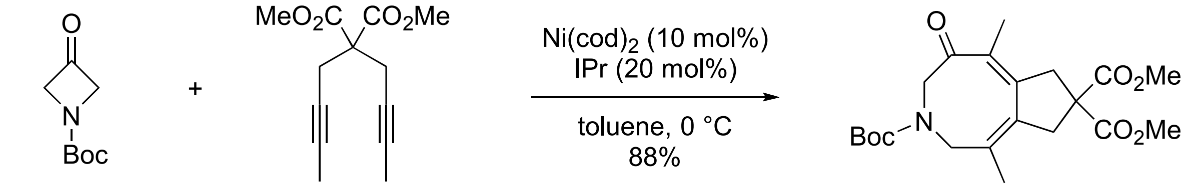
Problem Session (6)

2016.6.4 Shun Yoshioka

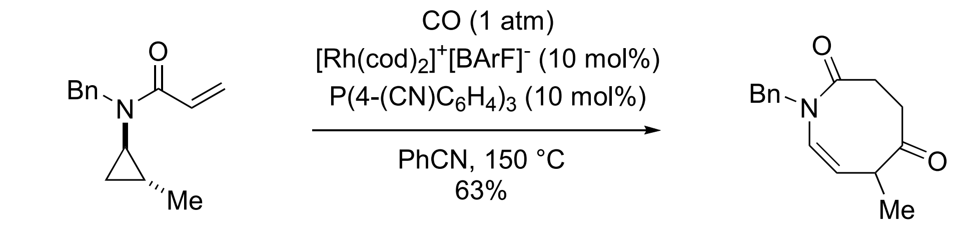
Please provide the reaction mechanisms.

(1)



1-1 **1-2** (1.2 eq.) **1-3**

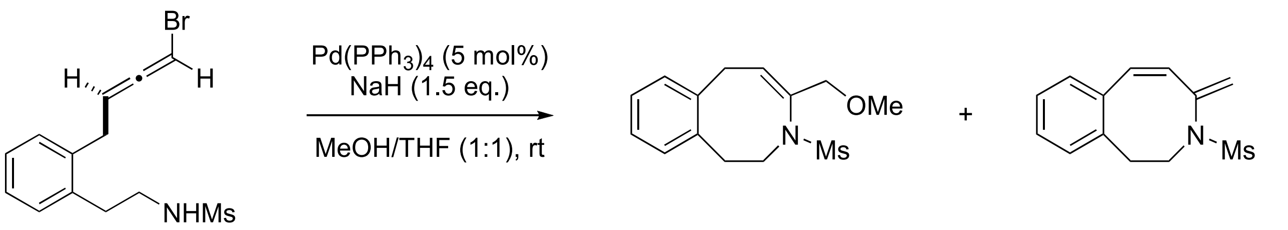
(2)



2-1
(racemic compound)

2-2

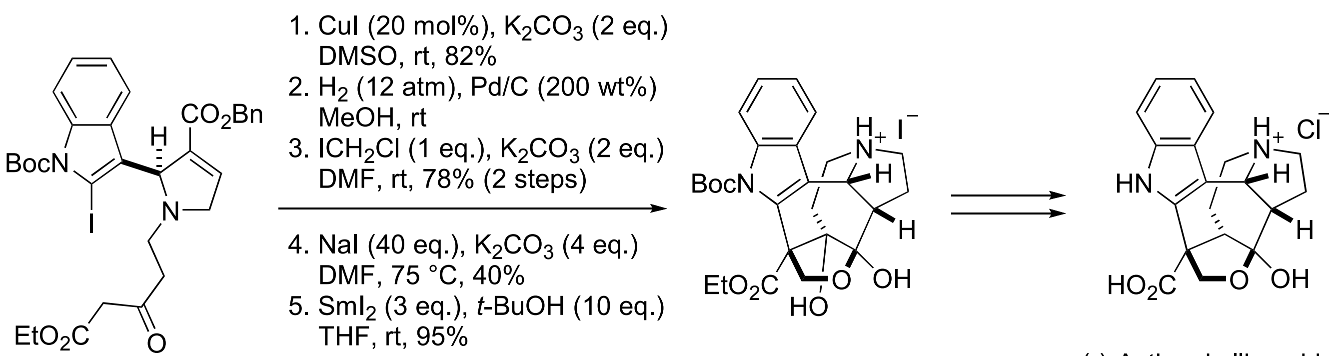
(3)



3-1
(racemic compound)

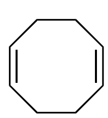
3-2 (60%) **3-3** (5%)

(4)

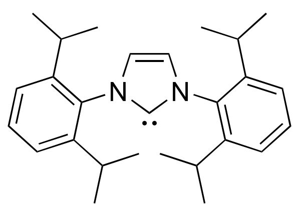


4-1 **4-2**

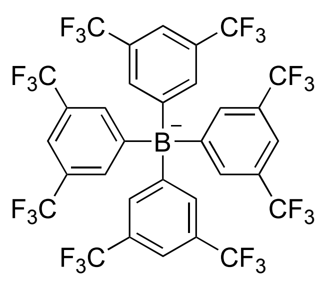
(-)-Actinophyllic acid hydrochloride (**4-3**)



