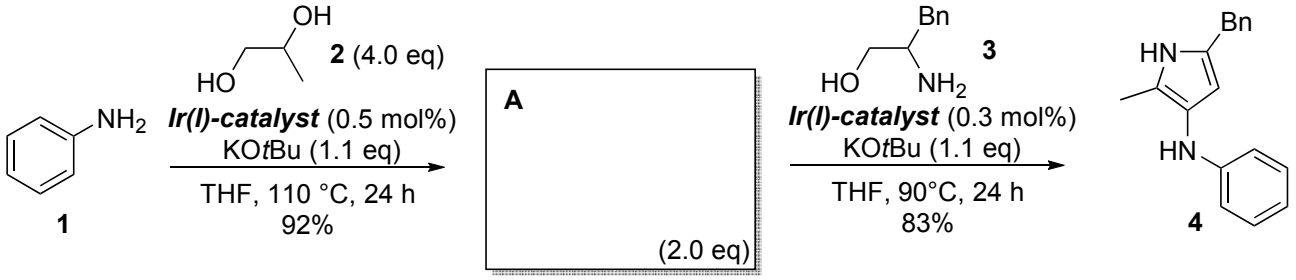
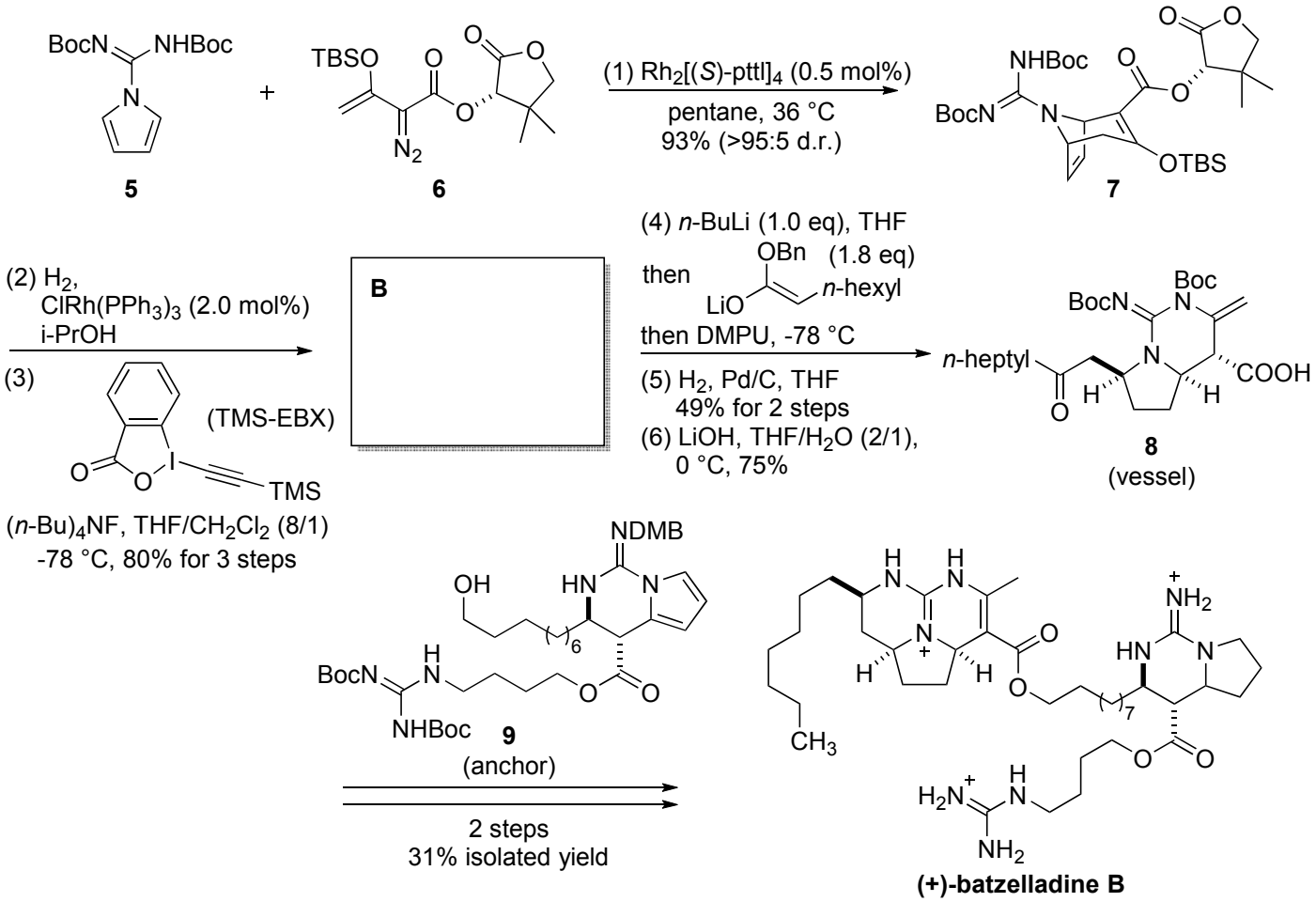
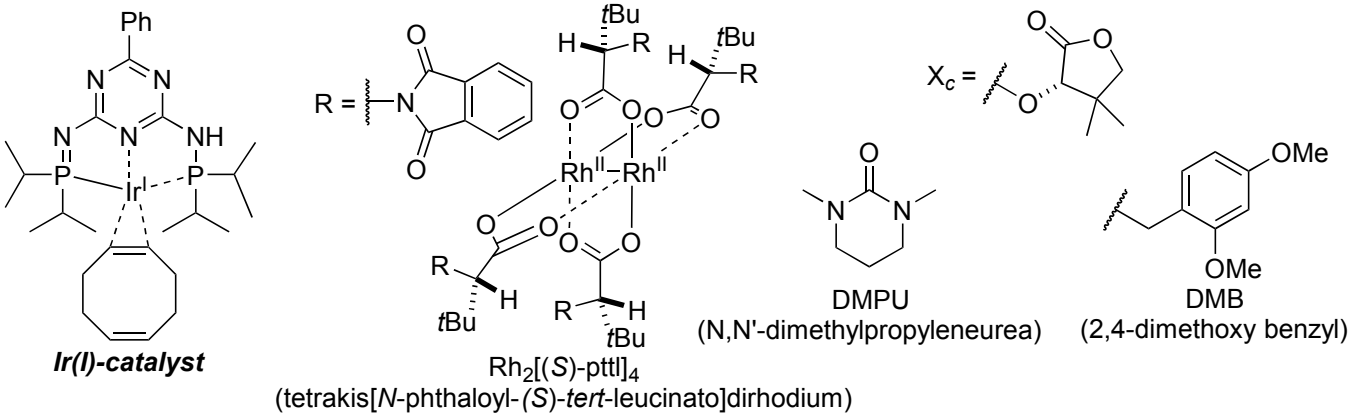
Problem Session No.1 30th/Jan/2016 Kai Kitamura

1. Please fill in the blank **A** and provide plausible reaction mechanisms.



2. Please fill in the blank **B**, provide plausible mechanisms of reactions, (1) to (6), and explain their stereoselectivity.



