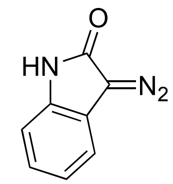
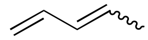
Problem Seminar (2)

17/02/10 Yuki Fujimoto

Please provide following reaction mechanisms

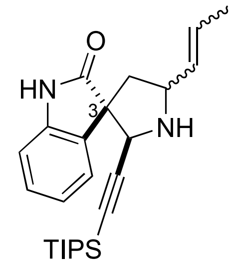


1-1

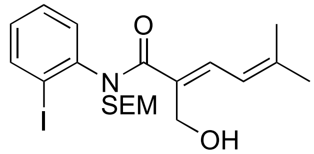
1.  piperylene

   $Rh_2(OAc)_4$ (1 mol%)
   benzene, reflux
   slow addition of **1-1** in CH_2Cl_2, 71 %

2. **1-3**, MgI_2 (1 eq.), THF, sealed tube, 75 °C
   68 % (dr = 6:1 at C3)
3. $Pd(PPh_3)_4$ (6 mol%), NDMBA (3.2 eq.)
   CH_2Cl_2, 30 °C, 86 %

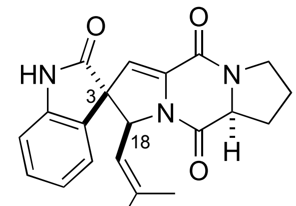


1-2



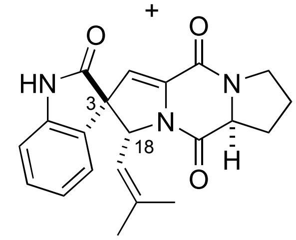
2-1

1. Dess-Martin periodinane, CH_2Cl_2, rt
2. **2-3**, *t*-BuOK
   CH_2Cl_2, -78 °C to rt, 64 % (2 steps)
3. $[Pd_2(dba)_3]\cdot CHCl_3$ (10 mol%)
   P(*o*-tol)$_3$ (40 mol%), AcOK
   THF, 70 °C, 72 % (dr = 1:1)
4. Me_2AlCl, CH_2Cl_2, -78 °C to rt
5. *i*-Pr_2NEt, MeOH, 45 °C, 93 ~ 95 % (2 steps)

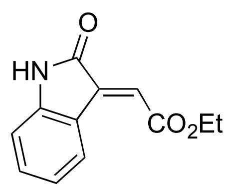


2-2 spirotryprostatin B

\+

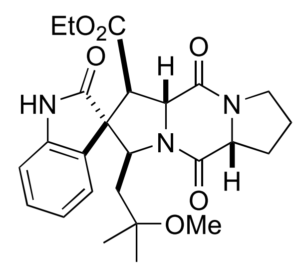


2-2' 3,18-epi-spirotryprostatin B

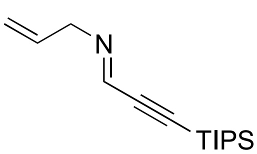


3-1

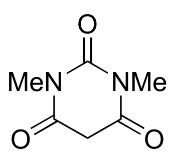
1. **3-3**, **3-4**, 3ÅMS, toluene, 60 °C, 82 %
2. H_2, $PdCl_2$ (1 eq.), THF/EtOH, 4 atm, rt, 99 %
3. D-Pro-OBn, BOP, Et_3N, MeCN, 0 °C to rt, 74 %
4. H_2, Pd/C, EtOH, rt
5. BOP, Et_3N, MeCN, rt, 94 % (2 steps)



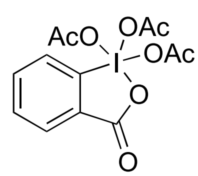
3-2



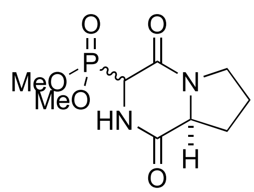
1-3



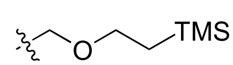
NDMBA



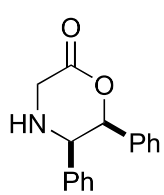
Dess-Martin periodinane



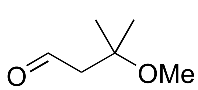
2-3



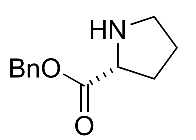
SEM



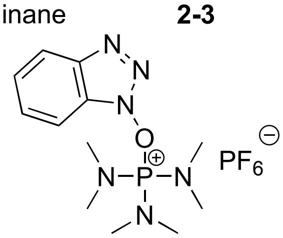
3-3



3-4



D-Pro-OBn

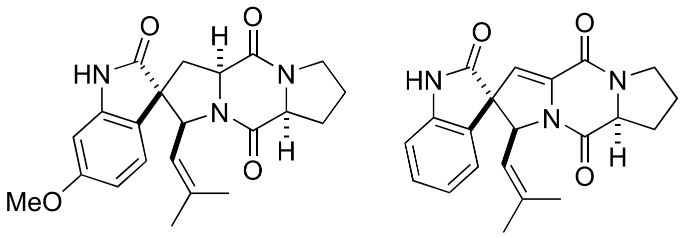


BOP

Problem Seminar (2)

17/02/10 Yuki Fujimoto

Topic: total synthesis of spirotryprostatin



spirotryprostatin A　　spirotryprostatin B

Isolation
fermentation broth of Aspergillus fumigatus
Osada, H. *et. al. J. Antibiot.* **1996**, *49*, 832.
Osada, H. *et. al. Tetrahedron* **1996**, *52*, 12651.