cod



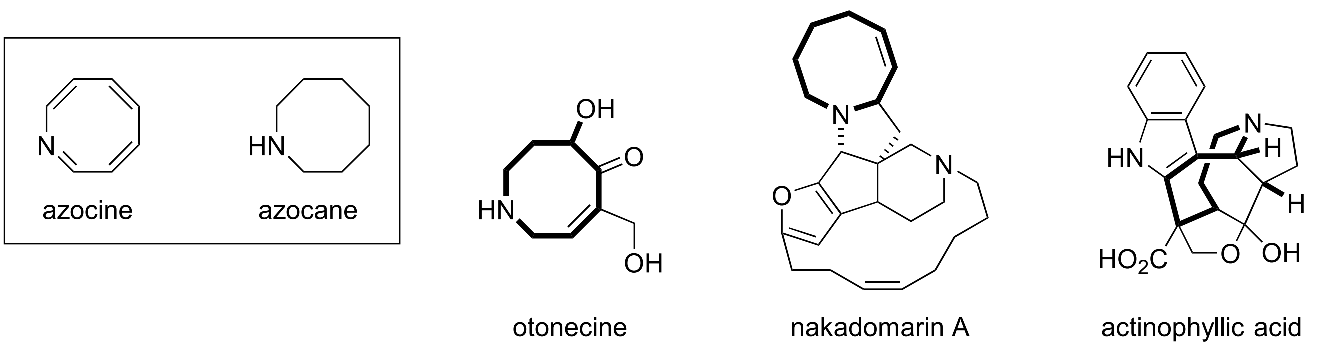
IPr



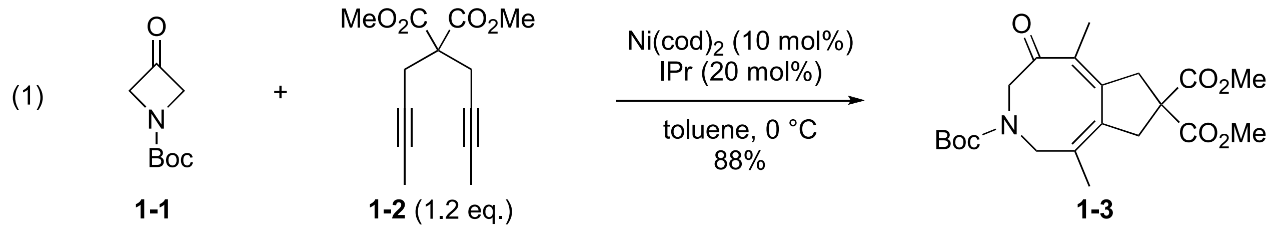
$[BArF]^-$

Problem Session (6) Answer - Azocine and Azocane -

2016.6.4 Shun Yoshioka

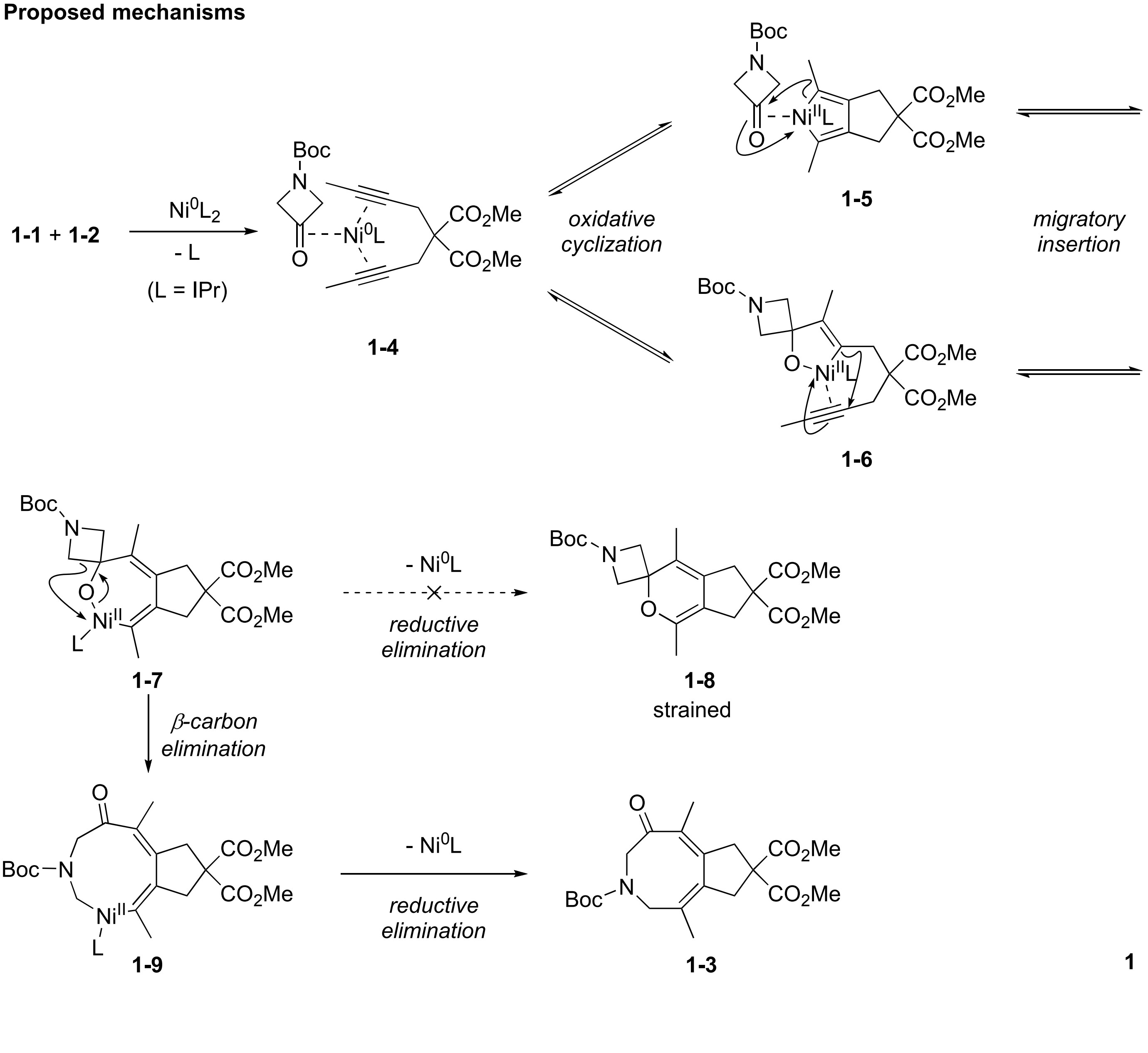


Problem 1: nickel catalyzed [4+2+2] ([4+4]) annulation



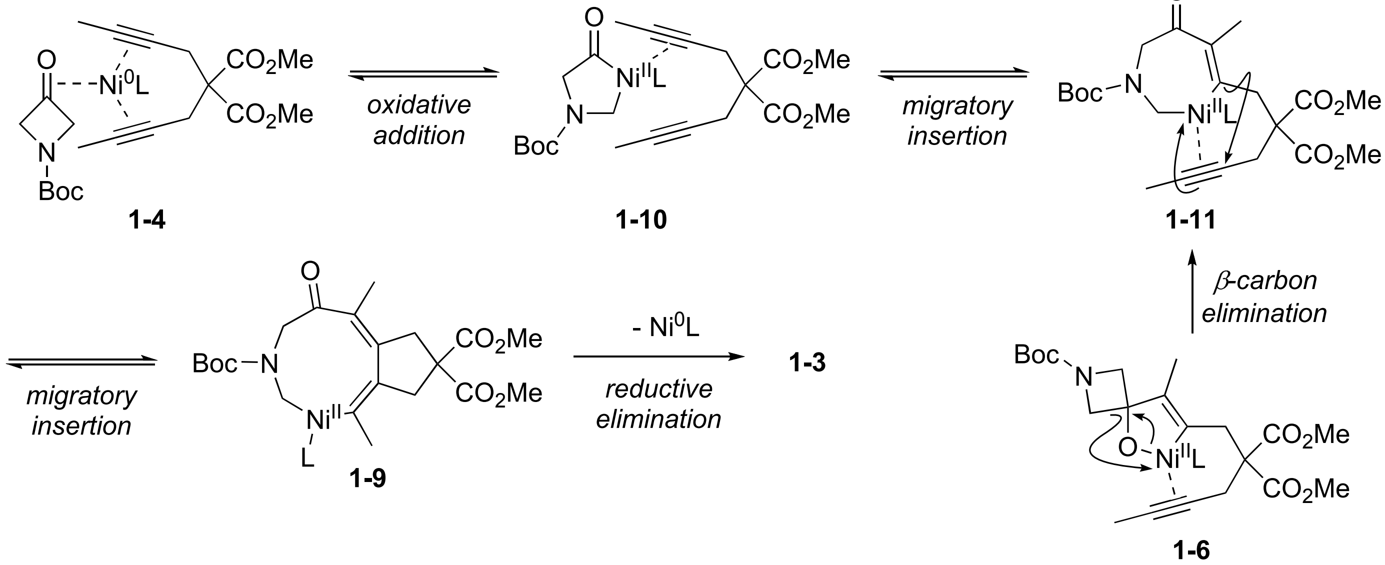
Kumar, P.;Zhang, K.; Louie, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 8602.

Proposed mechanisms

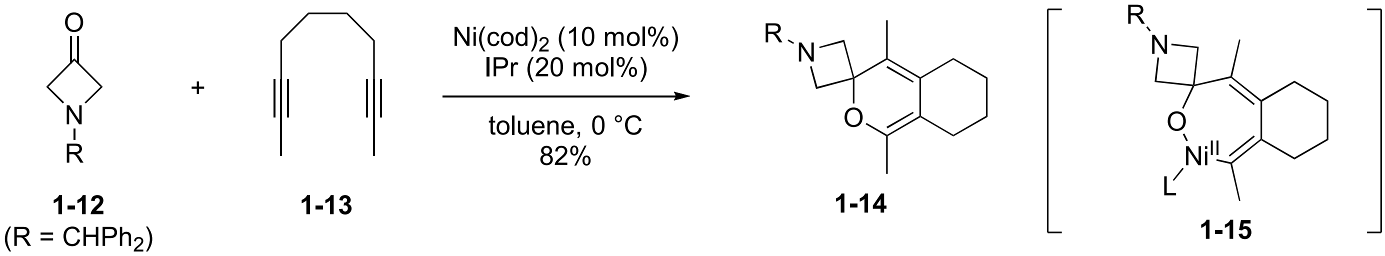


Discussion

(1) another possible pathway via nickelacycle **1-11**

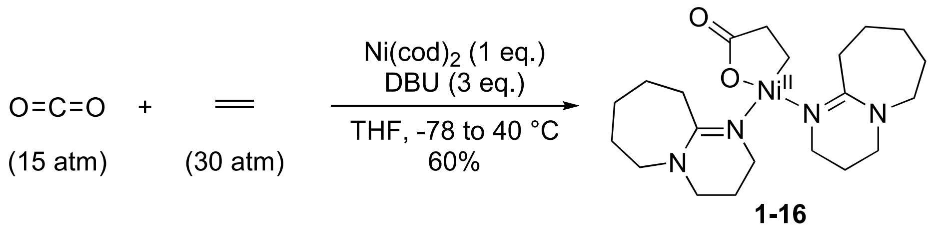


(2) spirocyclic pyran formation

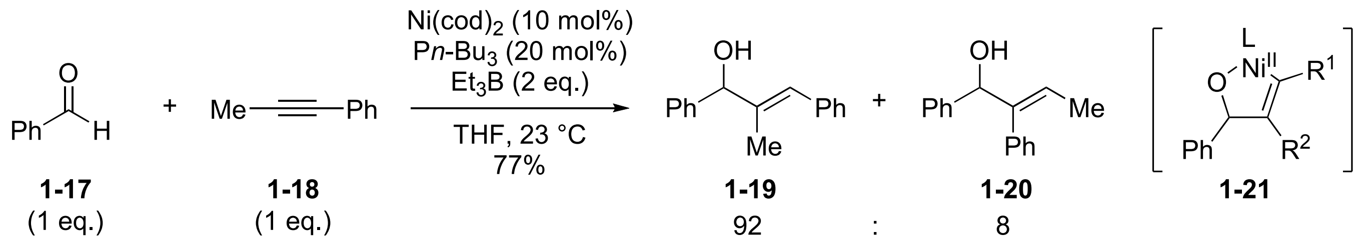


–> Intermediate **1-11** may not be passed.

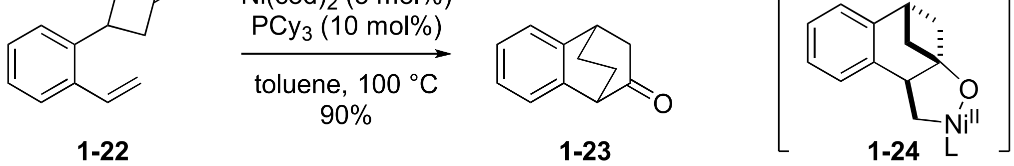
(3) nickel catalyzed coupling between carbonyl and alkyne/alkene



Hoberg, H.; Peres, Y.; Krüger, C.; Tsay, Y. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 771.