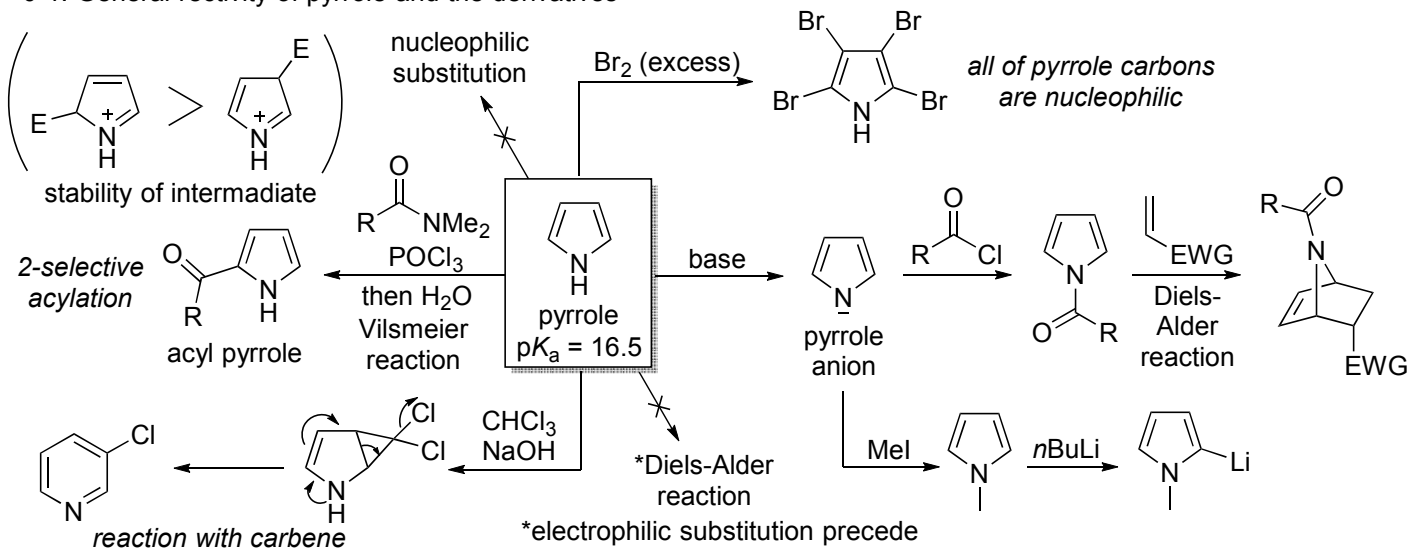


Problem Session No.1 -Answer- 5th/Feb/2016 Kai Kitamura

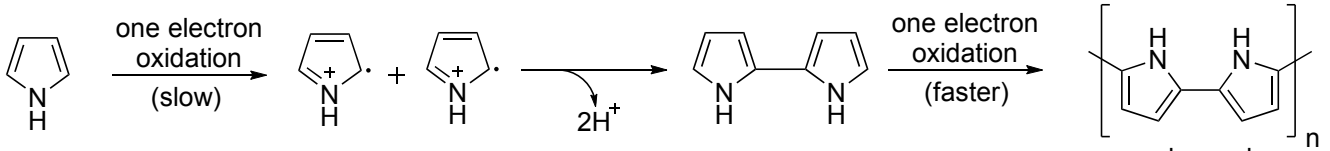
Recent remarkable chemistry related to pyrrole

0. Introduction

0-1. General rectivity of pyrrole and the derivatives



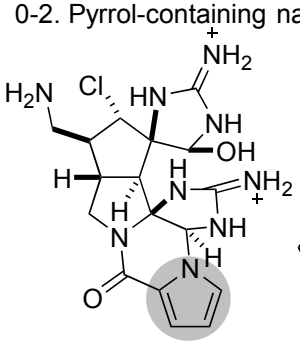
Reference: *Warren's organic chemistry (chapter 43)*



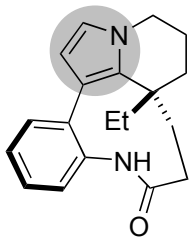
polypyrrole
(conducting polymer)

Reference: Choudhary, M. *et al. Dalton Trans.* **2014**, 43, 6396-405.

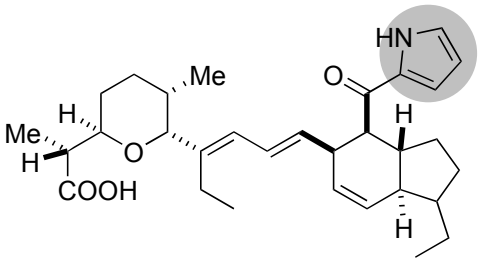
0-2. Pyrrol-containing natural products (Young, I. S. *et al. Nat. Prod. Rep.* **2010**, *27*, 1801-39.)



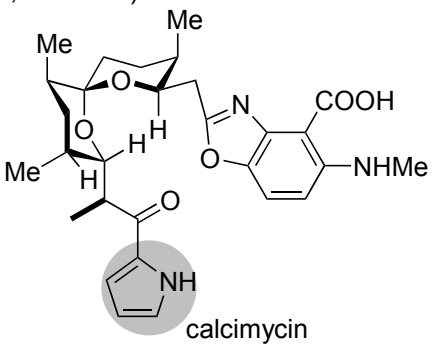
palau'amine



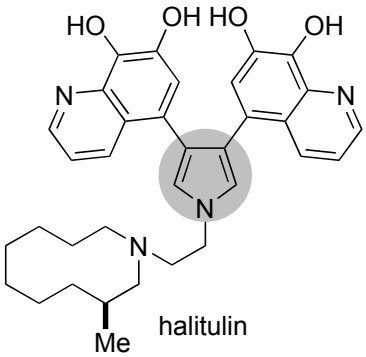
rhazinilam



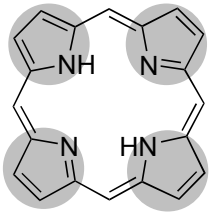
indanomycin



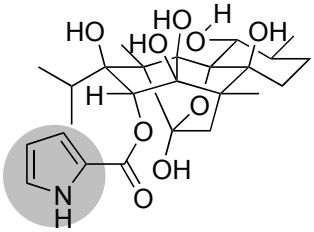
calcimycin
(A-23187)



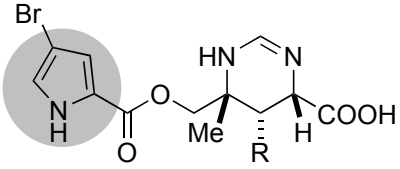
halitulin



porphyrin
(heme, chlorophyll, cyanocobalamin)

