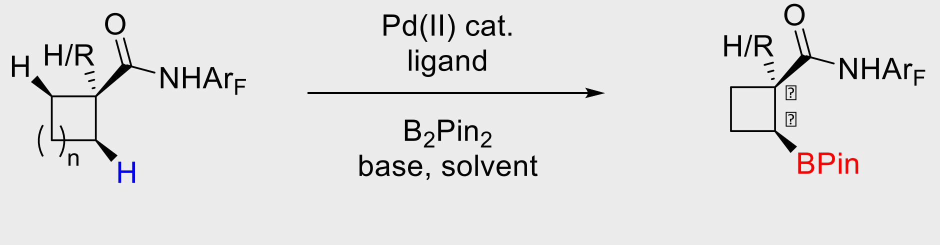
Pd(II)-Catalyzed Enantioselective C(sp^3)-H Borylation

Jian He, Qian Shao, Qingfeng Wu, and Jin-Quan Yu

J. Am. Chem. Soc., **2017**, *139*, 3344-3347

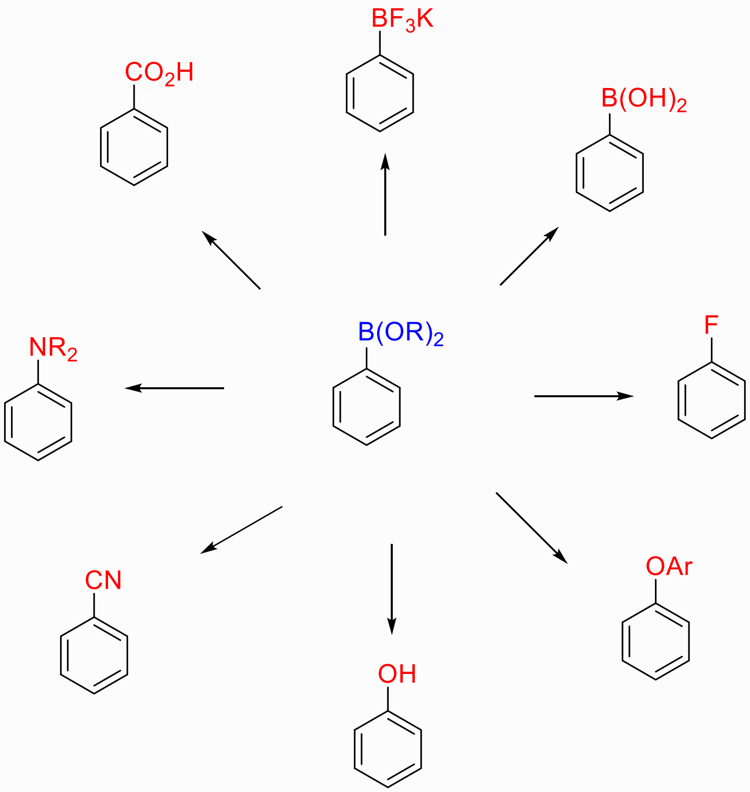
Serene Tai
Current literature 10 June 2017



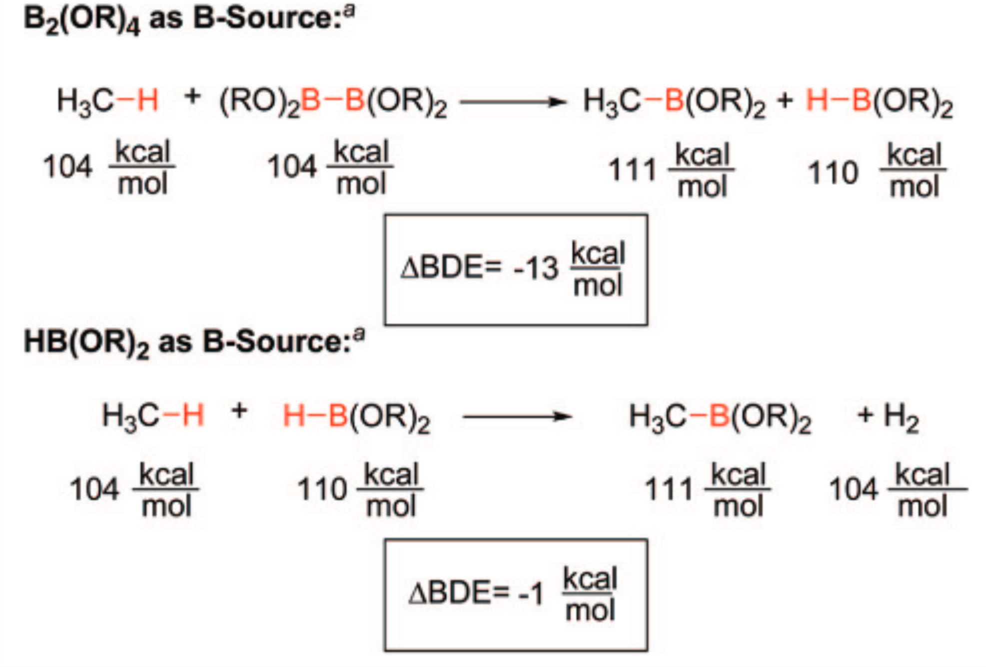
Ar$_F$ = 4-(CF$_3$)C$_6$F$_4$; n = 0, 1, 3

up to 99.8 % ee

Transformations of Boronates

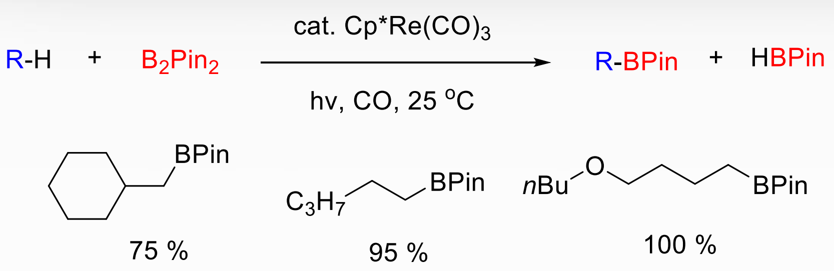


Thermodynamics of Methane Borylation

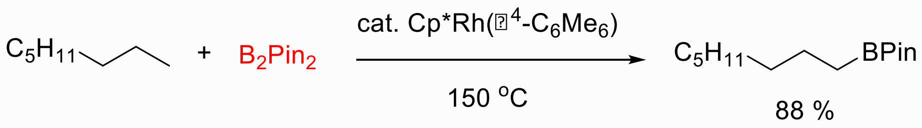


Chem. Rev., **2010**, *110*, 890-931

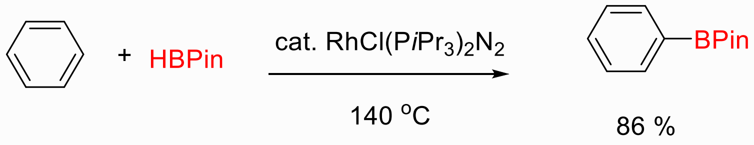
Catalytic C-H Borylation



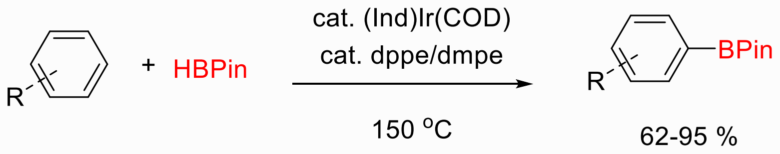
Rhenium (Hartwig, JACS 1999)