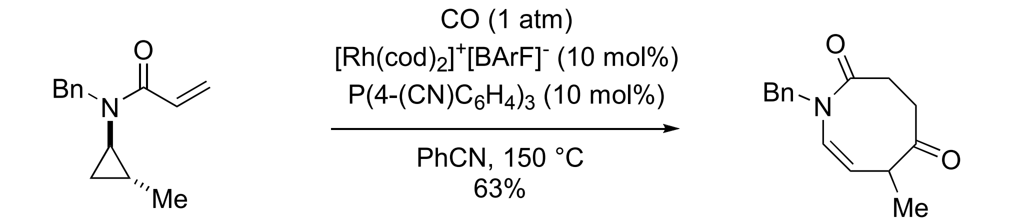
Huang, W. S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221.
McCarren, P. R.; Liu, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6654. (computational study)



Murakami, M.; Ashida, S. *Chem. Commun.* **2006**, 4599

Problem 2: rhodium catalyzed [7+1] annulation

(2)

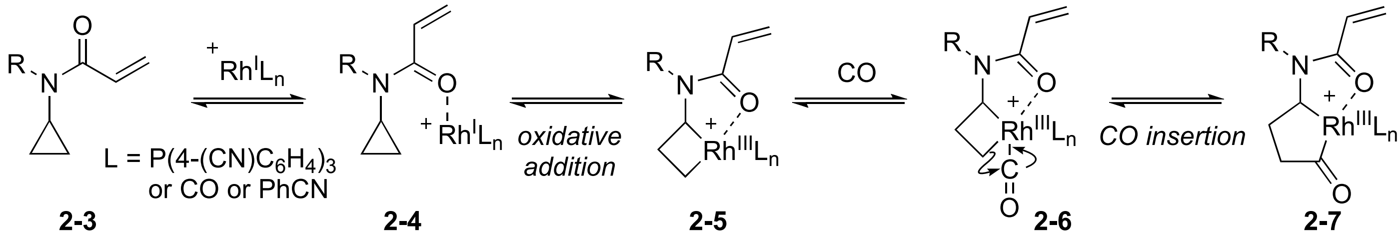


2-1 (racemic compound) → 2-2

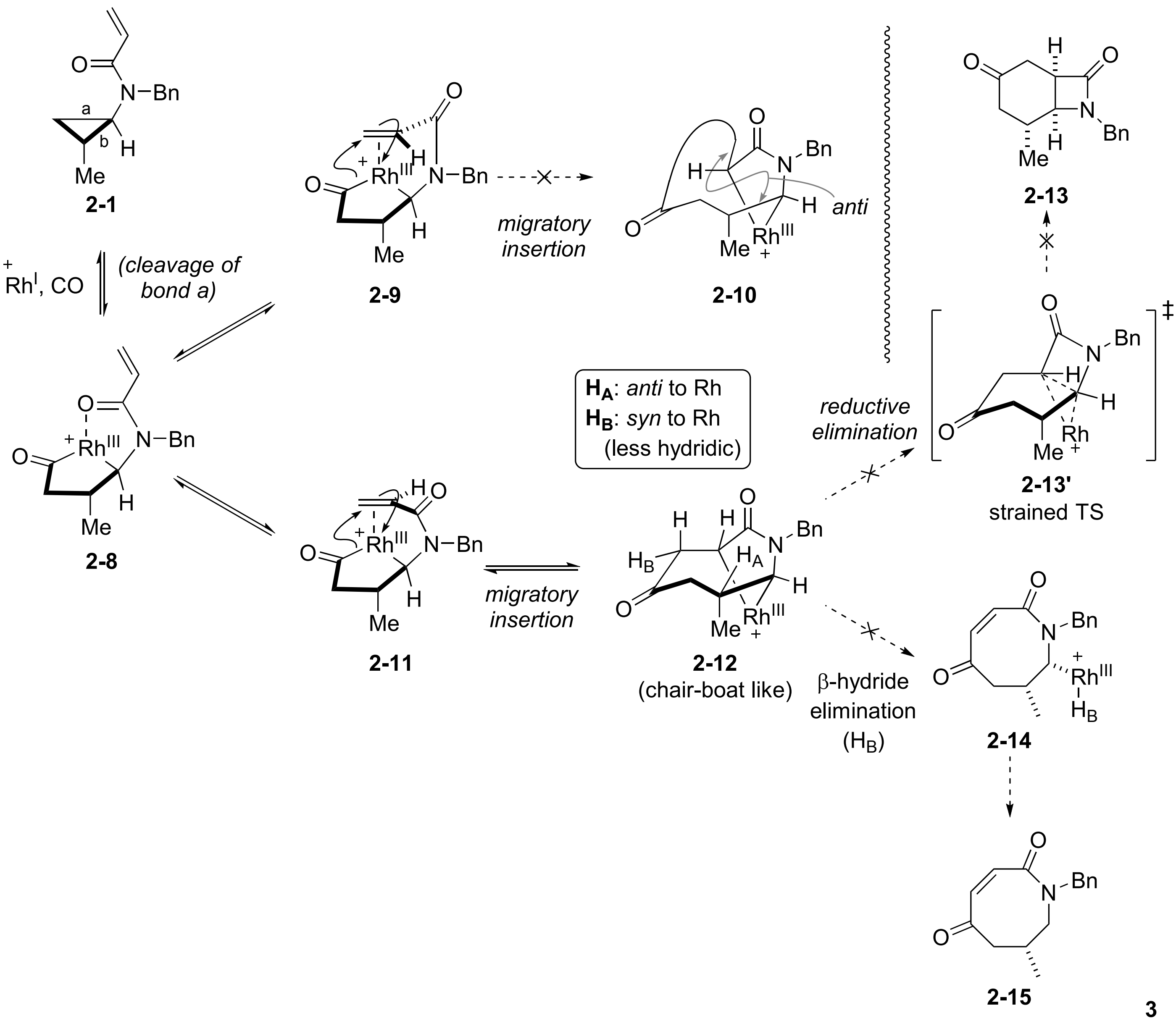
Shaw, M. H.; Croft, R. A.; Whittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 8054.

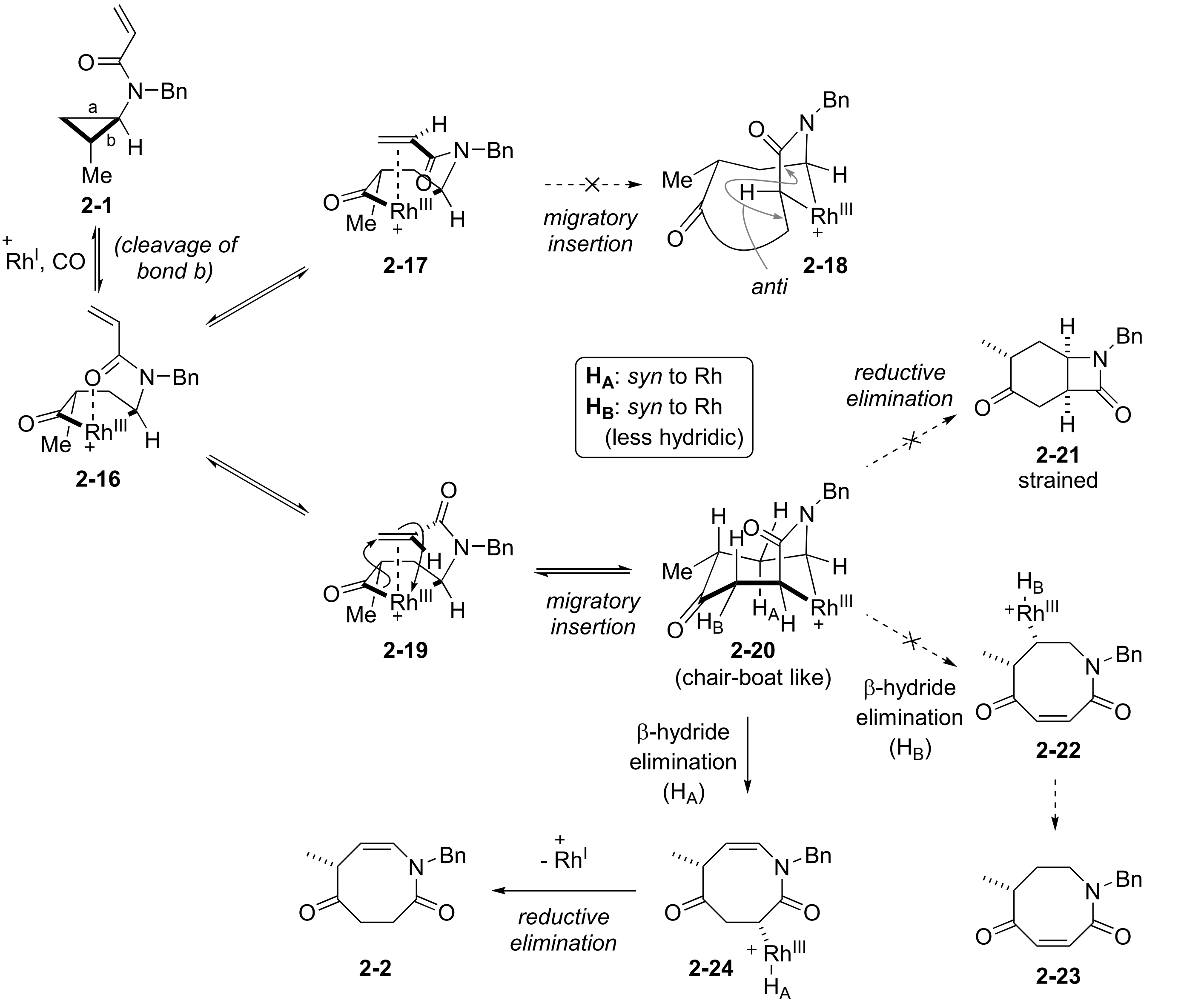
Proposed mechanisms

<general mechanism of C-C bond activation and CO insertion>



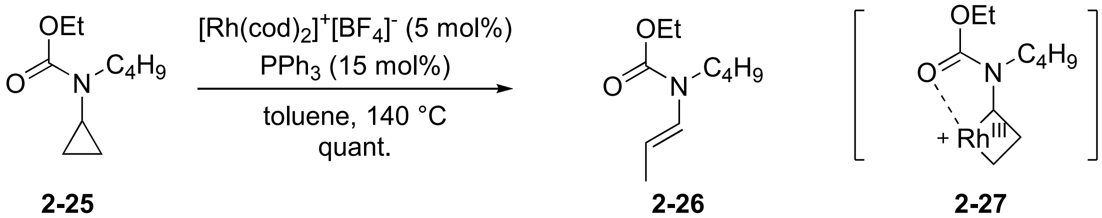
(Ligands are omitted.)