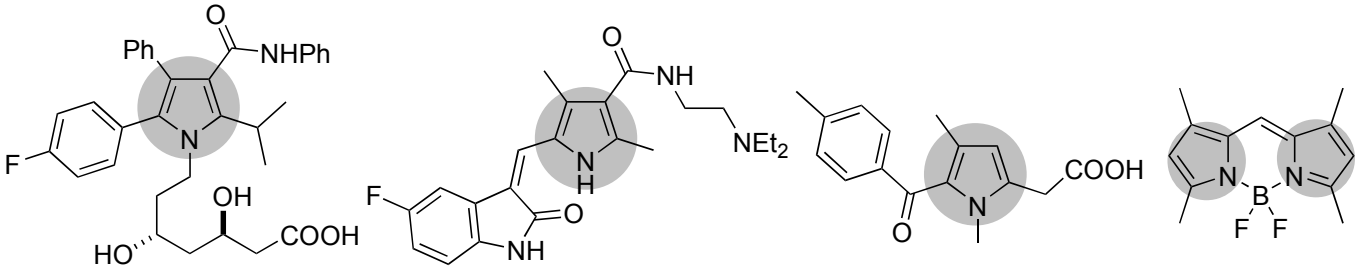


ryanodine



R = H; manzacidin A
R = OH; manzacidin B

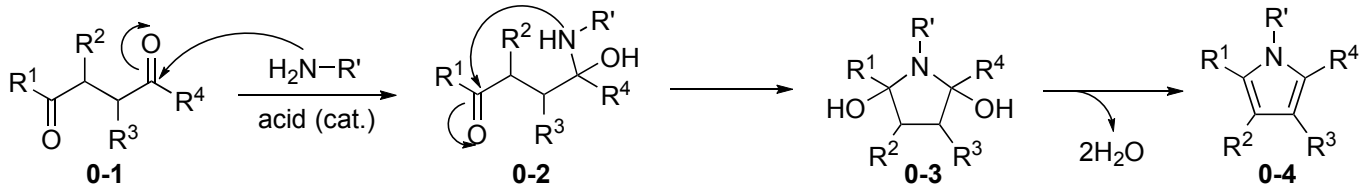
0-3. Pyrrole-containing drugs and functional molecules (Estévez, V. *et al. Chem. Soc. Rev.* **2014**, *43*, 4633-57.)



atorvastatin (HMG-CoA reductase inhibitor) | sunitinib (RTK inhibitor) | tolmetin (NSAIDs) | BODIPYs (fluorophore)

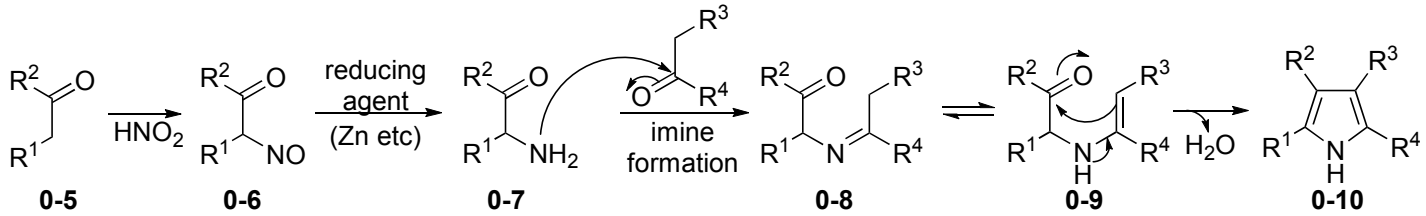
0-4. Conventional methods for pyrrole derivative synthesis

0-4-1. Paal-Knorr pyrrole synthesis (Named reactions no. 164)



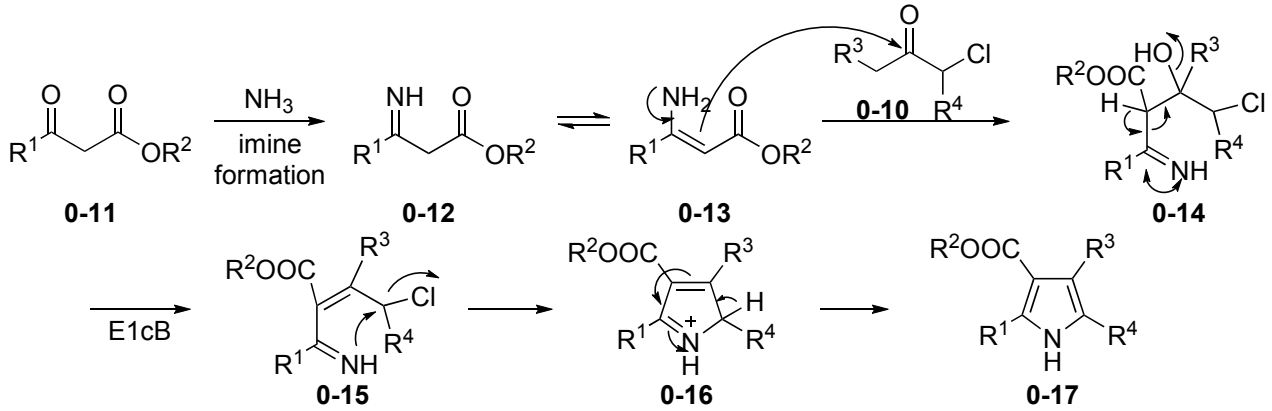
0-1 **0-2** **0-3** **0-4**

0-4-2. Knorr pyrrole synthesis (Named reactions no. 122)



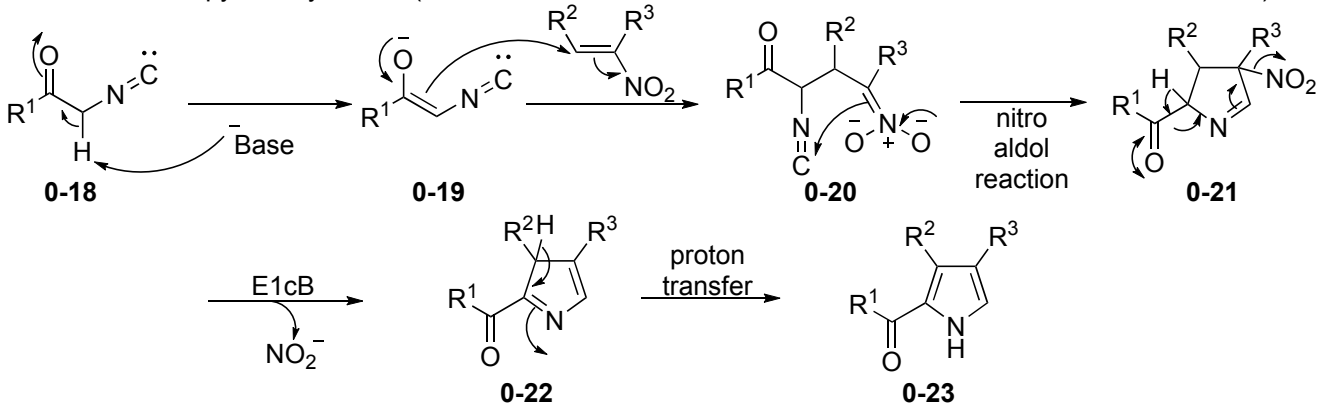
0-5 **0-6** **0-7** **0-8** **0-9** **0-10**

0-4-3. Hantzsch pyrrole synthesis (Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474-6)



0-11 **0-12** **0-13** **0-14** **0-15** **0-16** **0-17**

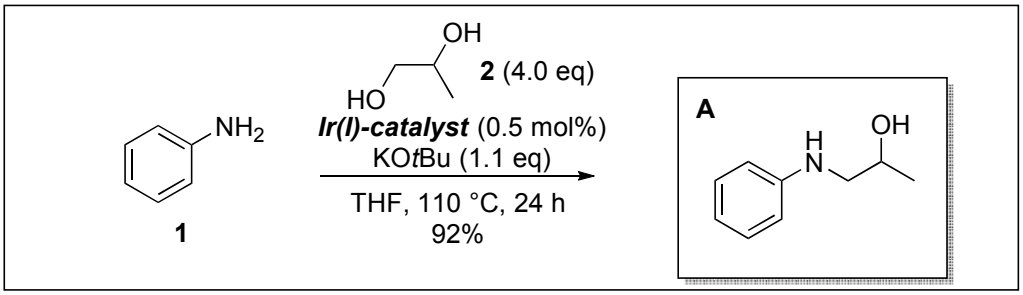
0-4-4. Barton-Zard pyrrole synthesis (Barton, D. H. R. *et al. J. Chem. Soc., Chem. Commun.* **1985**, 1098-100)