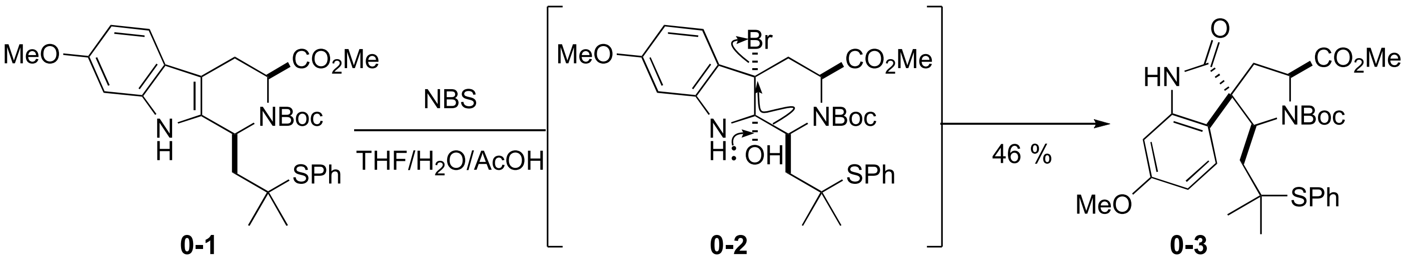
Biological activity
inhibition the G2/M phase of mammalian cell cycle

Structual features
•pentacyclic skeltone including spirooxyindole and diketopiperazine
•prenyl side chain

total synthesis
spirotryprostatin A
Danishefsky, S. J. *et. al. J. Am. Chem. Soc*. **1999**, *121*, 2147.
Williams, R. M. *et. al. Org. Lett.* **2003**, *5*, 3135
Horne. D. A. *et. al. Org. Lett.* **2004**, *6*, 4249.
Fukuyama, T. *et. al. Chem. Sci.* **2014**, *5*, 904.

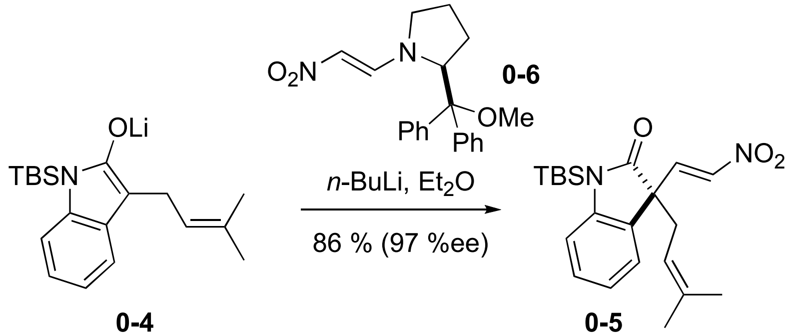
spirotryprostatin B
Sebahar. P. R. and Williams, R. M. *J. Am. Chem. Soc*. **2000**, *122*, 5666. (problem 3)
Wang. H. and Ganesan, A. J. *Org. Chem.* **2000**, *65*, 4685.
Overman, L. E. and Rosen, M. D. *Angew. Chem. Int. Ed*. **2000**, *39*, 4596. (problem 2)
von Nussbaum. F. and Danishefsky. S. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2175.
Fuji. K. *et. al. Org. Lett*. **2002**, *4*, 249.
Meyers, C. and Carreira, E. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 694. (problem 1)
Horne, D. A. *et. al. Angew. Chem. Int. Ed*. **2004**, *43*, 5357.
Trost, B. M. and Stiles, D. T. *Org. Lett.* **2007**, *9,* 2763.

How to construction C3 stereocenter
Danishefsky (spirotryprostatin A), Ganesan: oxidative pinacol rearrangement