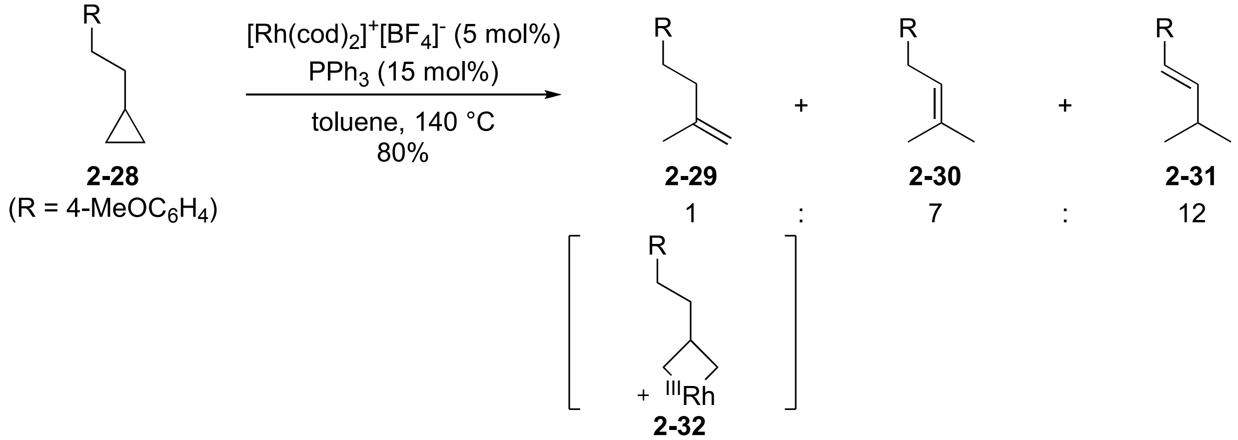




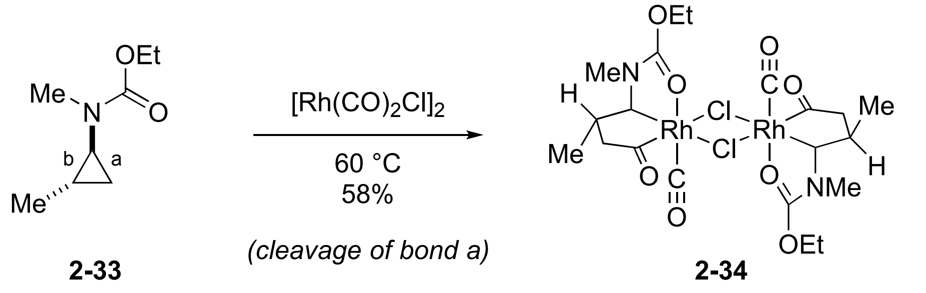
Discussion

(1) directing-group-controlled oxidative addition

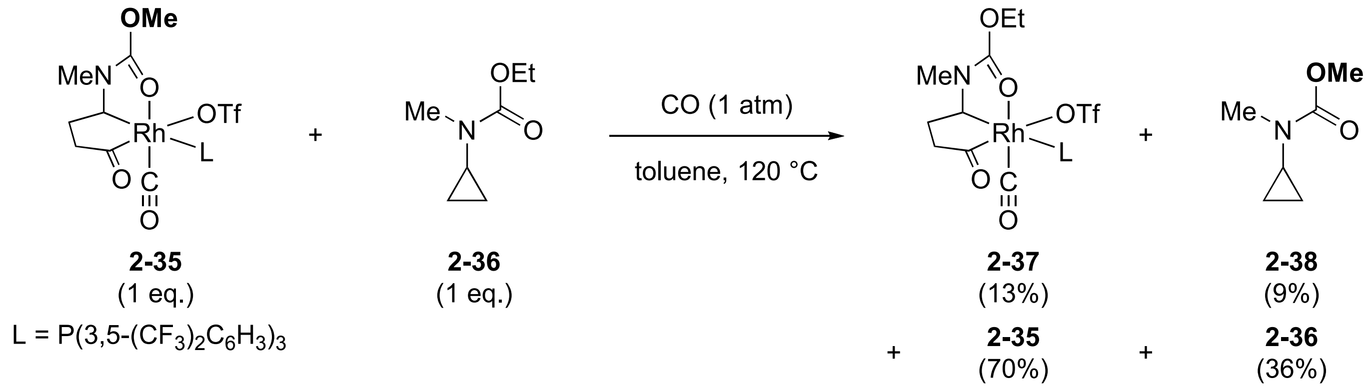




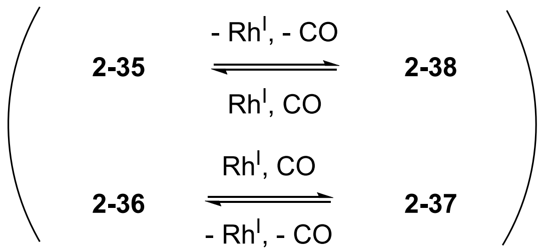
(2) regioselectivity and reversibility of rhodacyclopentanone formation



regiochemically favored complex

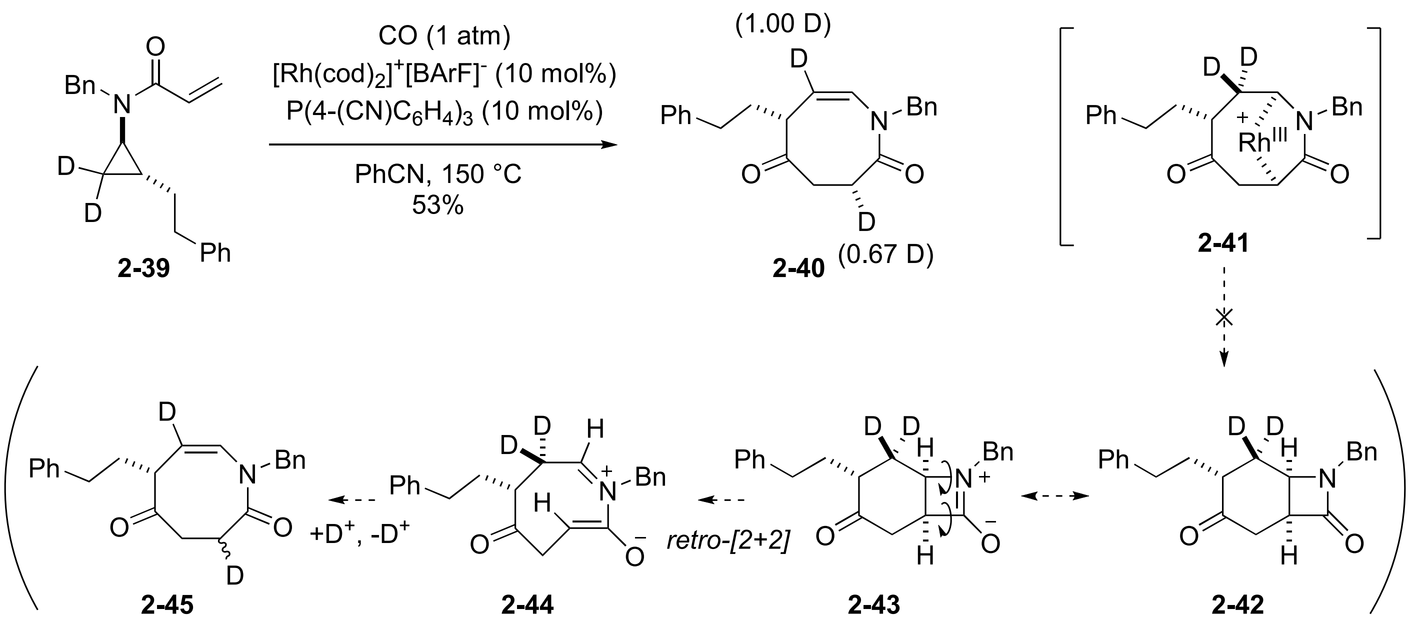


Shaw, M. H.; McCreanor, N. G.; Whittingham, W. G.; Bower, J. F. *J. Am. Chem. Sco.* **2015**, *137*, 463.

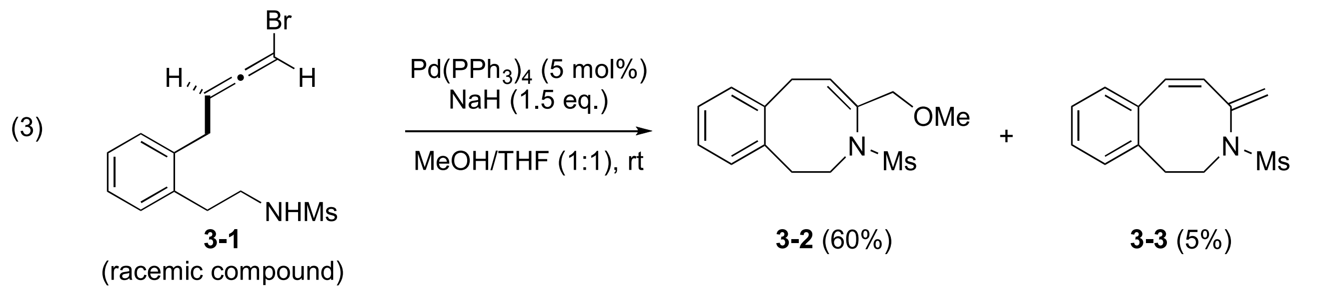


–> Rhodacyclopentanone formation is reversible.