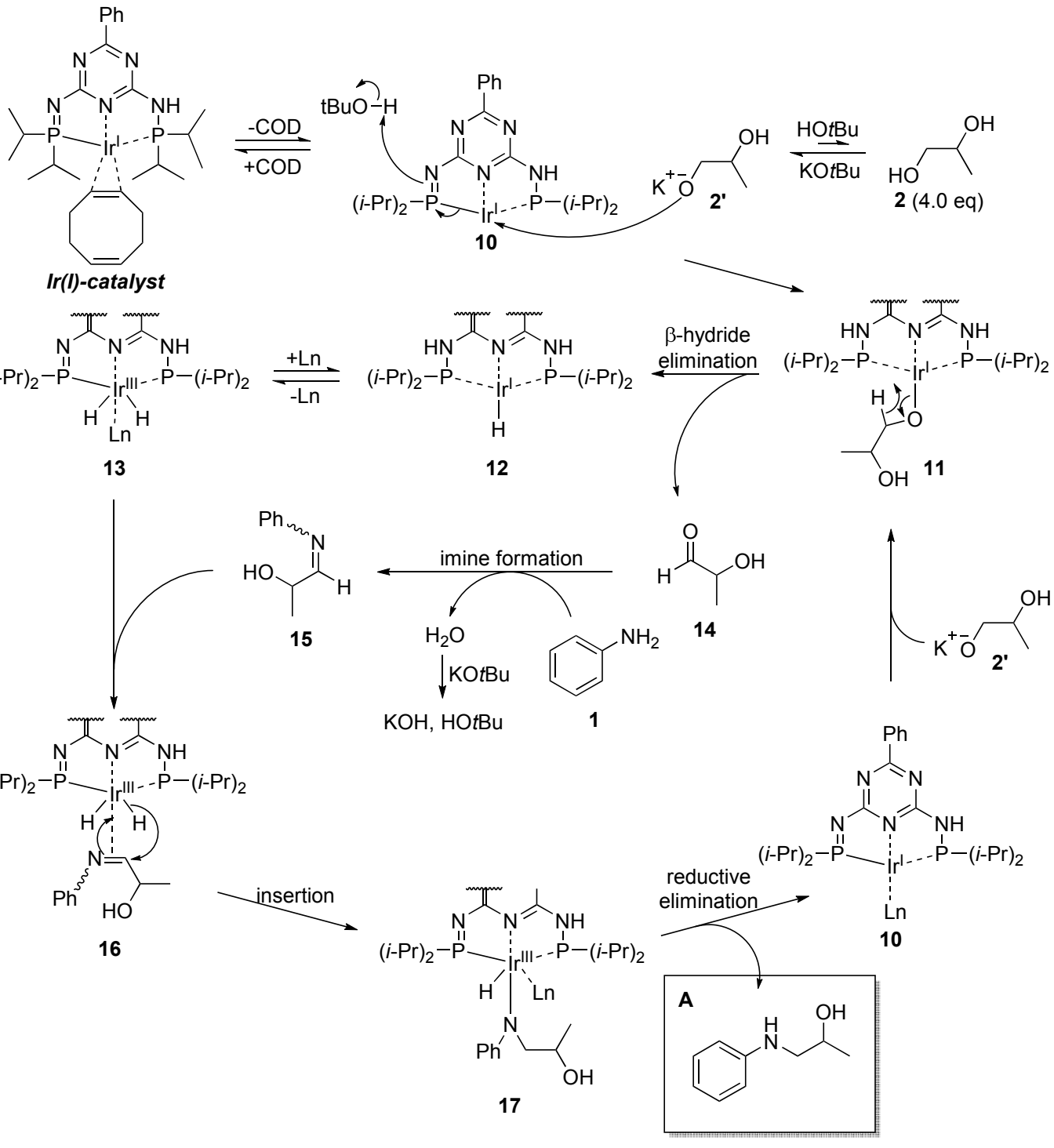


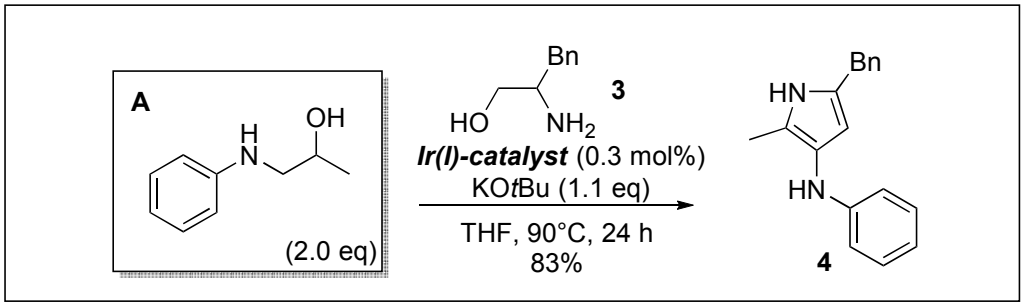
0-18 **0-19** **0-20** **0-21** **0-22** **0-23**

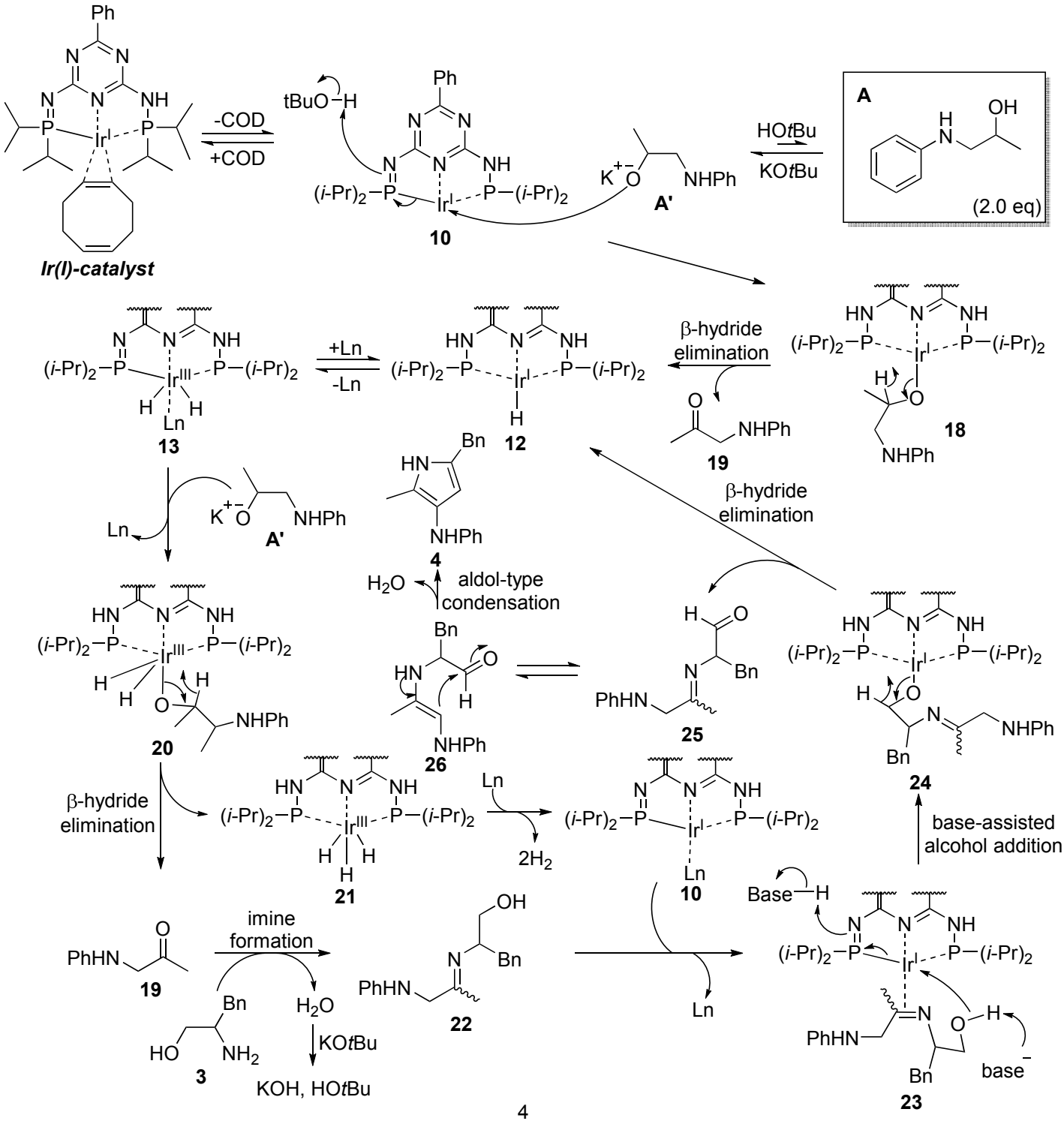
1. Problem 1. (Michlik, S. and Kempe, R. *Nat. Chem.* **2013**, *5*, 140-144)