Rhodium (Hartwig, Science 2000)



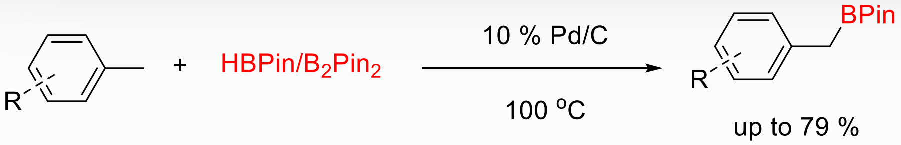
Rhodium (Marder, ACIE 2001)



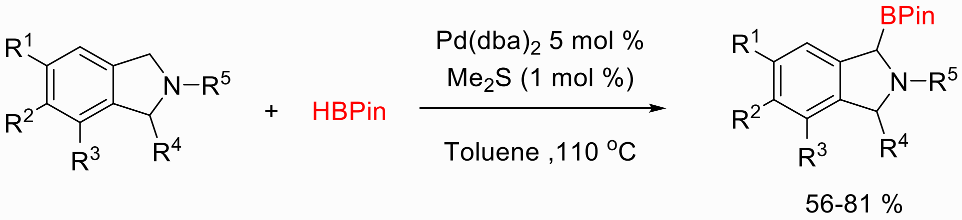
Iridium (Smith, Science 2002)