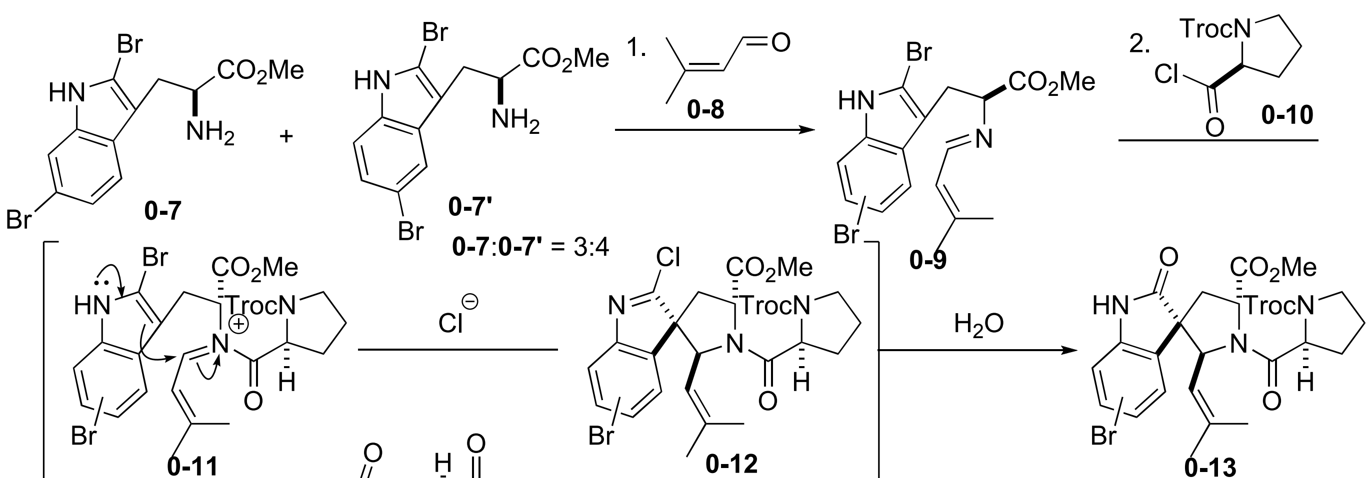
Danishefsky, S. J. *et. al. J. Am. Chem. Soc*. **1999**, *121*, 2147.

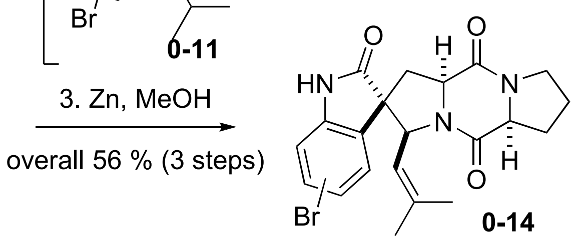
Fuji: asymmetric nitroolefination



Fuji, K. *et. al. Synlett* **1995**, *367*.

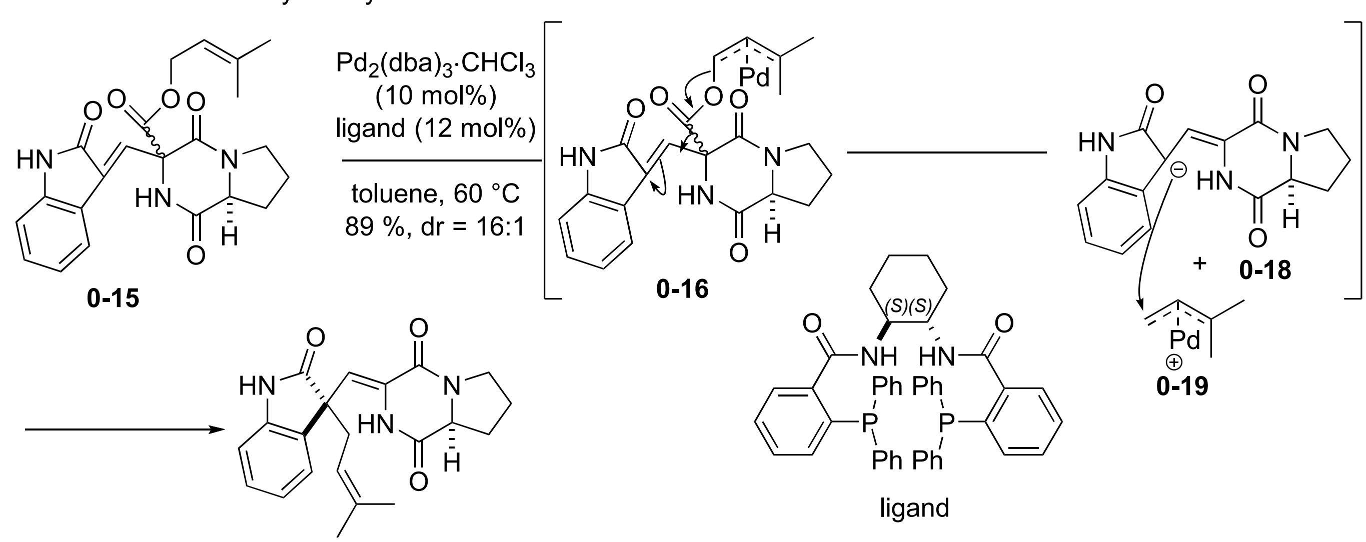
Danishefsky (spirotryprostatin B), Horne: Mannich type cyclization





Horne. D. A. *et. al. Org. Lett.* **2004**, *6*, 4249.