(3) deuterium labeling study



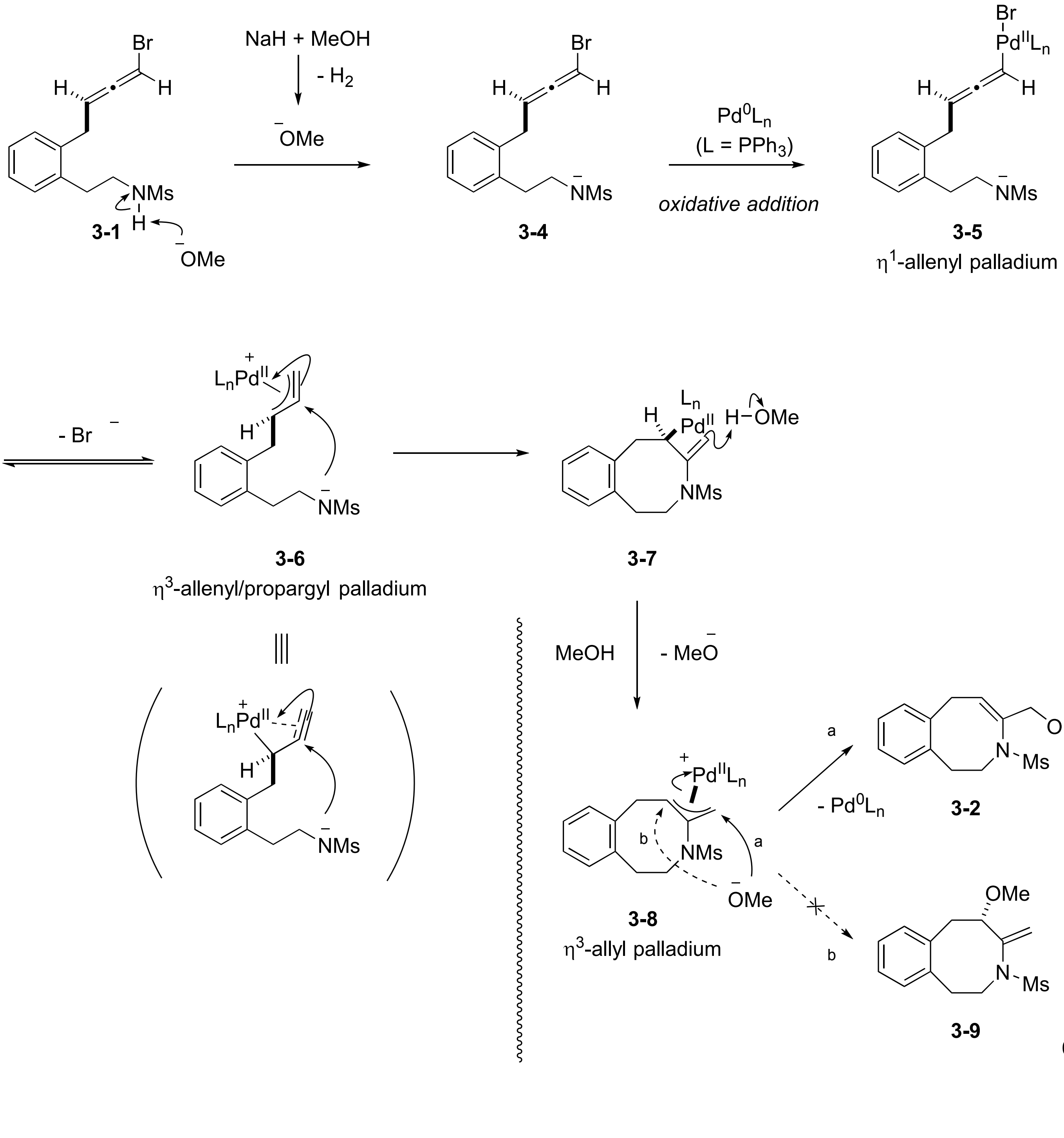
Problem 3: η3-allenyl/propargyl palladium mediated cyclization

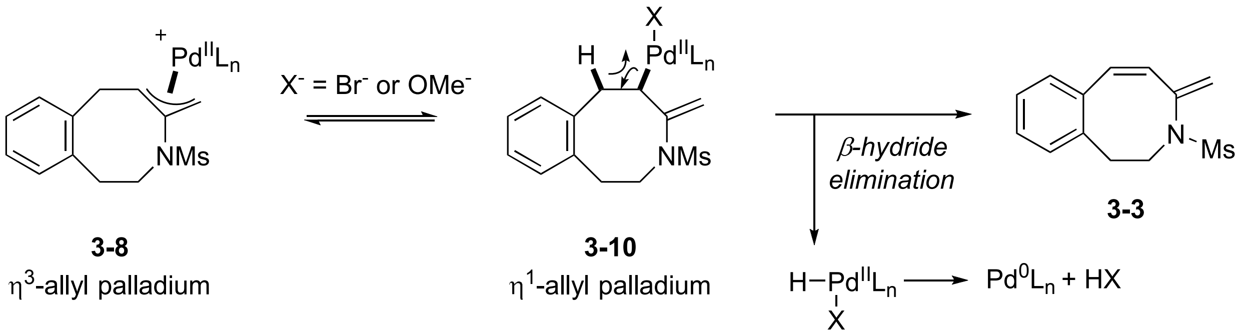


Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744.

Proposed mechanisms

	H-H	**H**−OMe	**H**−N(Me)Ts
pKa	35	16	12

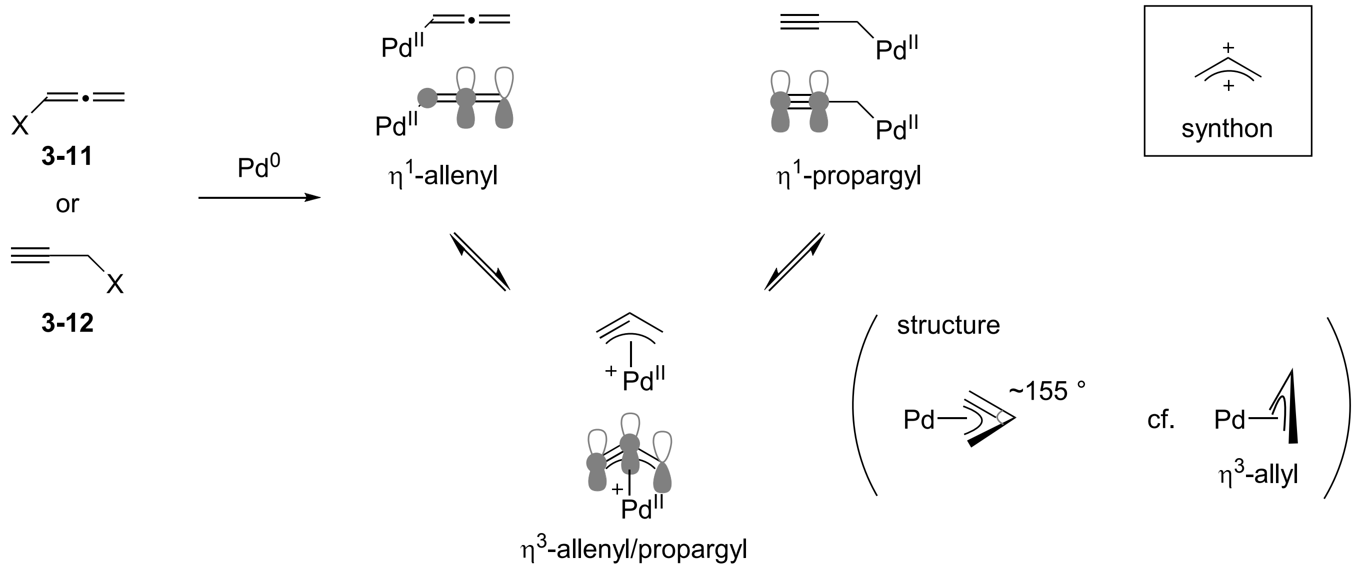




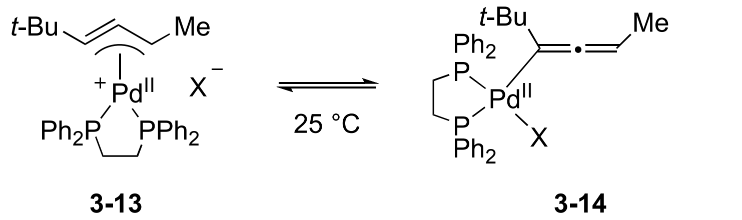
Discussion

(1) allenyl/propargyl palladium complex

(1-1) preparation and structure



(1-2) equilibrium of η^3/η^1complex

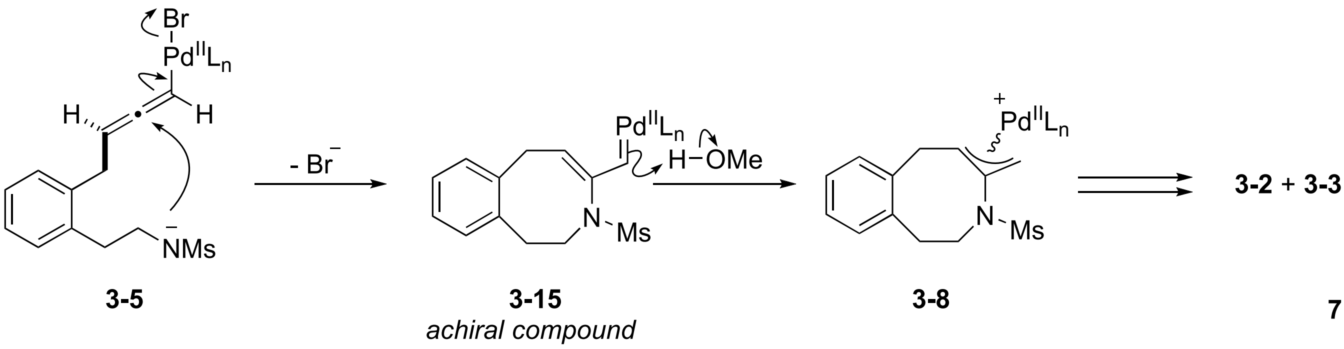


entry	X	solvent	**3-13/3-14**
1	Cl	$CDCl_3$	75/25
2	Cl	DMF-d_7	89/11
3	Cl	C_6D_6	0/100
4	Br	$CDCl_3$	68/32

Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687.