Chem. Rev., **2010**, *110*, 890-931

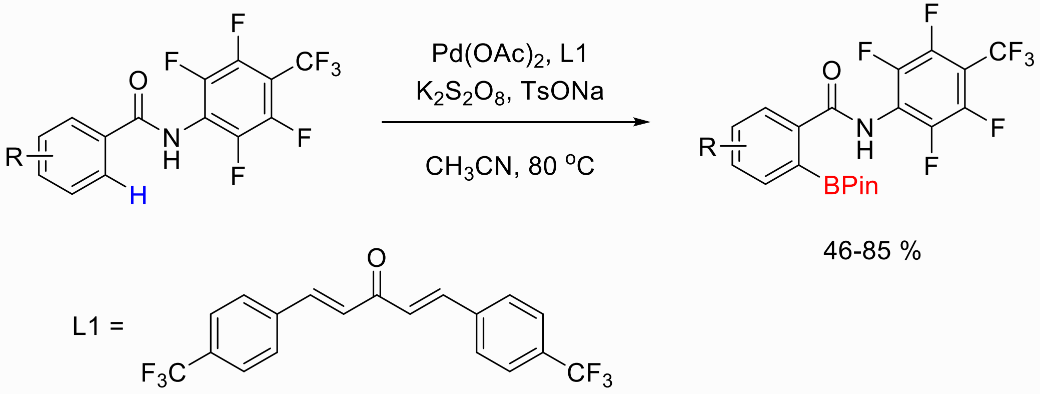
Pd-Catalyzed C-H Borylation



Miyaura, Chem. Lett. 2001

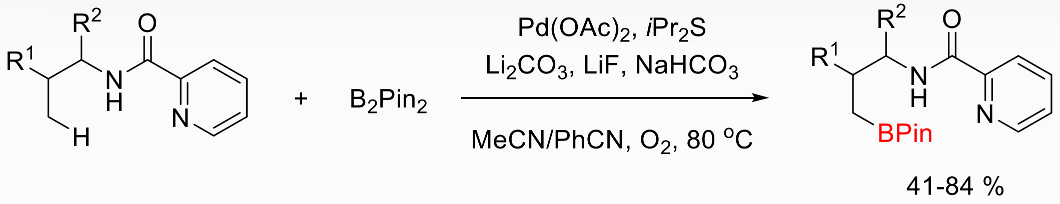


Suginome, JACS 2009

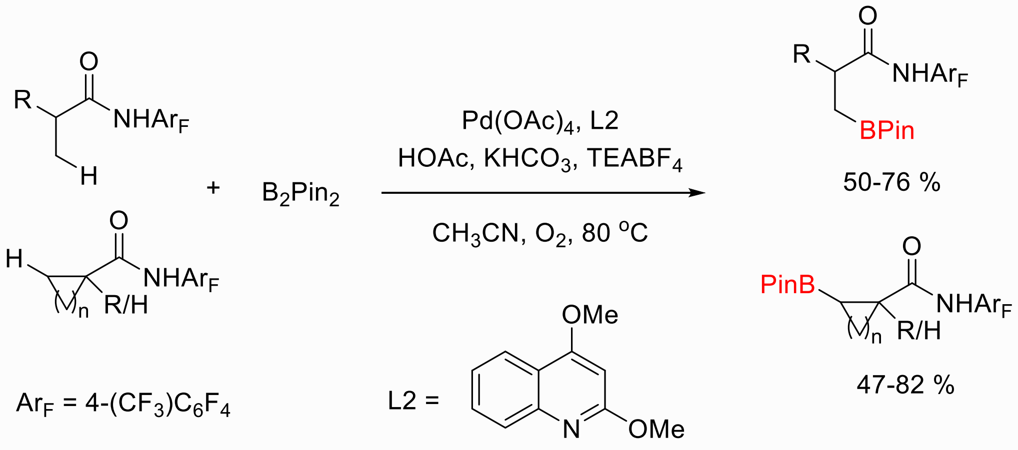


Yu, JACS 2012

Pd-Catalyzed C(sp^3)-H Borylation



Shi, ACIE 2014

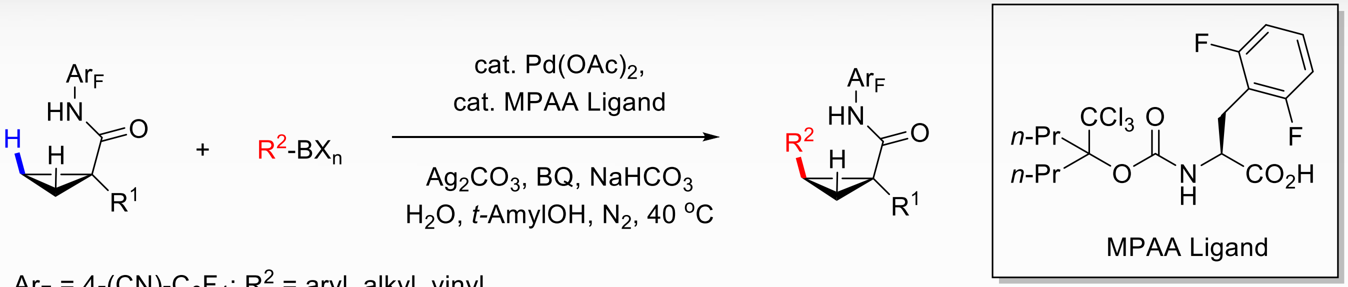


$Ar_F = 4\text{-}(CF_3)C_6F_4$

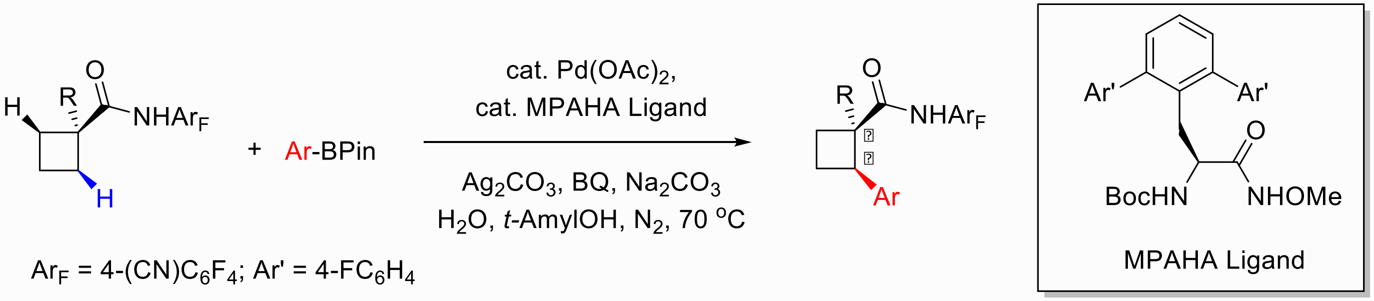
Yu, ACIE 2016

Angew. Chem. Int. Ed., **2014**, *53*, 3899
Angew. Chem. Int. Ed., **2016**, *55*, 785

Enantioselective Pd-Catalyzed C(sp³)-H Activation



Ar_F = 4-(CN)-C_6F_4; R^2 = aryl, alkyl, vinyl

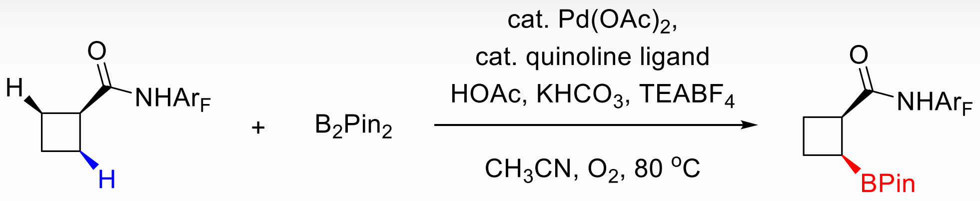


Ar_F = 4-(CN)C_6F_4; Ar' = 4-FC_6H_4

Limited to substrates containing α-quarternary carbon centers

J. Am. Chem. Soc., **2011**, *133*, 19598
J. Am. Chem. Soc., **2014**, *136*, 8138

Quinoline-based Ligands



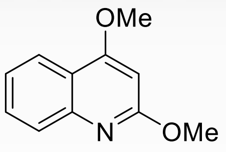
cat. $Pd(OAc)_2$,
cat. quinoline ligand
HOAc, $KHCO_3$, $TEABF_4$

CH_3CN, O_2, 80 °C

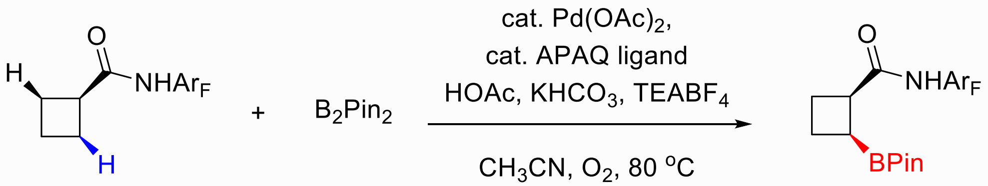
1a

Ar_F = 4-$(CF_3)C_6F_4$

rac 2a, 80 %



Quinoline Ligand



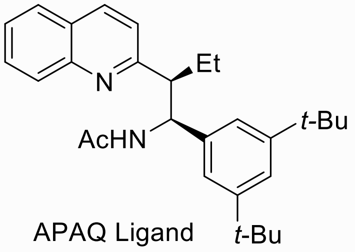
cat. $Pd(OAc)_2$,
cat. APAQ ligand
HOAc, $KHCO_3$, $TEABF_4$

CH_3CN, O_2, 80 °C

1a

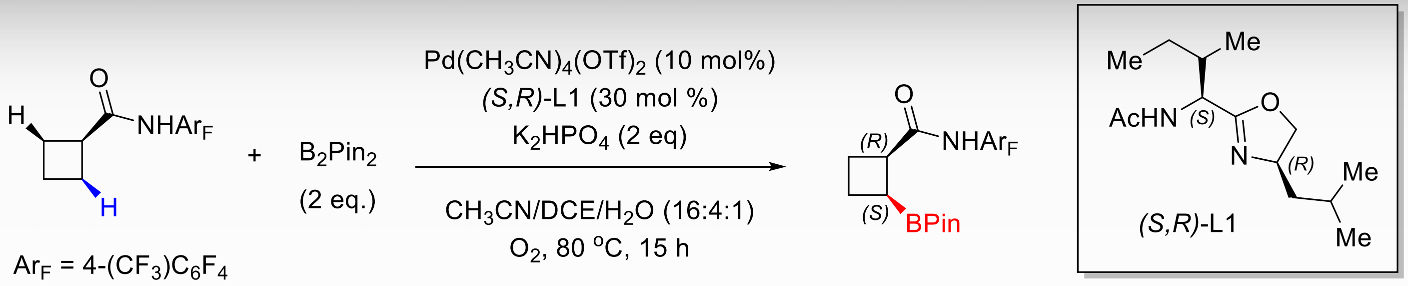
Ar_F = 4-$(CF_3)C_6F_4$

2a, n.d.



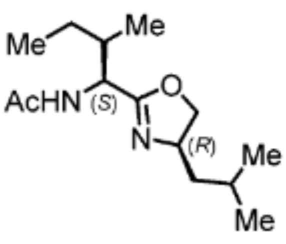
APAQ Ligand

Conditions Optimization

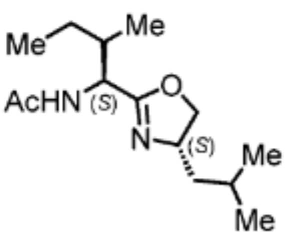


Entry	Variation from standard conditions	Yield (%)	ee (%)
1	none	82	95.6
2	No $Pd(CH_3CN)_4(OTf)_2$	n.d.	-
3	No K_2HPO_4	n.d.	-
4	No *(S,R)*-L1	21	0
5	*(S,R)*-L1 (20 mol%)	85	93.4
6	$Pd(CH_3CN)_4(OTf)_2$ (5 mol%)	67	89.0
7	$Pd(OAc)_2$	63	78.4
8	$KHCO_3$	58	89.4
9	CH_3CN only	64	93.4
10	DCE only	19	72.4
11	CH_3CN/DCE (4:1)	65	95.6
12	60 °C	38	95.4
13	Under air (cap vial)	61	94.8