Trost: Asmmetric Allylic Alkylation

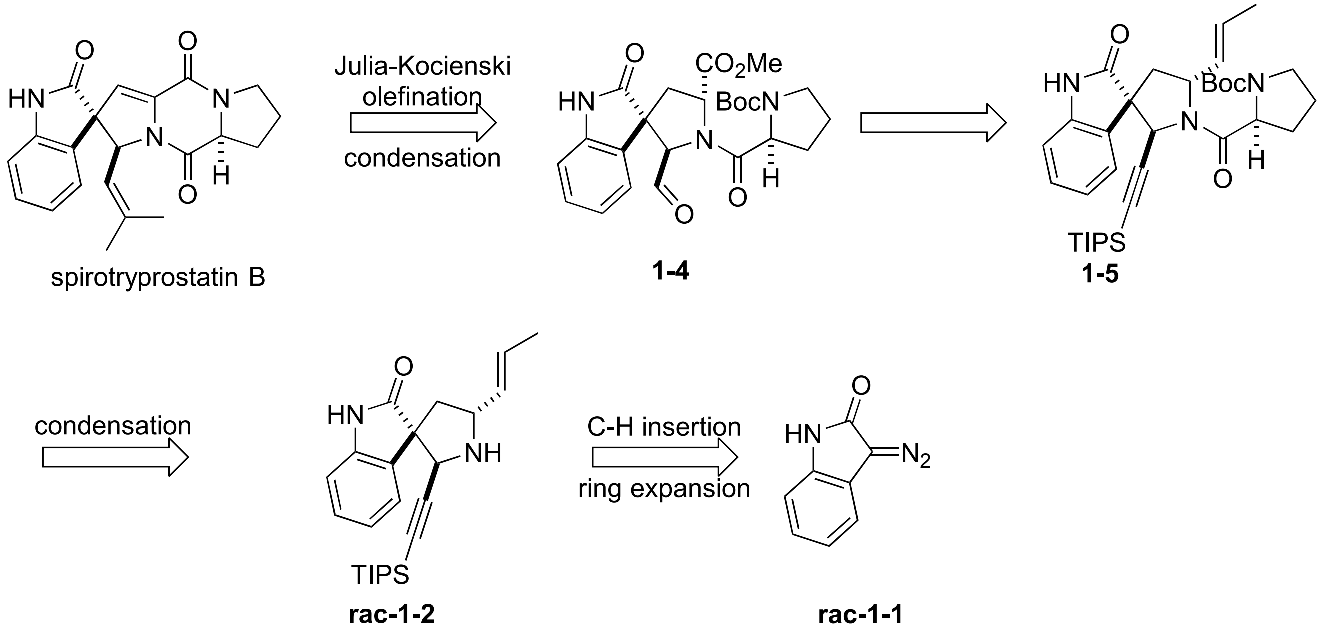


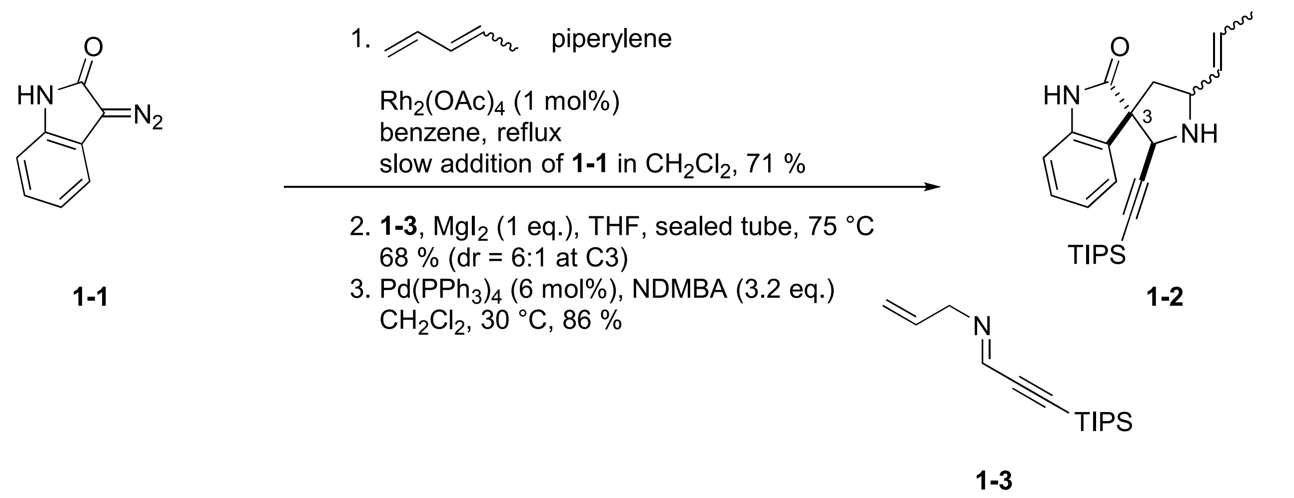
0-20

Trost, B. M. and Stiles, D. T. *Org. Lett.* **2007**, *9,* 2763.

Fukuyama: Heck reaction

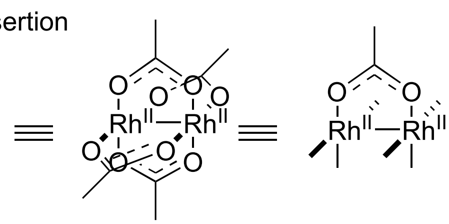
Problem 1: Carreira's synthesis
Retrosynthetic analysis



