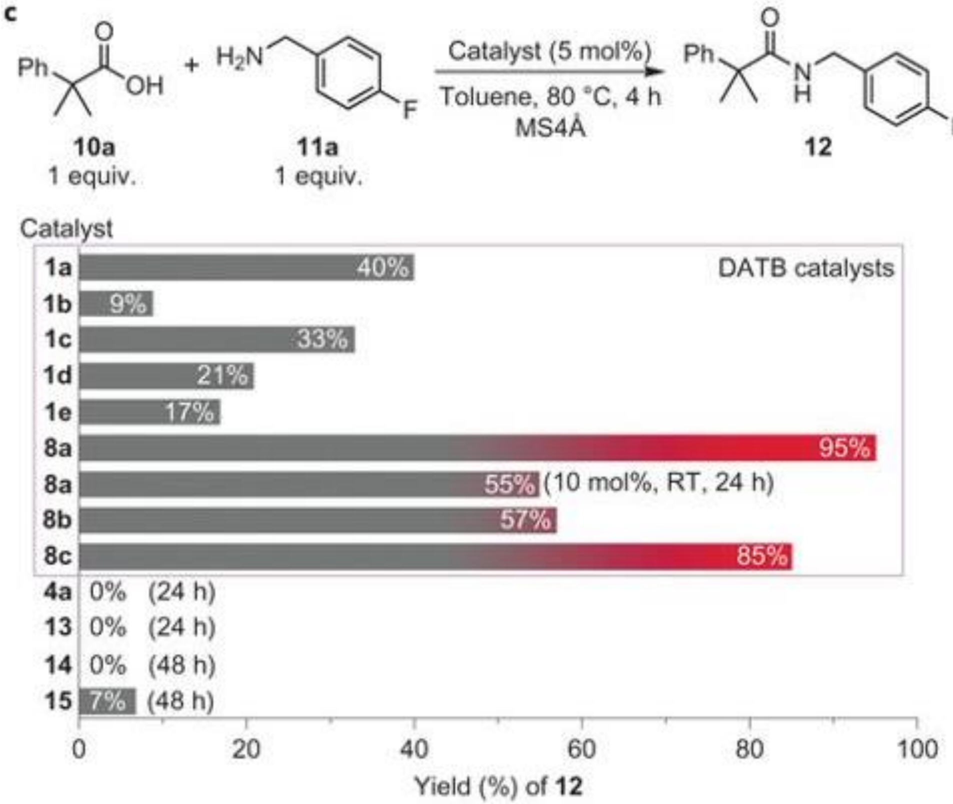
Shibasaki (2017)