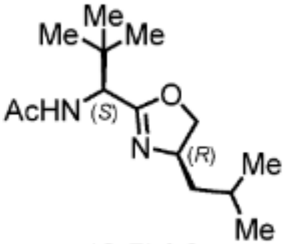
Ligand Optimization


(*S*,*R*)-**L1**

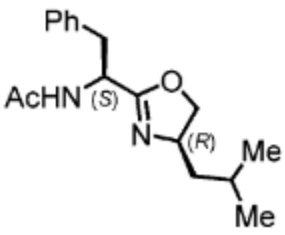
82%, 95.6% ee


(*S*,*S*)-**L1**

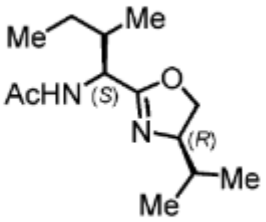
24%, 50.4% ee


(*S*,*R*)-**L2**

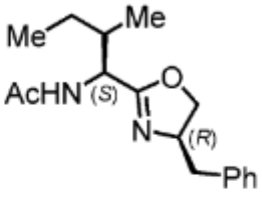
82%, 95.0% ee


(*S*,*R*)-**L3**

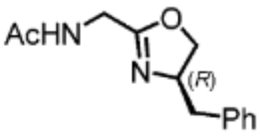
72%, 93.6% ee


(*S*,*R*)-**L4**

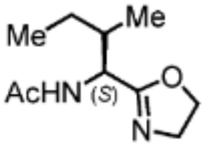
71%, 92.6% ee


(*S*,*R*)-**L5**

76%, 92.2% ee

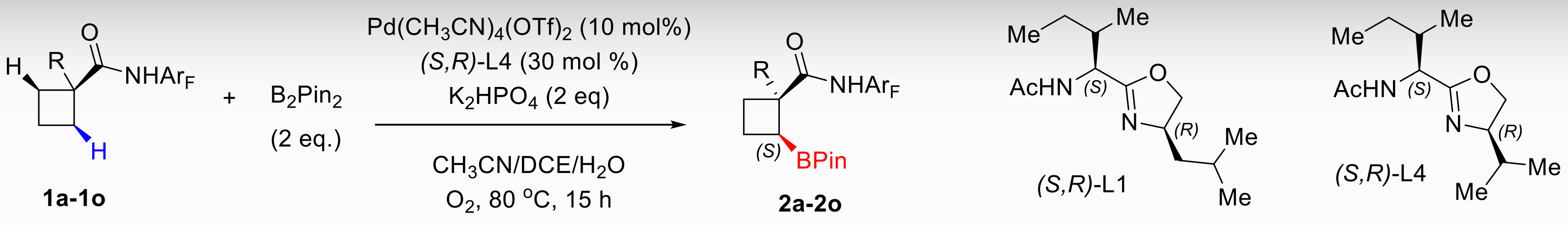

(*R*)-**L6**

13%, 51.0% ee


(*S*)-**L7**

57%, 78.8% ee

Substrate Scope for Cyclobutanecarboxylic Amides

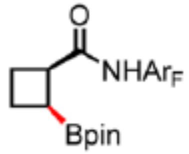


1a-1o

2a-2o

(S,R)-L1

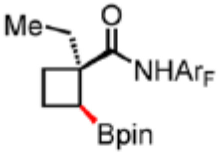
(S,R)-L4



2a

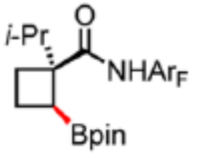
78%, 95.6% ee[c]

***(S,R)*-L1**



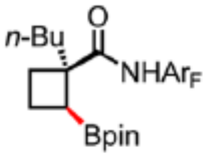
2b

75%, 99.2% ee



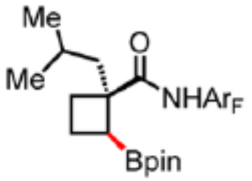
2c

75%, 98.4% ee



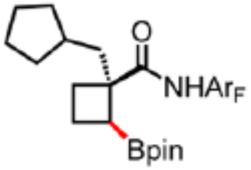
2d

73%, 99.2% ee
(56%, 99.2% ee)[f]



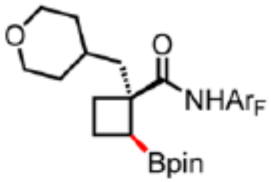
2e

77%, 98.5% ee



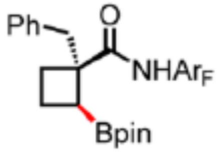
2f

73%, 99.1% ee
(52%, 97.2% ee)[f]



2g

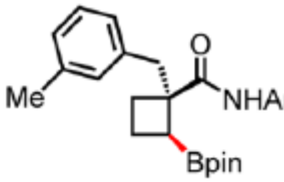
67%, 98.2% ee



2h

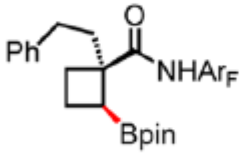
70%, 97.2% ee[d]

***(S,R)*-L5**



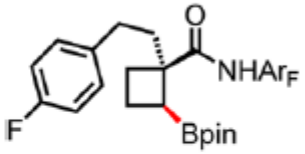
2i

69%, 96.6% ee



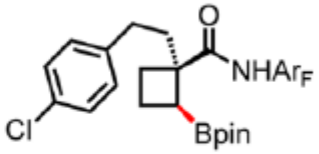
2j

72%, 99.4% ee



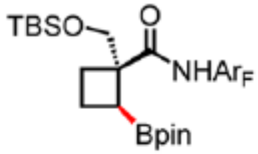
2k

75%, 99.8% ee
(60%, 97.6% ee)[f]



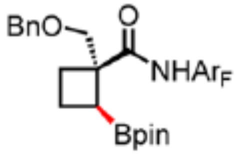
2l

75%, 97.9% ee



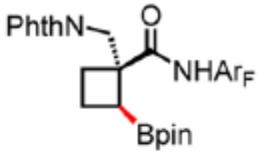
2m

58%, 98.0% ee



2n

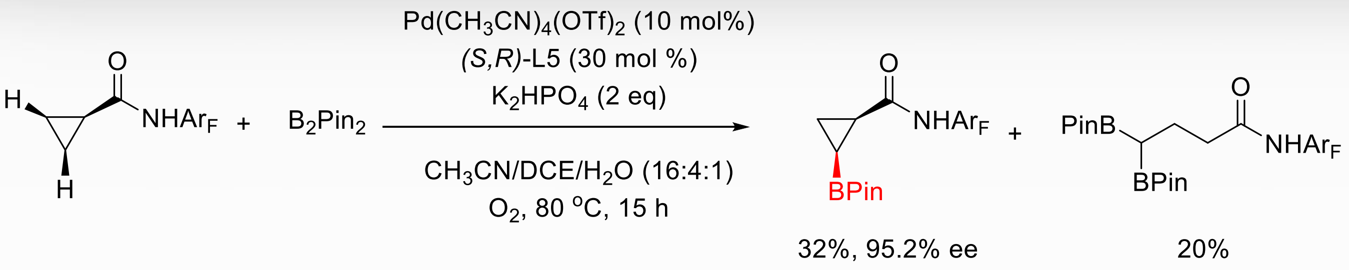
77%, 97.4% ee



2o

52%, 88.3% ee[e]