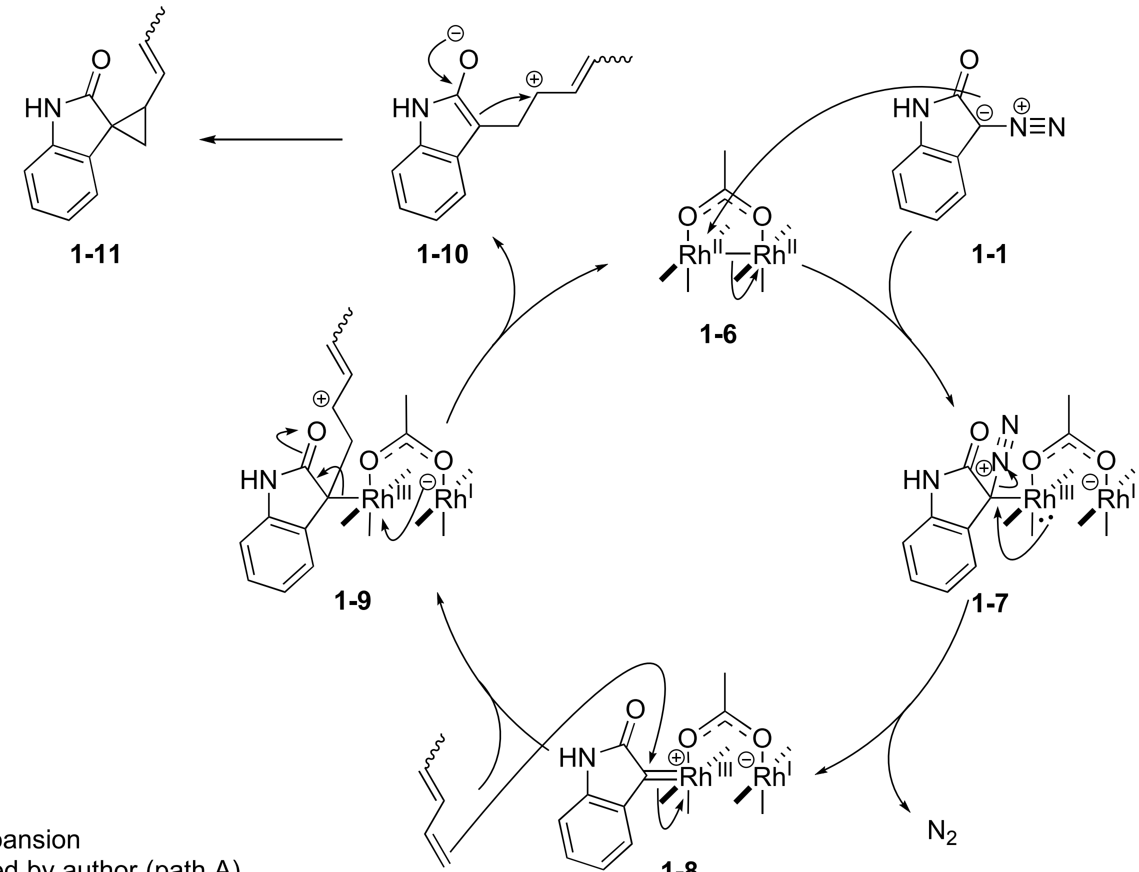


Meyers, C. and Carreira, E. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 694.