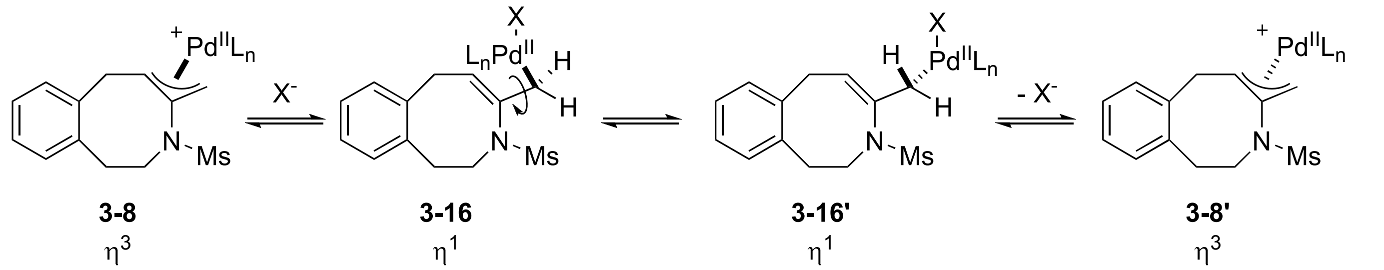
-> **3-13** tend to be generated more easily in a polar solvent.

(2) another possible pathway via palladium carbenoid **3-15**

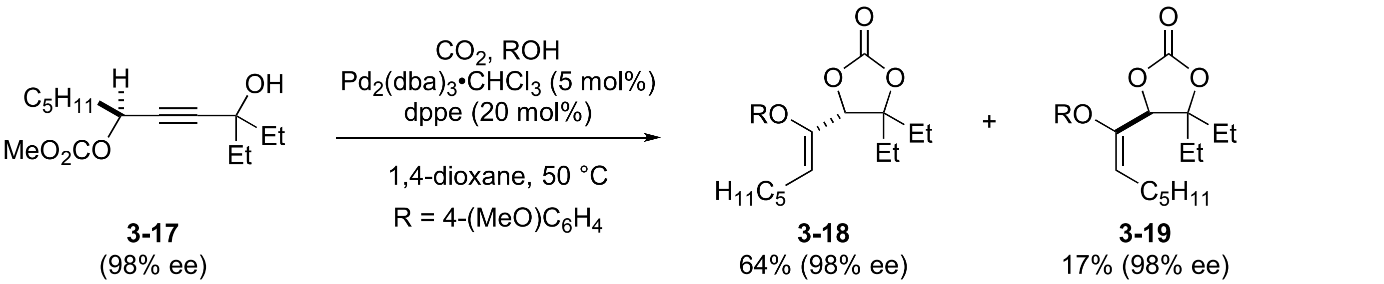


<Attention>

In this substrate, racemization can occur via η^3-η^1-η^3 rearrangement of allyl palladium.

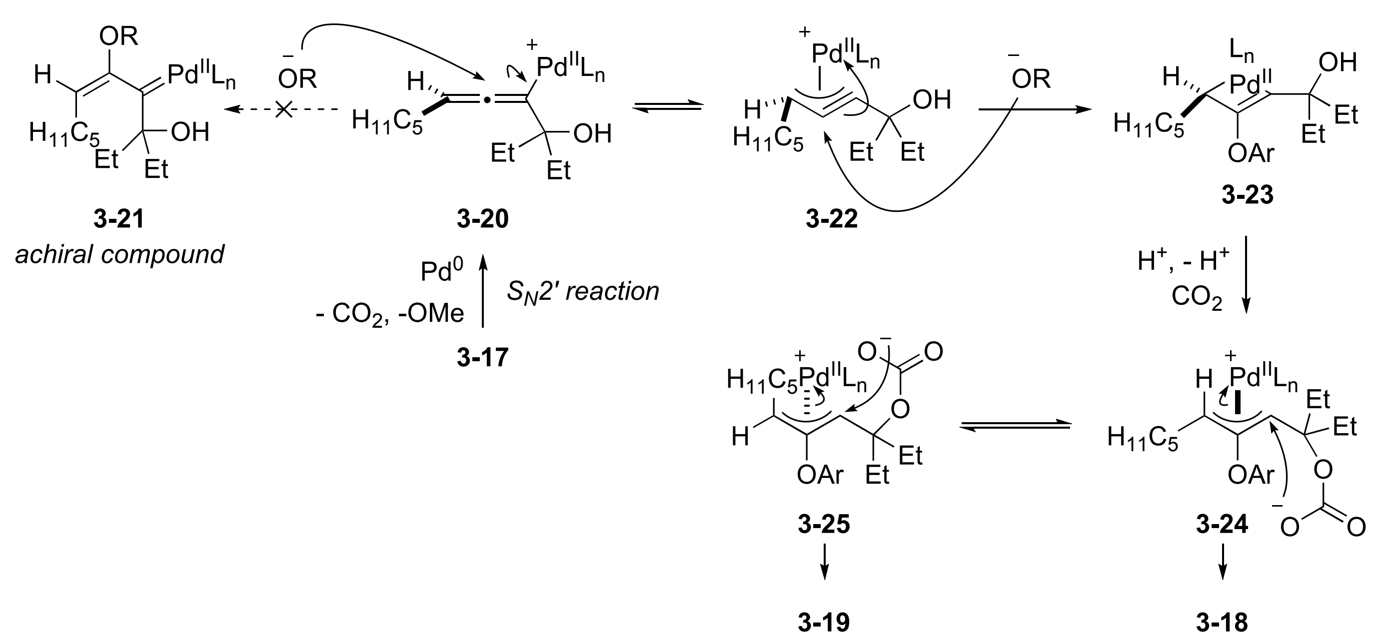


(3) example of enantio-specific reaction



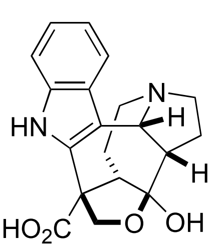
-> palladium carbenoid may not be passed.

<proposed mechanism>



Yoshida, M.; Fujita, M; Ihara, M. *Org. Lett.* **2003**, *5*, 3325.

Problem 4: total synthesis of actinophyllic acid



actinophyllic acid

Isolation: leaves of tree *Alstonia actinophylla*

Bioactivity: inhibitor of zinc-dependent carboxypeptidase U (CPU) (IC_{50}: 0.84 μM)
potent inhibitor of blood clot formation

Carroll, A. R.; Hyde, E.; Smith, J.; Quinn, R. J.; Guymer, G.; Forster, P. I. *J. Org. Chem.* **2005**, *70*, 1096.

Total synthesis:

Overman (2008)

(a) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568. (Hoshikawa, T. PS 2008/6/28)
(b) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894.

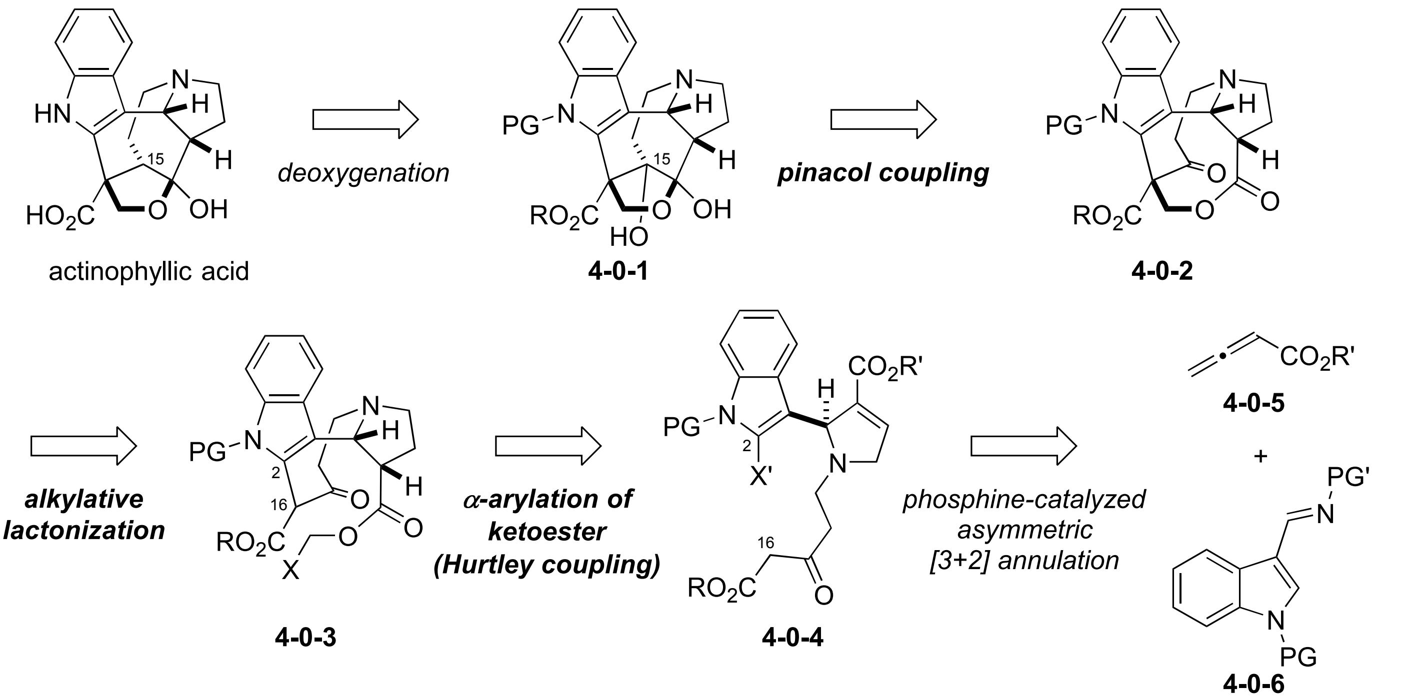
Martin (2013)