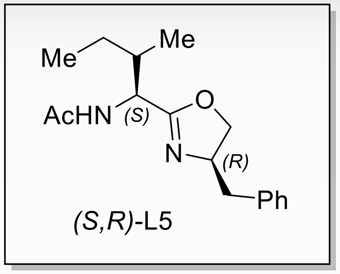
Substrate Scope for Other Cyclic Amides



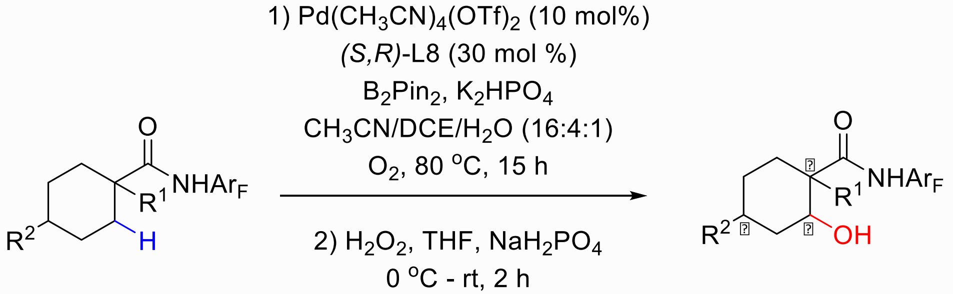
$Pd(CH_3CN)_4(OTf)_2$ (10 mol%)
(S,R)-L5 (30 mol %)
K_2HPO_4 (2 eq)
$CH_3CN/DCE/H_2O$ (16:4:1)
O_2, 80 °C, 15 h

32%, 95.2% ee

20%

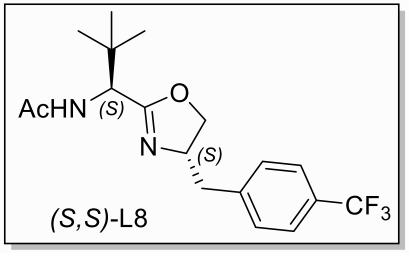


(S,R)-L5

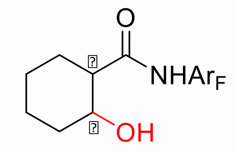


1) $Pd(CH_3CN)_4(OTf)_2$ (10 mol%)
(S,R)-L8 (30 mol %)
B_2Pin_2, K_2HPO_4
$CH_3CN/DCE/H_2O$ (16:4:1)
O_2, 80 °C, 15 h

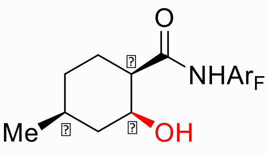
2) H_2O_2, THF, NaH_2PO_4
0 °C - rt, 2 h



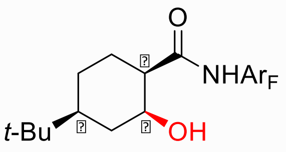
(S,S)-L8



cis, 23%, 92.4% ee
trans, 40%, 93.2% ee

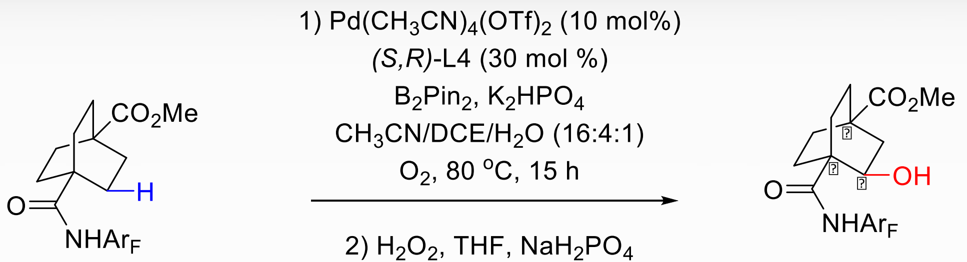


53%, 95.2% ee
(d.r. > 10:1)



48%, 91.7% ee
(d.r. > 10:1)

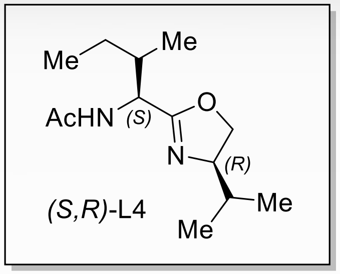
Substrate Scope for Other Cyclic/Acyclic Amides



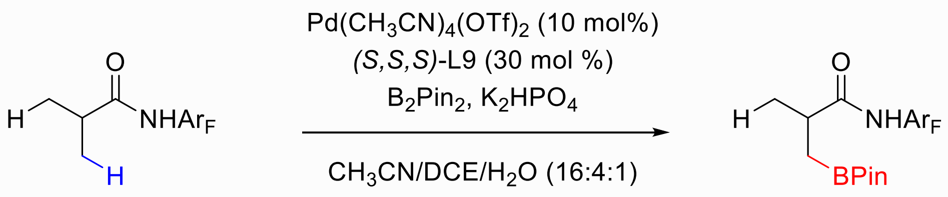
1) $Pd(CH_3CN)_4(OTf)_2$ (10 mol%)
(S,R)-L4 (30 mol %)
B_2Pin_2, K_2HPO_4
$CH_3CN/DCE/H_2O$ (16:4:1)
O_2, 80 °C, 15 h