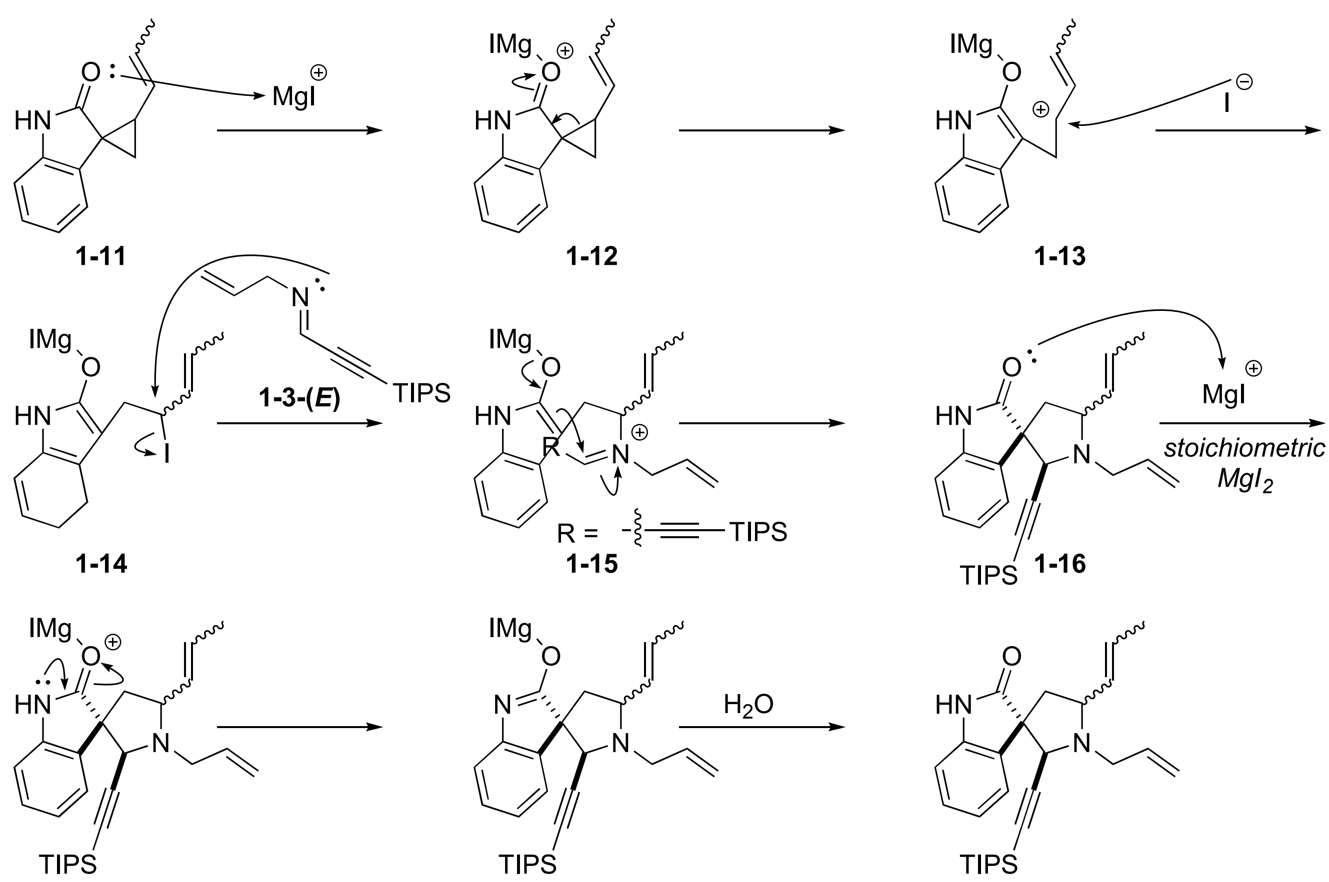
1. C-H insertion

$Rh_2(OAc)_4$ ≡ 

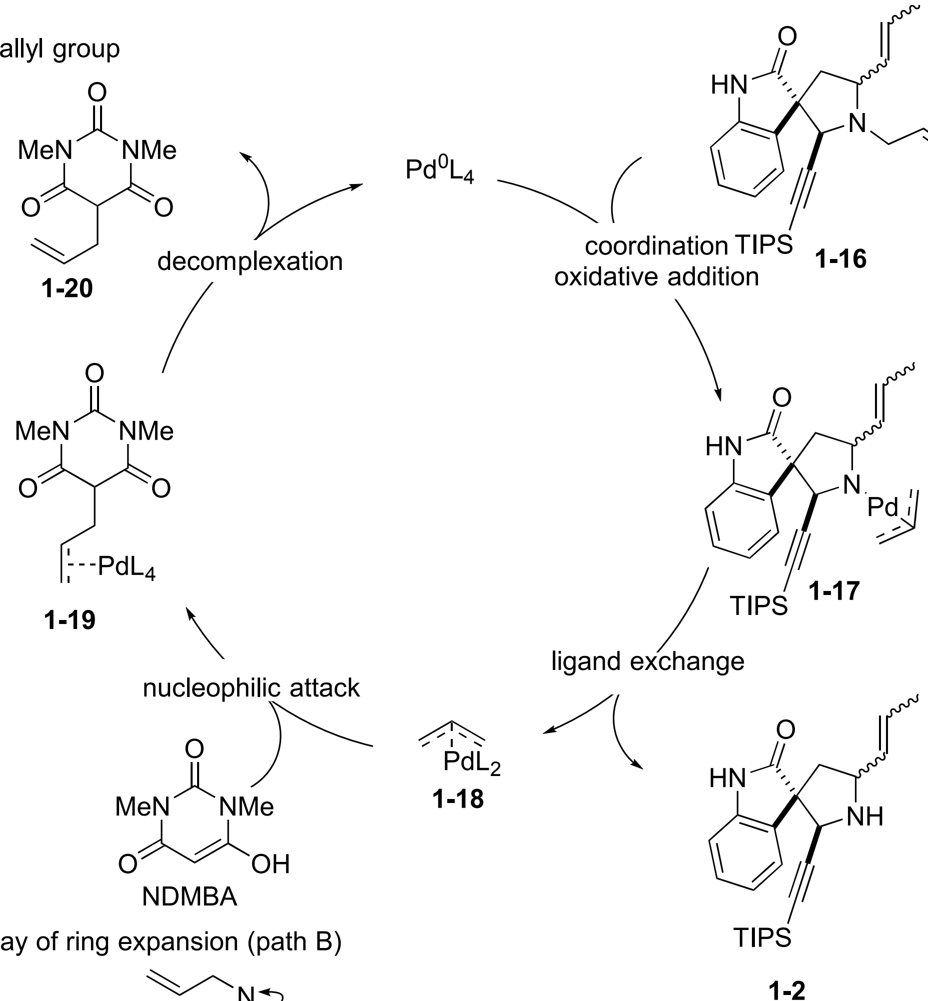
1-6



2. ring expansion
proposed by author (path A)