1-1. Plausible reaction mechanisms



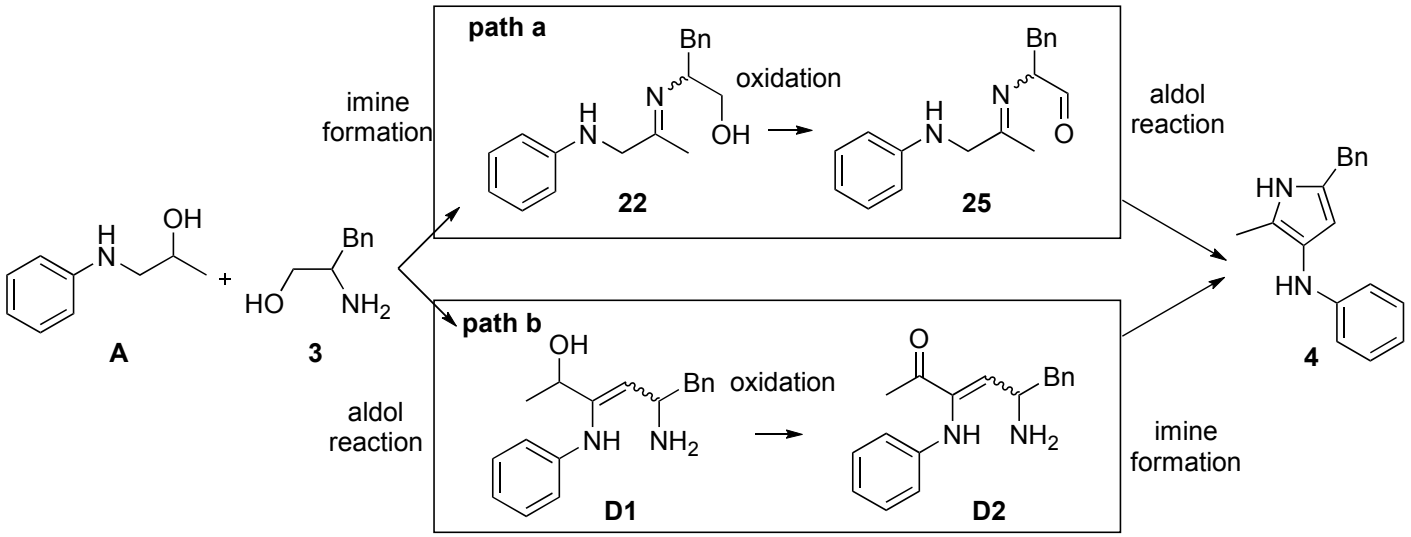



A
(2.0 eq)
Bn
HO
NH2
3
Ir(I)-catalyst (0.3 mol%)
KOtBu (1.1 eq)
THF, 90°C, 24 h
83%
Bn
HN
HN
4


Ir(I)-catalyst
-COD
+COD
tBuO–H
10
A'
HOtBu
KOtBu
A
(2.0 eq)
+Ln
-Ln
13
12
β-hydride elimination
18
19
Ln
A'
4
H2O
aldol-type condensation
β-hydride elimination
20
26
25
24
β-hydride elimination
21
2H2
10
base-assisted alcohol addition
imine formation
19
3
H2O
KOtBu
KOH, HOtBu
22
Base–H
23
base–

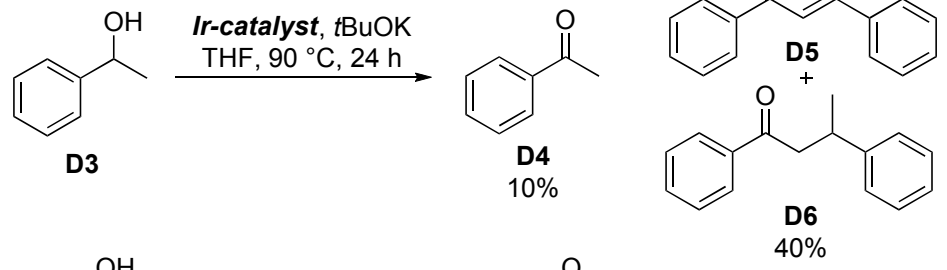
1-2. Discussion

1-2-1. Pathway analysis

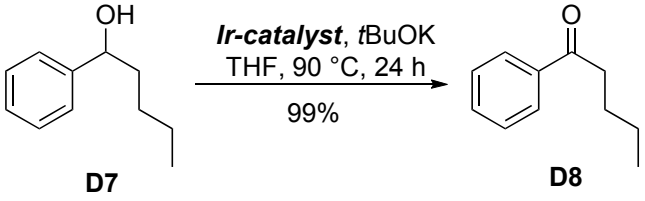


Experiment

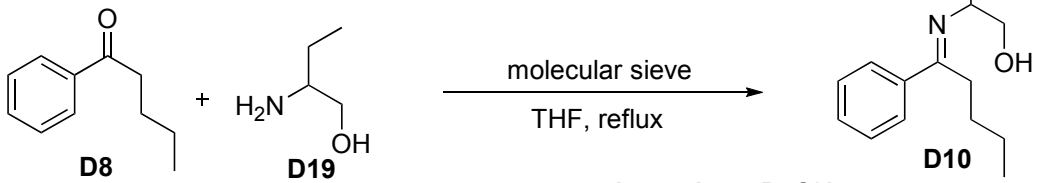
(1) ***Ir-catalyst***, *t*BuOK, THF, 90 °C, 24 h