2) H_2O_2, THF, NaH_2PO_4
0 °C - rt, 2 h

32%, 70% ee



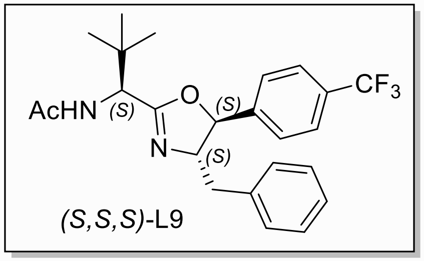
(S,R)-L4



$Pd(CH_3CN)_4(OTf)_2$ (10 mol%)
(S,S,S)-L9 (30 mol %)
B_2Pin_2, K_2HPO_4

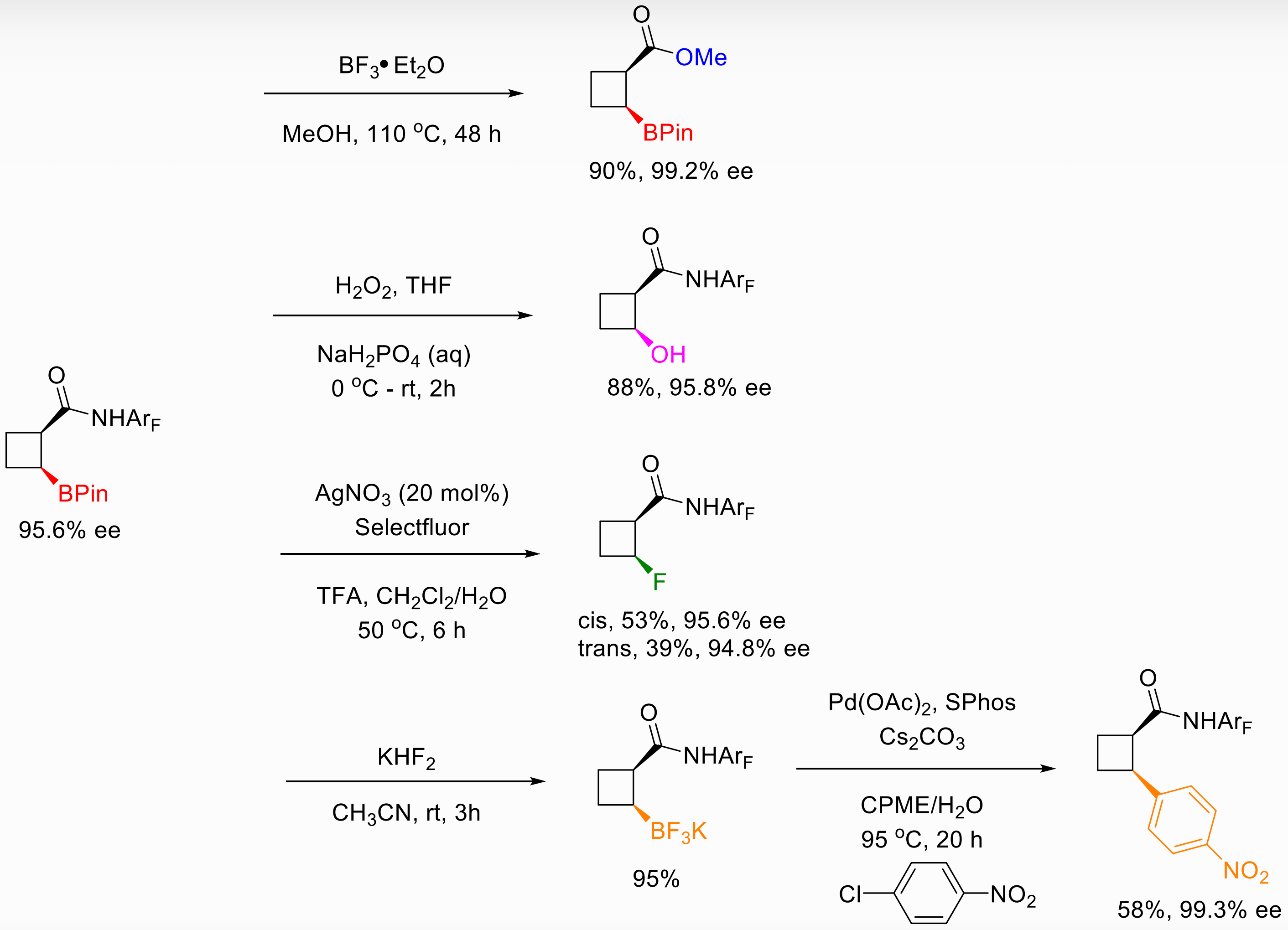
$CH_3CN/DCE/H_2O$ (16:4:1)
O_2, 80 °C, 15 h

54%, 66% ee



(S,S,S)-L9

Synthetic Applications



95.6% ee

$BF_3 \cdot Et_2O$
MeOH, 110 °C, 48 h
90%, 99.2% ee

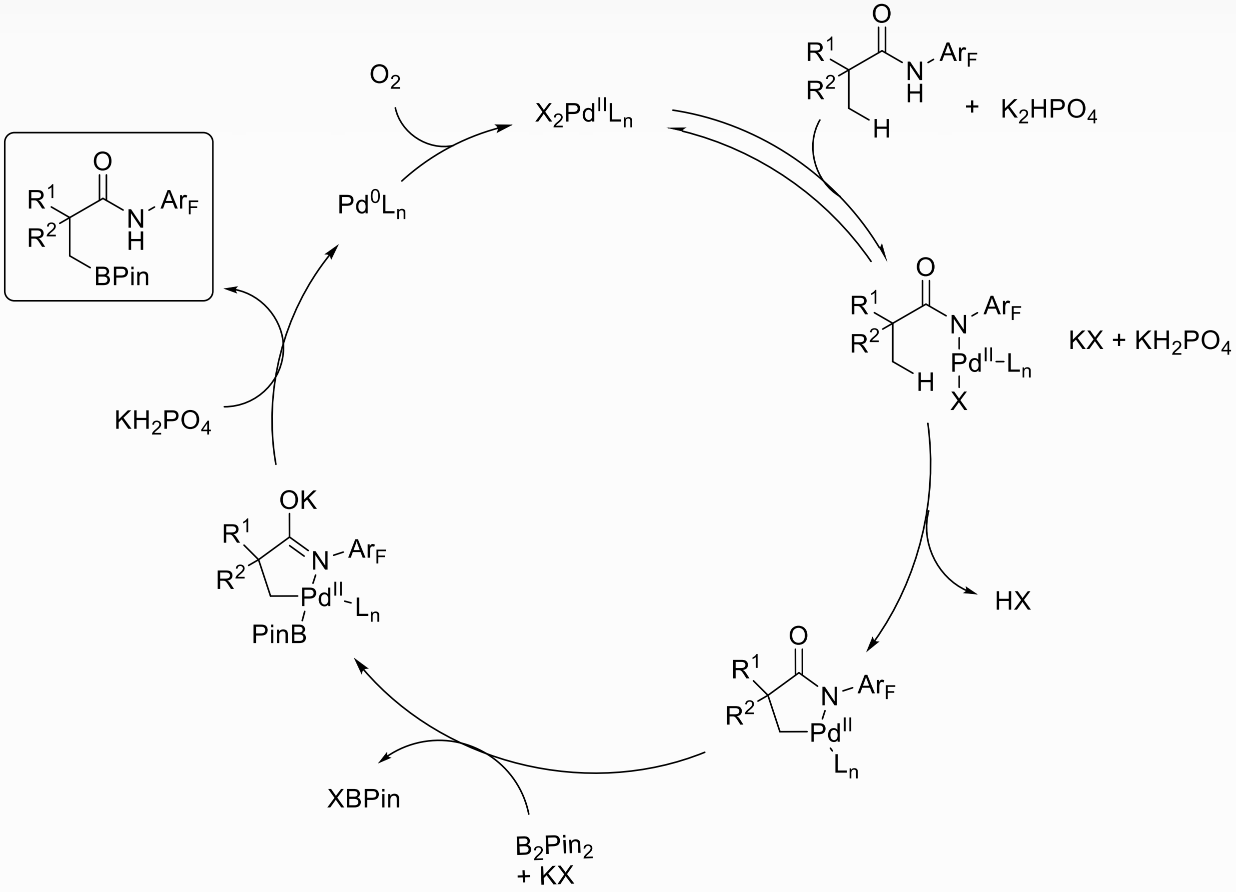
H_2O_2, THF
NaH_2PO_4 (aq)
0 °C - rt, 2h
88%, 95.8% ee

$AgNO_3$ (20 mol%)
Selectfluor
TFA, CH_2Cl_2/H_2O
50 °C, 6 h
cis, 53%, 95.6% ee
trans, 39%, 94.8% ee