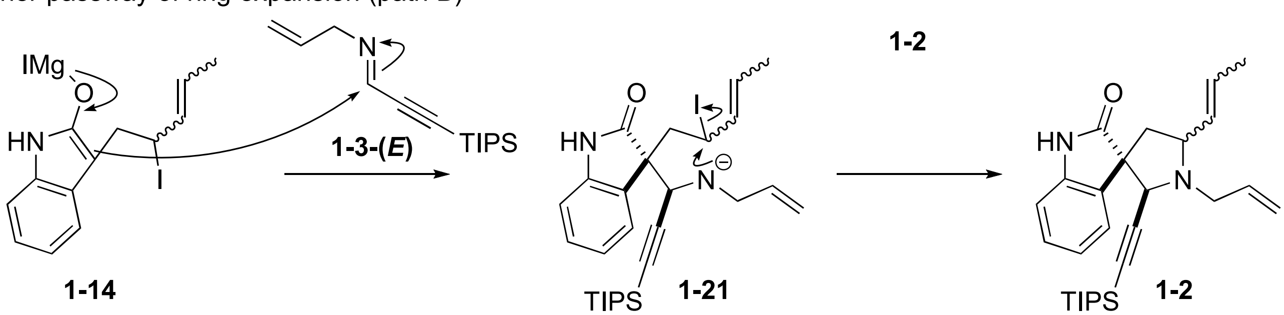


3. removal of allyl group



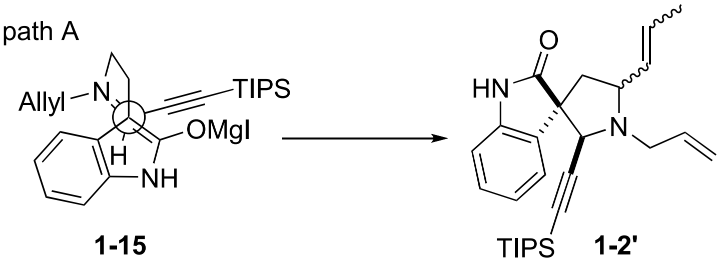
Discussion

another passway of ring expansion (path B)



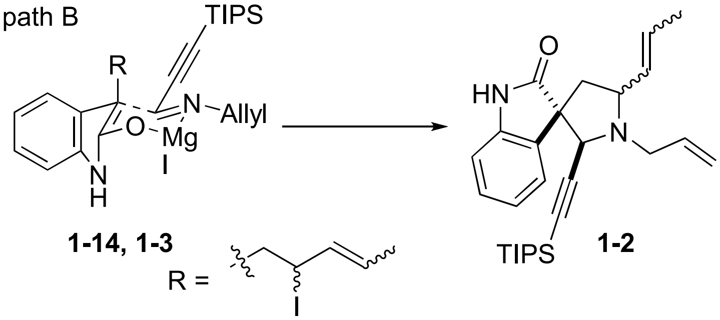
my proposal of stereoselectivity

path A



bulky TIPS group avoid benzene ring

path B

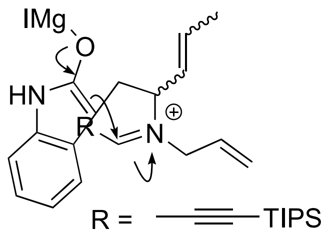


6-membered TS make stereochemistry of **1-2**

→ring expansion would proceed via pass B

5-endo-trig VS 5-exo-tet

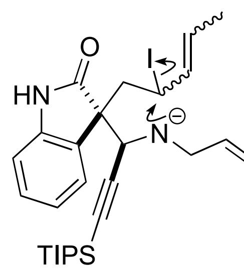
path A



1-15

5-endo-trig (disfavored)

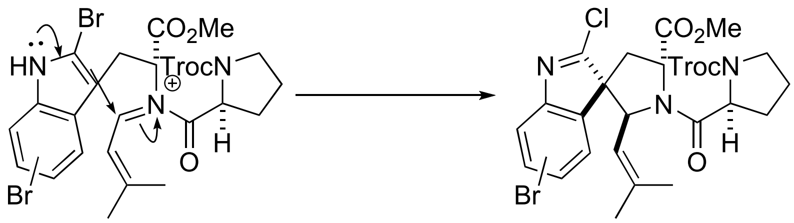
path B



1-21

5-exo-tet (favored)

example of 5-endo-trig

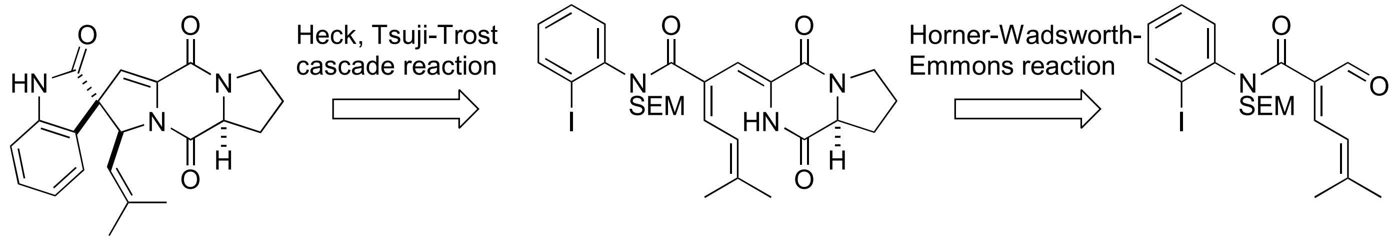


0-11 **0-12**

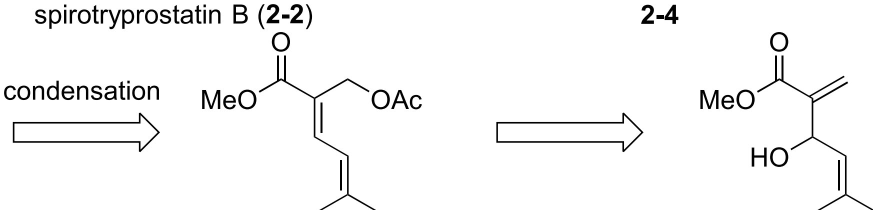
5-endo-trig cyclization seems to be allowed. But overlap of orbital is not good.