(2) ***Ir-catalyst***, *t*BuOK, THF, 90 °C, 24 h, 99%

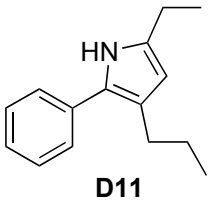


(3) molecular sieve, THF, reflux

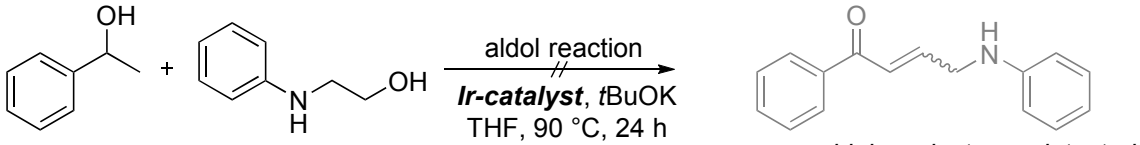


Ir-catalyst, *t*BuOK, THF, 90 °C, 24 h, 47% by GC

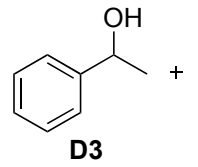
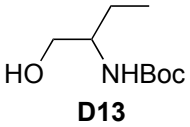
Ir-catalyst, *t*BuOK, THF, 90 °C, 24 h, 48% by GC



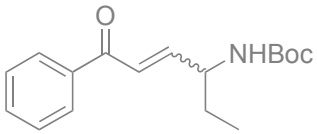
(4) aldol reaction // ***Ir-catalyst***, *t*BuOK, THF, 90 °C, 24 h



no cross aldol-product was detected

(5)  **D3** +  **D13**

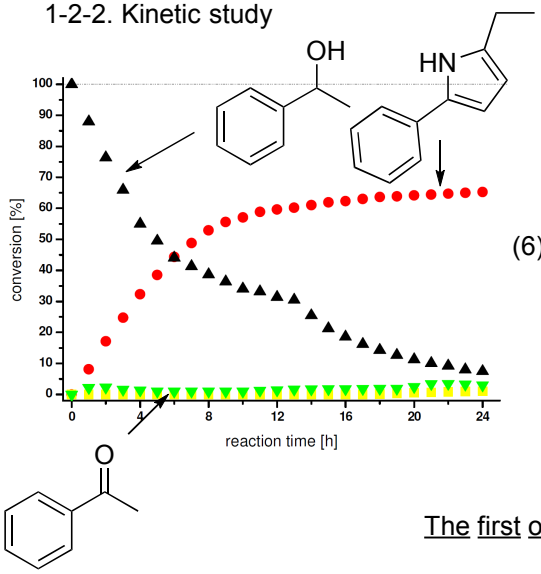
aldol reaction
//
Ir-catalyst, *t*BuOK
THF, 90 °C, 24 h

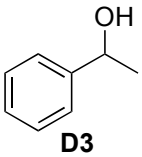
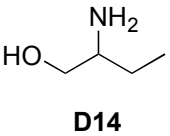


no cross aldol-product was detected

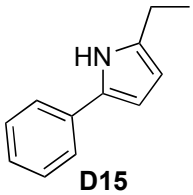
Considering these results, **path a** is more plausible.

1-2-2. Kinetic study



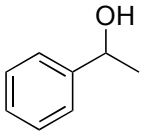
(6)  **D3** +  **D14**

Ir-catalyst, *t*BuOK
THF, 110 °C, 24 h

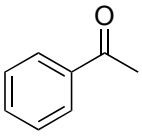
 **D15**

The first oxidation is the rate-determining step

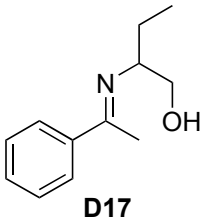
1-2-3. The role of the base

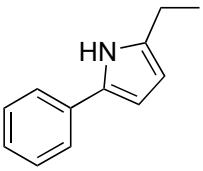
(7)  **D3**

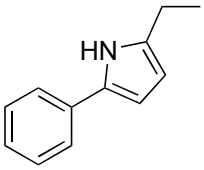
Ir-catalyst
THF, 90 °C, 24 h
(without base)

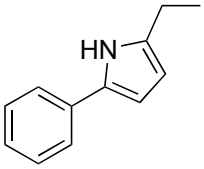
 **D16**
40%

and starting material

(8)  **D17**

without base → 
4% by GC

Ir-catalyst, *t*BuOK
THF, 90 °C, 24 h → 
97% by GC

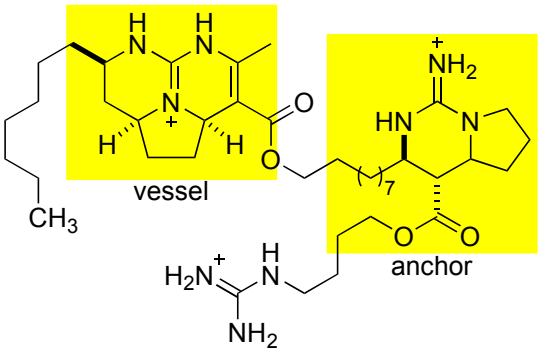
without catalyst → 
3% by GC

D18

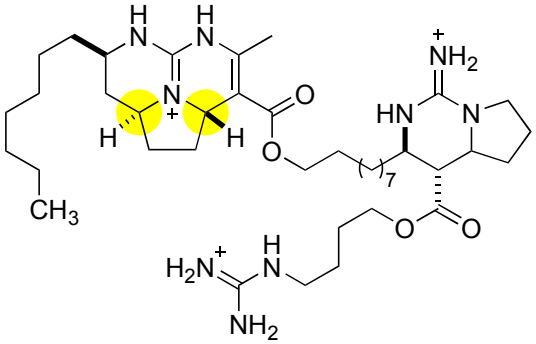
The base mediates the C-C coupling/condensation step and accerates the alcohol oxidation

2. Problem 2. (Parr, B. T.; Economou, C. and Herzon, S. B. *Nature* **2015**, *525*, 507-510)

2-1. Batzelladine B



(+)-batzelladine B
this study (first total synthesis)
Synthesis and structural configulation of the vessel moiety:
Shaka A. J. *et al. JOC* **1999**, *64*, 1512-19.

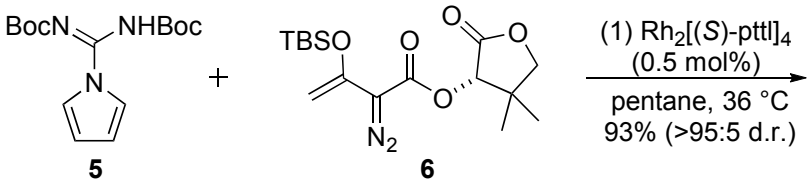


(+)-batzelladine A
Gin, D. Y. *et al. JACS* **2006**, 128, 13255-60.
Nagasawa, K *et al. Chem. Eur. J.* **2005**, *11*, 6878-88.
Nagasawa, K *et al. ACIE* **2004**, *43*, 1559-62.