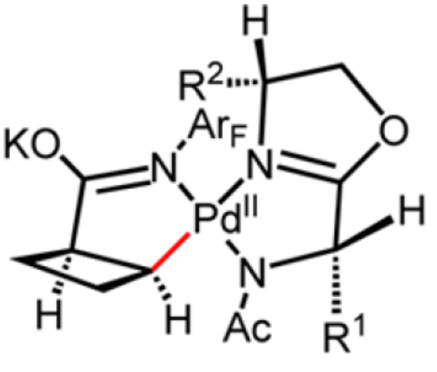
KHF_2
CH_3CN, rt, 3h
95%

$Pd(OAc)_2$, SPhos
Cs_2CO_3
CPME/H_2O
95 °C, 20 h
58%, 99.3% ee

Proposed Catalytic Cycle

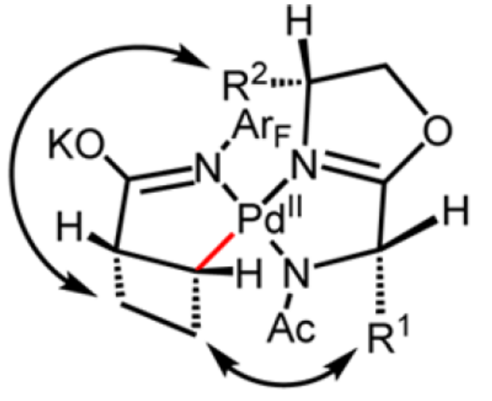


Proposed Asymmetric Induction Model



Intermediate A, favored

vs



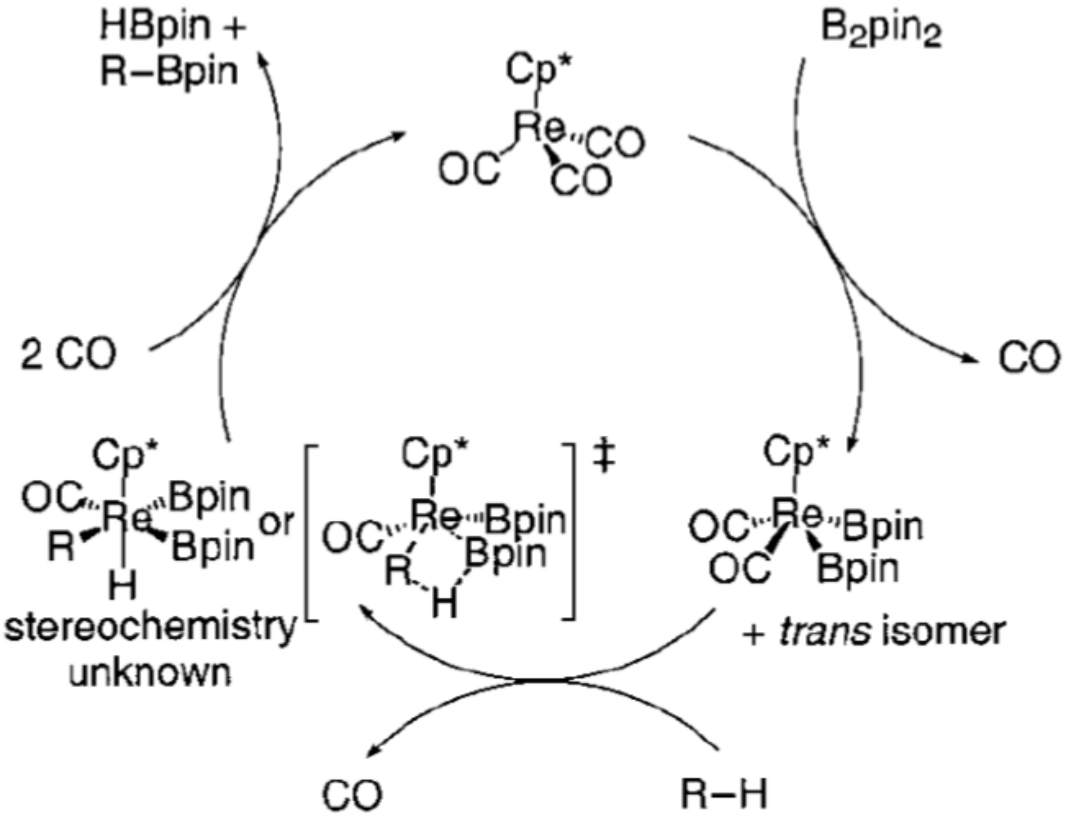
Intermediate B, disfavored

Conclusions

- First enantioselective Pd(II)-catalyzed C(sp^3)-H borylation was developed
- Chiral bidentate APAO ligand induce excellent enantioselectivity
- This method is compatible with substrates containing α-tertiary and α-quarternary carbon centers
- Borylated carbocyclics can serve as useful small building blocks to other functionalities