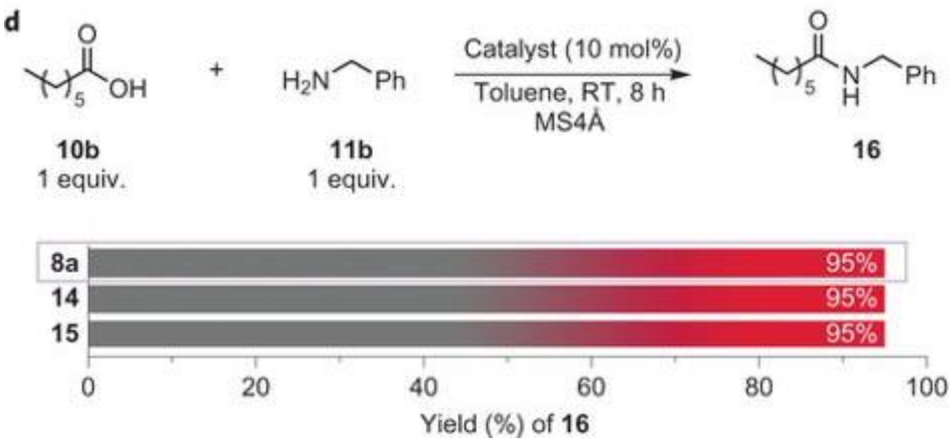


8a: X = H
8b: X = F
8c: X = Me

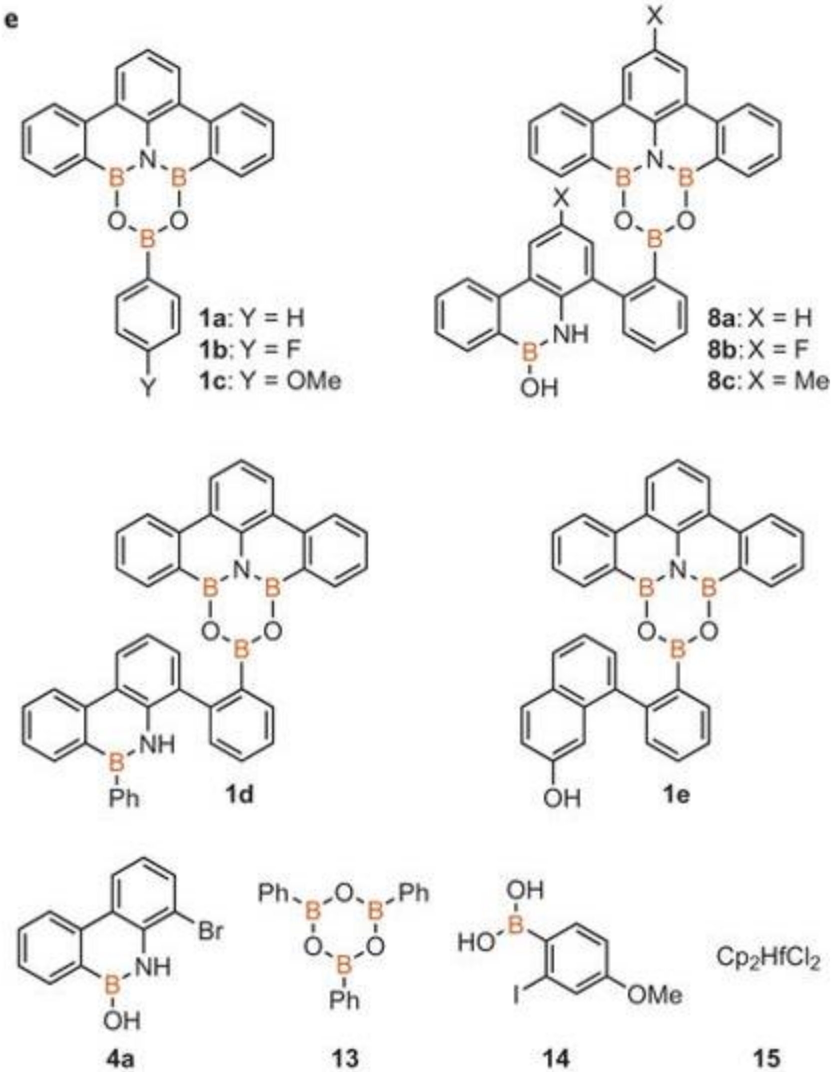
c


Ph
OH
+
H2N
F
Catalyst (5 mol%)
Toluene, 80 °C, 4 h
MS4Å
N
H
10a
1 equiv.
11a
1 equiv.
12
Catalyst
DATB catalysts
1a 40%
1b 9%
1c 33%
1d 21%
1e 17%
8a 95%
8a 55% (10 mol%, RT, 24 h)
8b 57%
8c 85%
4a 0% (24 h)
13 0% (24 h)
14 0% (48 h)
15 7% (48 h)
0 20 40 60 80 100
Yield (%) of 12

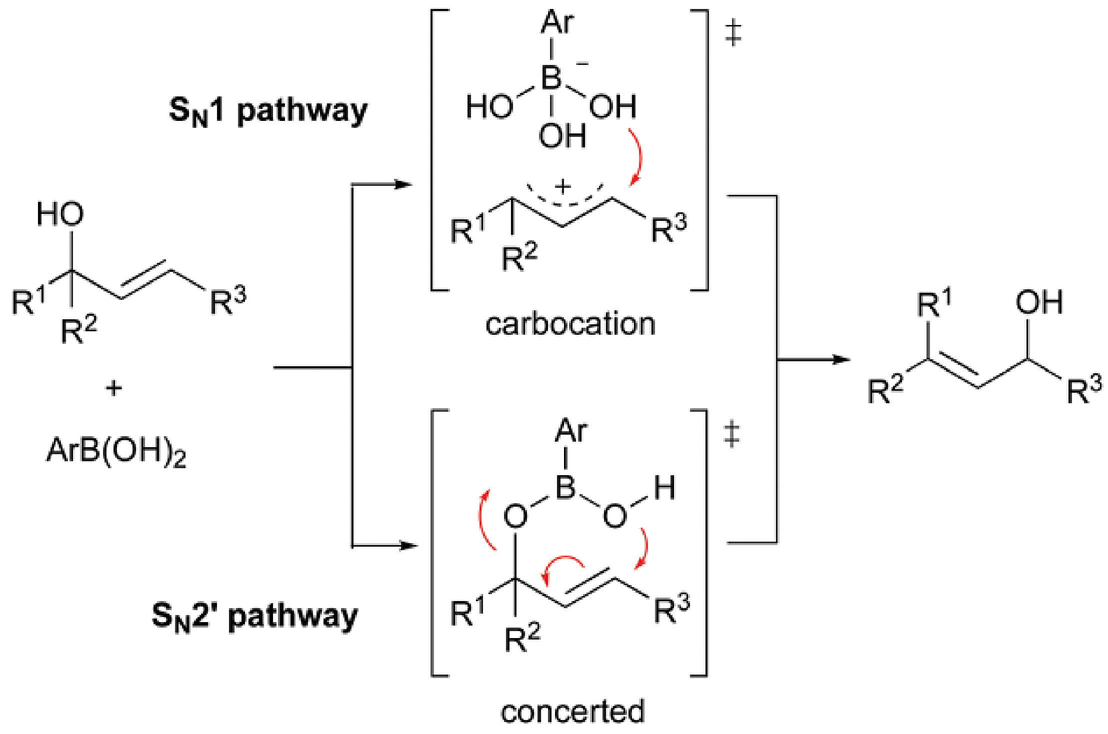
d


OH
+
H2N
Ph
Catalyst (10 mol%)
Toluene, RT, 8 h
MS4Å
N
H
Ph
10b
1 equiv.
11b
1 equiv.
16
8a 95%
14 95%
15 95%
0 20 40 60 80 100
Yield (%) of 16

e


1a: Y = H
1b: Y = F
1c: Y = OMe
8a: X = H
8b: X = F
8c: X = Me
1d
1e
Br
NH
OH
Ph
OMe
Cp2HfCl2
4a
13
14
15

1,3-Transposition of allylic alcohols with two possible mechanisms



Proposed ion-redistribution mechanism of Friedel–Crafts benzylation

Hall (2015)