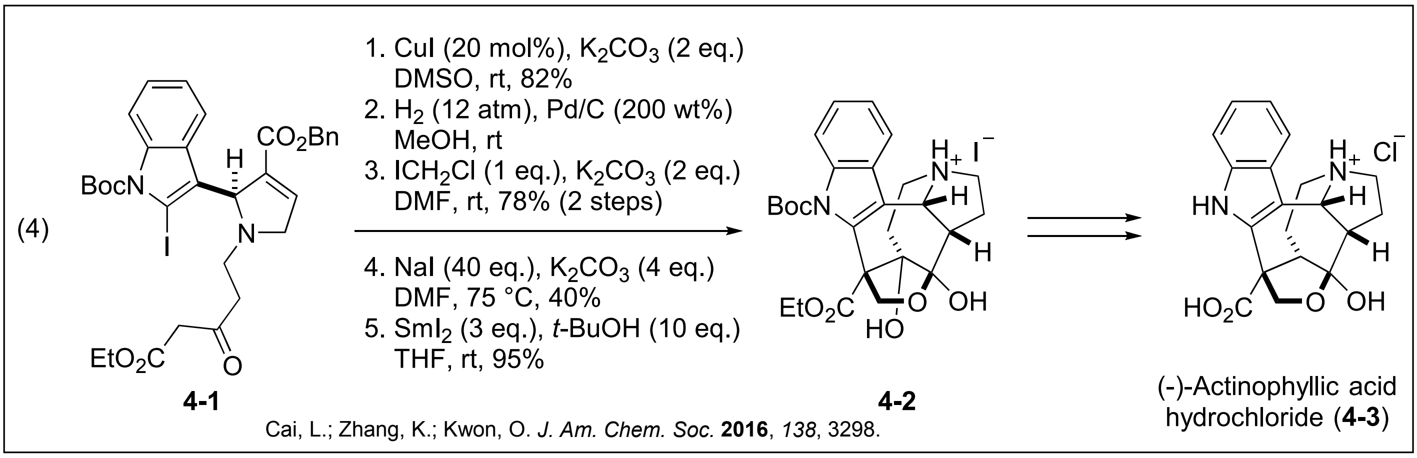
(a) Granger, B. A.; Jewett, I. T.; Butler, J. D.; Hua, B.; Knezevic, C. E.; Parkinson, E.; I.; Hergenrother, P. J.; Martin, S. F. *J. Am. Chem. Soc.* **2013**, *135*, 12984.
(b) Grangerm B. A.; Jewett, I. T.; Butler, J. D.; Martin, S. F. *J. Am. Chem. Soc.Tetrahedron* **2014**, *70*, 4049.

Kwon (2016)

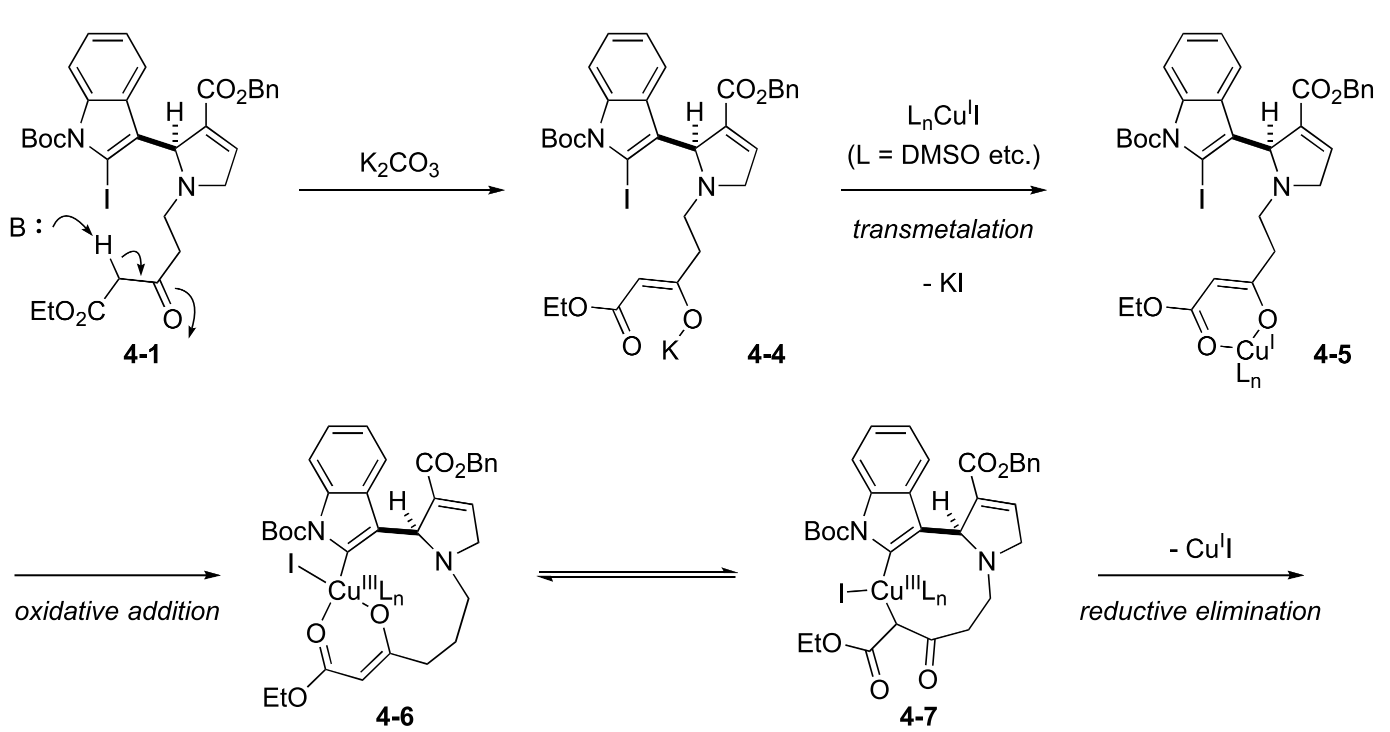
Cai, L.; Zhang, K.; Kwon, O. *J. Am. Chem. Soc.* **2016**, *138*, 3298.