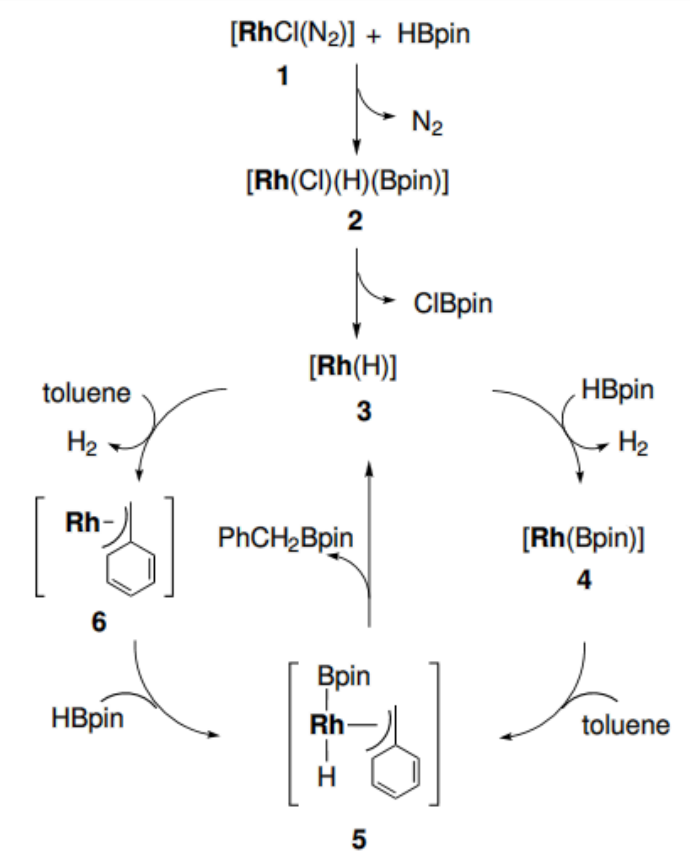
Rhenium cat. - Hartwig

Catalytic cycle

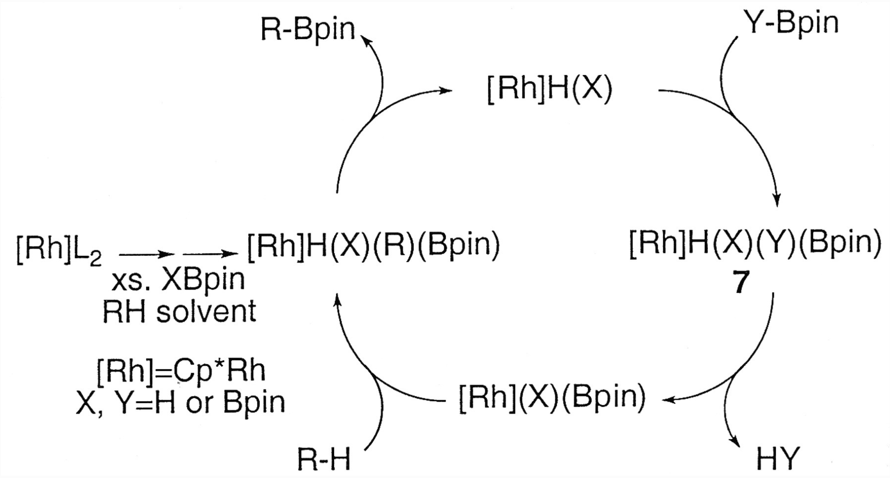


Rhodium cat. – Hartwig/Marder

Catalytic cycle Marder

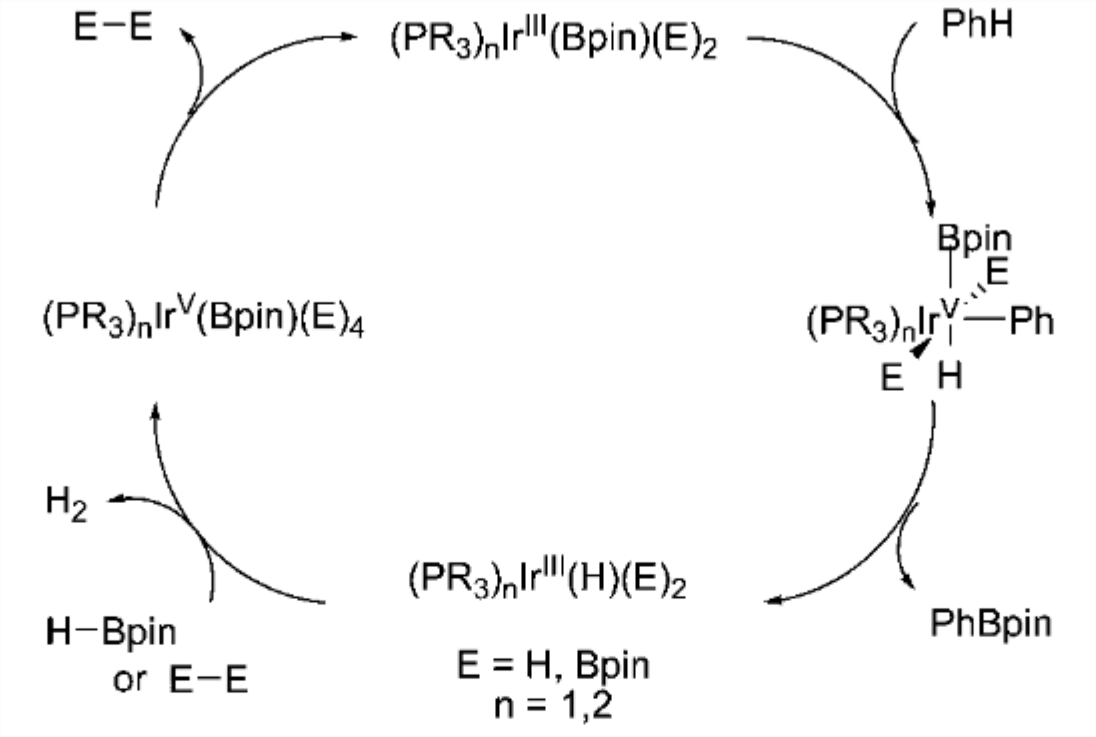


Catalytic cycle Hartwig

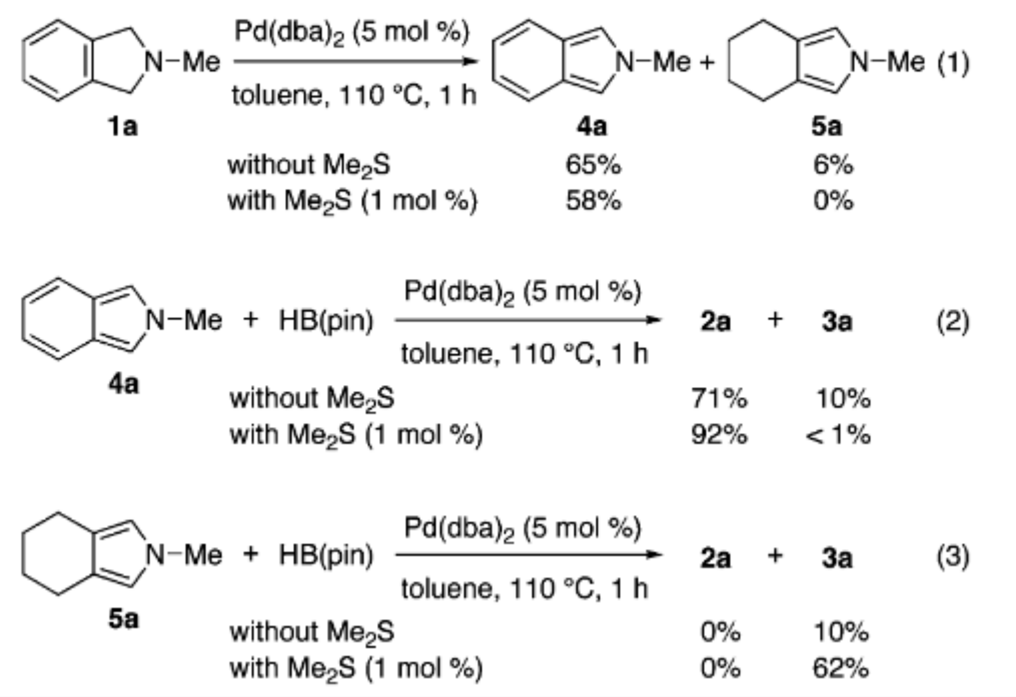


Iridium cat. – Smith

Catalytic cycle



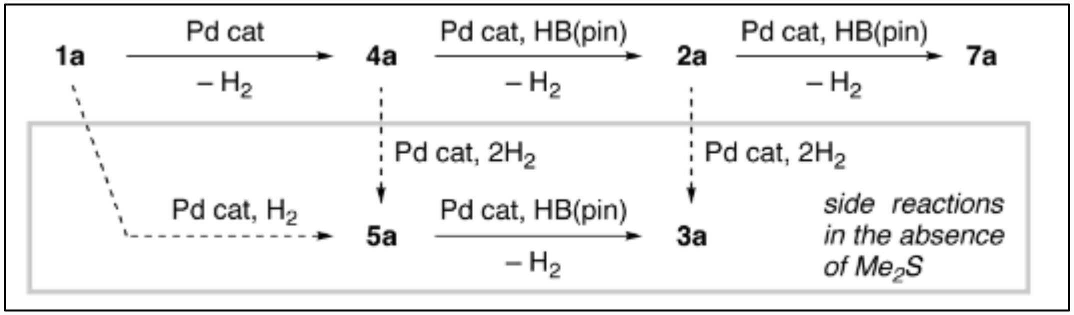
Palladium cat. - Suginome



	4a	5a
without Me_2S	65%	6%
with Me_2S (1 mol %)	58%	0%

	2a	3a
without Me_2S	71%	10%
with Me_2S (1 mol %)	92%	< 1%

	2a	3a
without Me_2S	0%	10%
with Me_2S (1 mol %)	0%	62%



$$\begin{tikzcd}
\mathbf{1a} \arrow[r, "\text{Pd cat}", "-H_2"'] \arrow[dr, dashed, "\text{Pd cat, }H_2"'] & \mathbf{4a} \arrow[r, "\text{Pd cat, HB(pin)}", "-H_2"'] \arrow[d, dashed, "\text{Pd cat, }2H_2"] & \mathbf{2a} \arrow[r, "\text{Pd cat, HB(pin)}", "-H_2"'] \arrow[d, dashed, "\text{Pd cat, }2H_2"] & \mathbf{7a} \\
 & \mathbf{5a} \arrow[r, "\text{Pd cat, HB(pin)}", "-H_2"'] & \mathbf{3a} &
\end{tikzcd}$$

side reactions in the absence of Me_2S

Palladium cat. – Ortho-borylation Yu