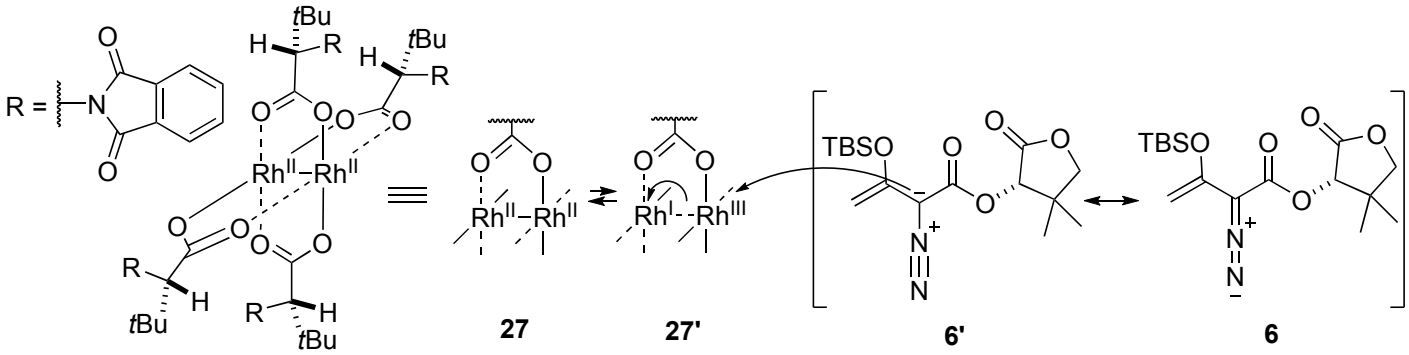
***Isolation**: Potts, B. C. M. *et al. JOC* **1995**, *60*, 1182-88.
*At least 15 batzelladine alkaloids, which contain a vessel moiety, have been isolated.
(*JOC* **1997**, *62*, 1814-19; *Tetrahedron* **2007**, *63*, 11179-88; *J. Nat. Prod.* **2009**, *72*, 1589-94.)
Biological activity: anti HIV (inhibition of HIV-gp120 binding to human CD4 receptor.)

2-2. Plausible reaction mechanisms

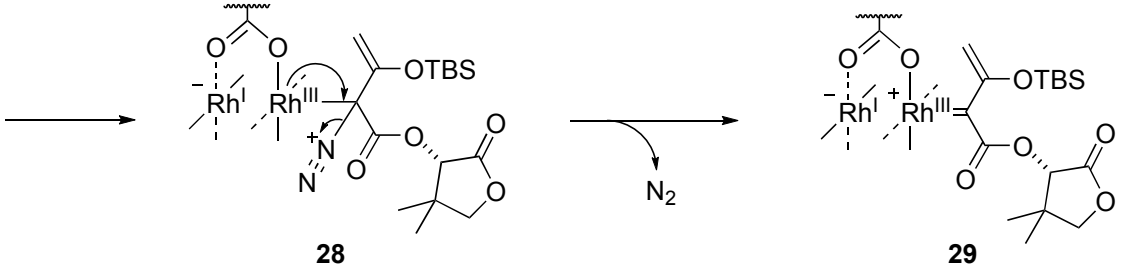
(1) Rhodium-catalyzed formal [4+3] cycloaddition



5 **6** **7**



27 **27'** **6'** **6**



28 **29**

*For this selectivity, see below.

*stereoselective addition

30 (=29)

5

rhodium carbenoid formation (see page 7)

N_2

6

31

32

27'

Cope-rearrangement

33

33'

7'

7 *disfavored (si face blocked by the auxiliary)*

Stereoselectivity (*JACS* **2009**, *131*, 7230-1, *JACS* **1996**, *118*, 10774-82.)

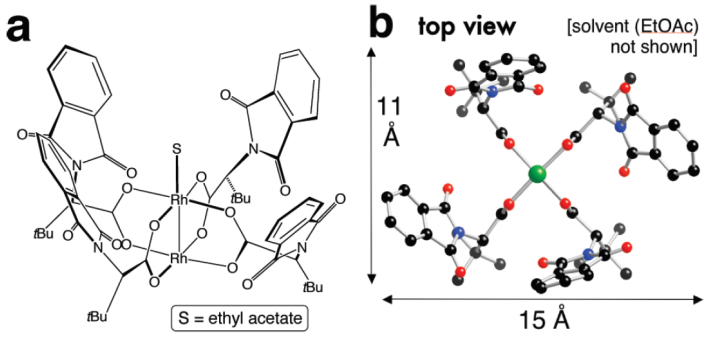


Figure 1. X-ray crystal structure of Rh_2(*S*-PTTL)$_4$ crystallized from ethyl acetate. The unit cell contained two nearly identical (but symmetry-unique) molecules.

(*JACS* **2009**, *131*, 7230-1.)

c

(blocked by the ligand)

(blocked by the ligand)

favored (re face)

30'

minimumized steric interactions between the auxiliary and "wall" of the catalyst.

30''

re face attack

31'

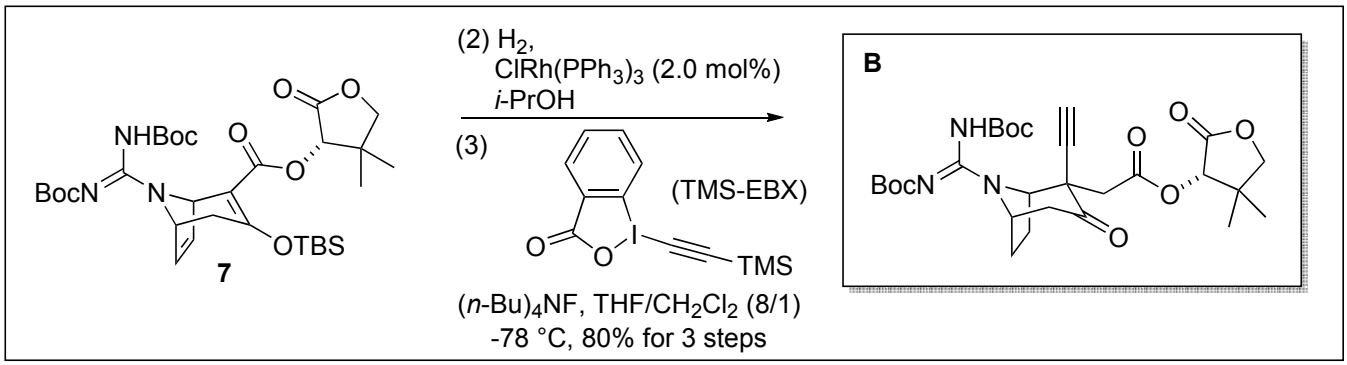
32'