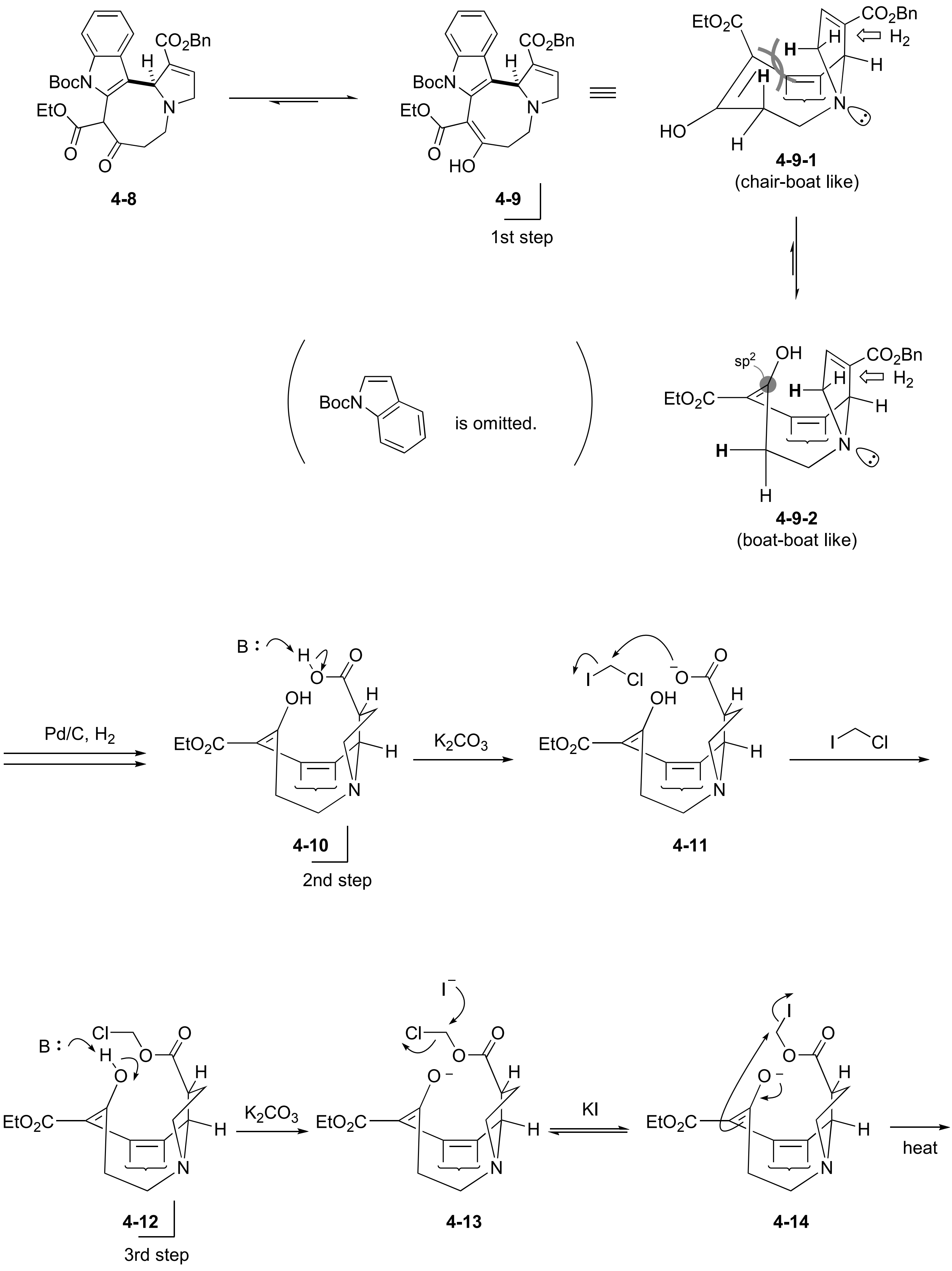
Retrosynthesis

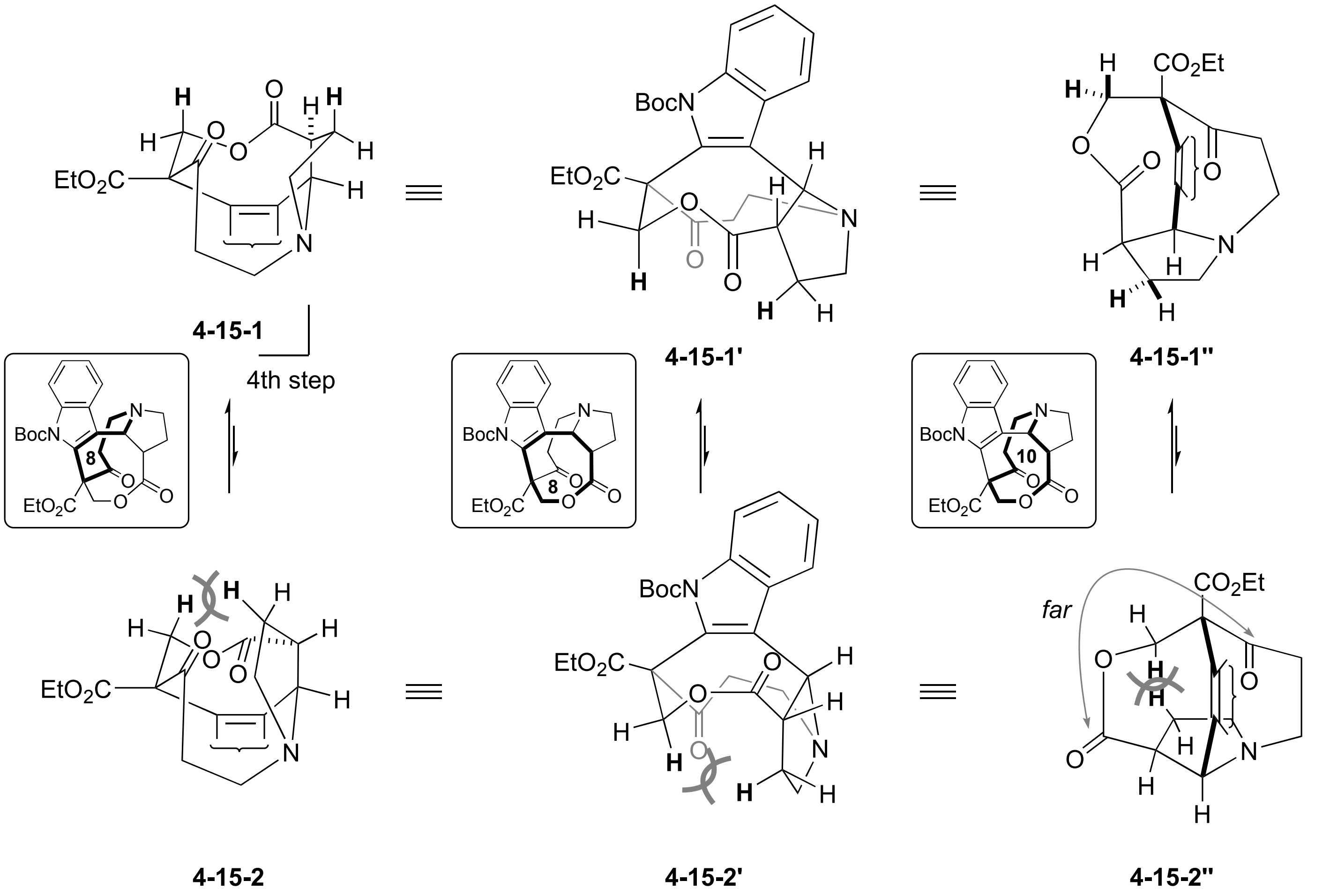




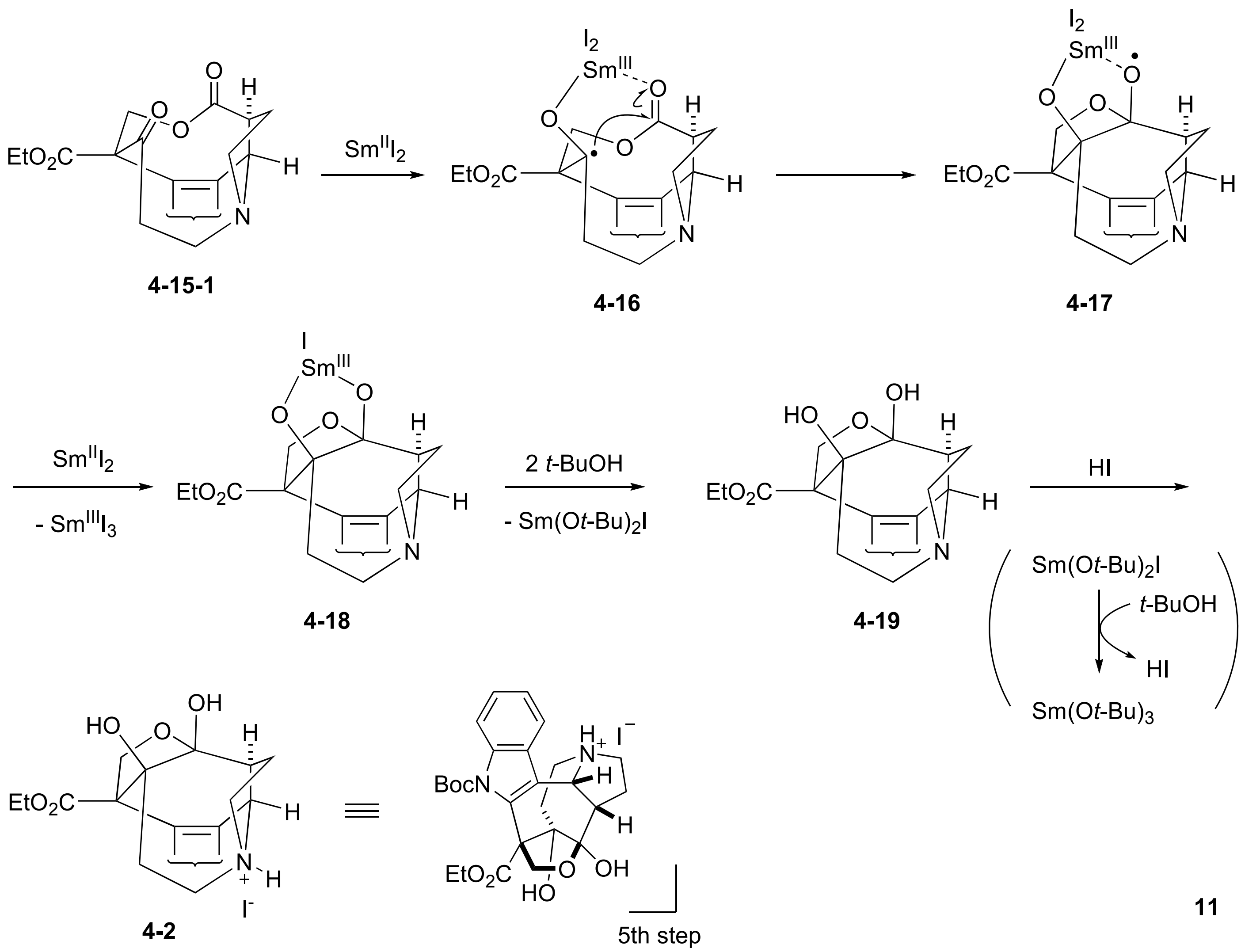
Proposed mechanisms




4-8
4-9
1st step
4-9-1
(chair-boat like)
4-9-2
(boat-boat like)
sp2
H2
BocN
is omitted.
Pd/C, H2
4-10
2nd step
K2CO3
4-11
4-12
3rd step
K2CO3
4-13
KI
4-14
heat



4-15-1
4th step
4-15-1'
4-15-1''
BocN
EtO2C
CO2Et
8
10
far
4-15-2
4-15-2'
4-15-2''



4-15-1
SmIII2
4-16
4-17
SmIII2
- SmIIII3
4-18
2 t-BuOH
- Sm(Ot-Bu)2I
4-19
HI
Sm(Ot-Bu)2I
t-BuOH
HI
Sm(Ot-Bu)3
4-2
5th step