33'-diastereomer

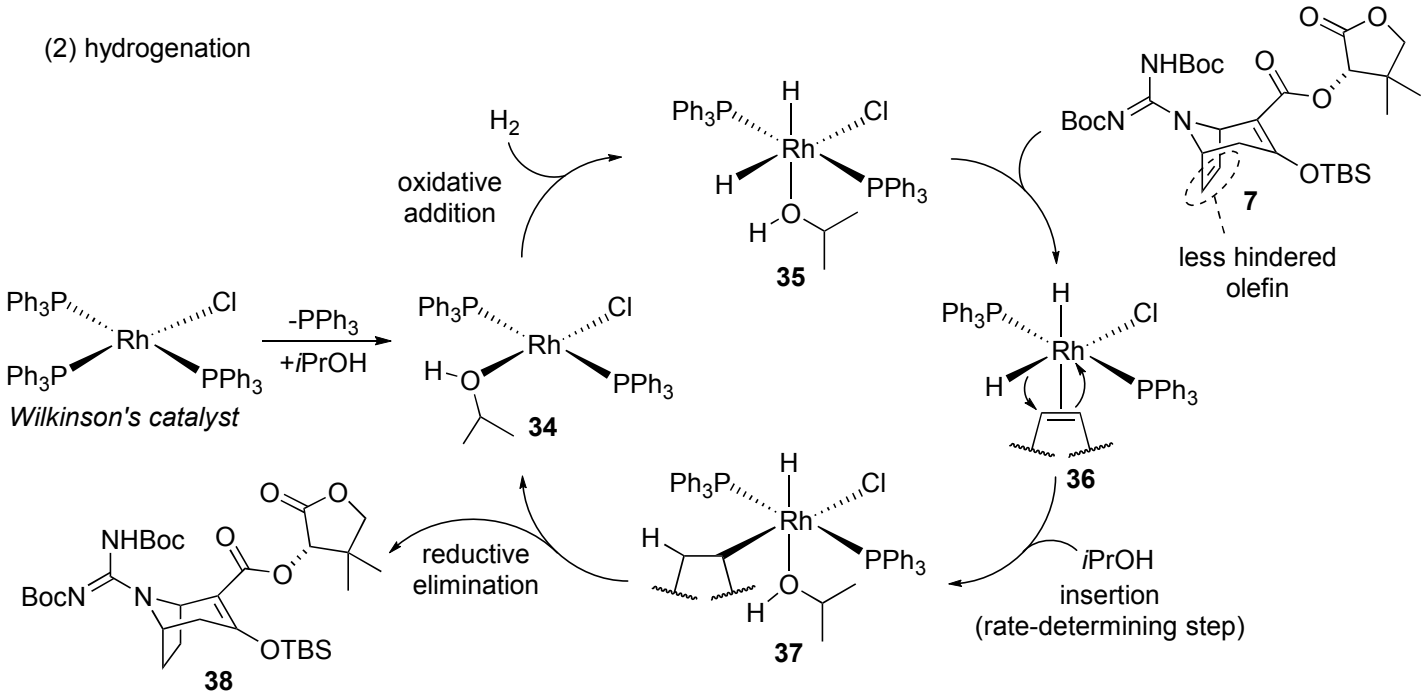
33'

Cope-rearrangement

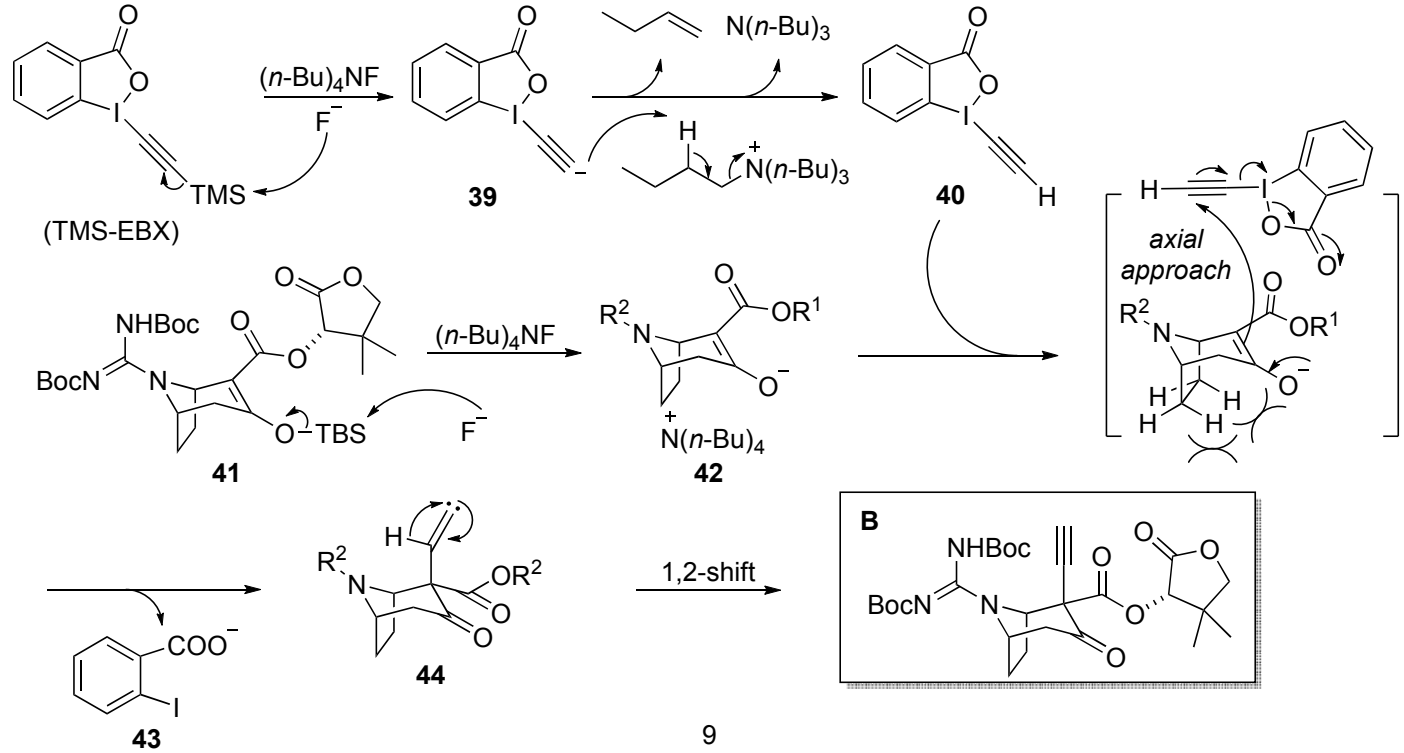
Cope-rearrangement

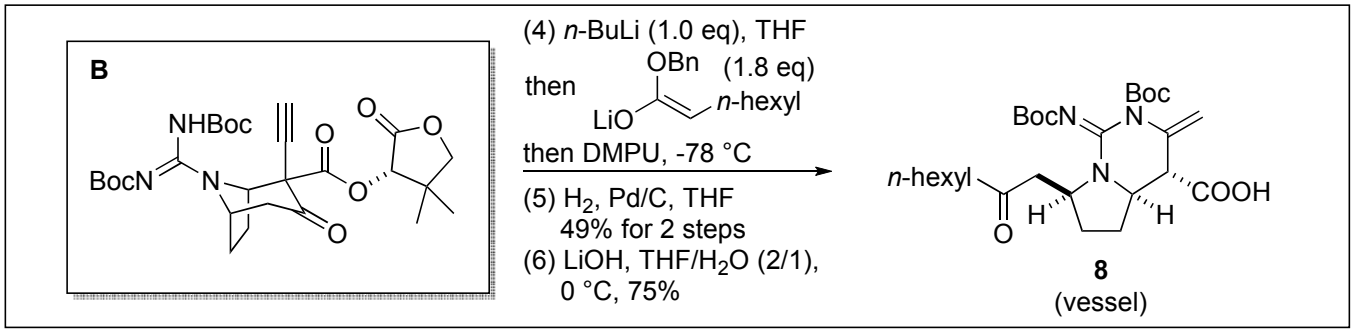


(2) hydrogenation



(3) Electrophilic alkynylation (*Chem. Eur. J.* **2010**, *16*, 9457-61.)





(4) Cascade reaction