Problem 2: Overman's synthesis

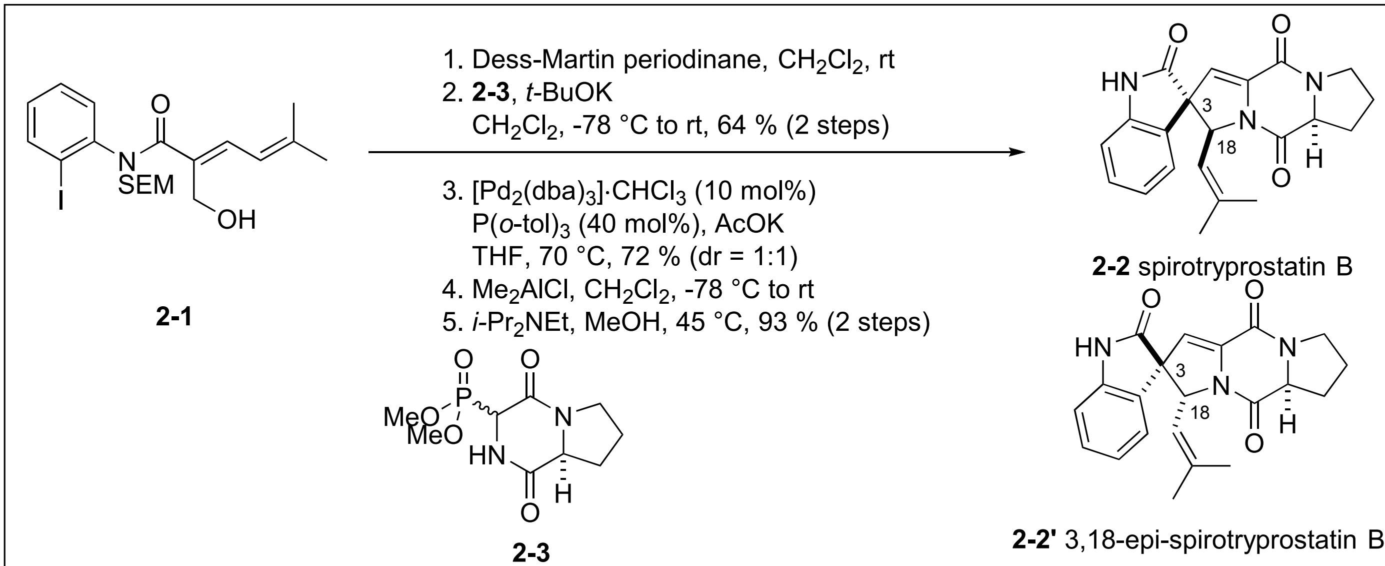
Retrosynthetic analysis



spirotryprostatin B (**2-2**) **2-4** **2-5**

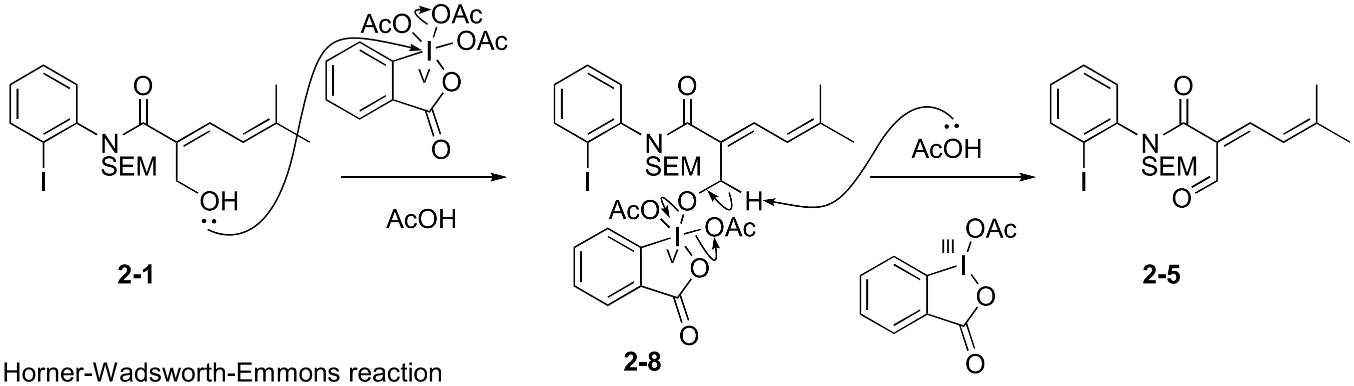


2-6 **2-7**

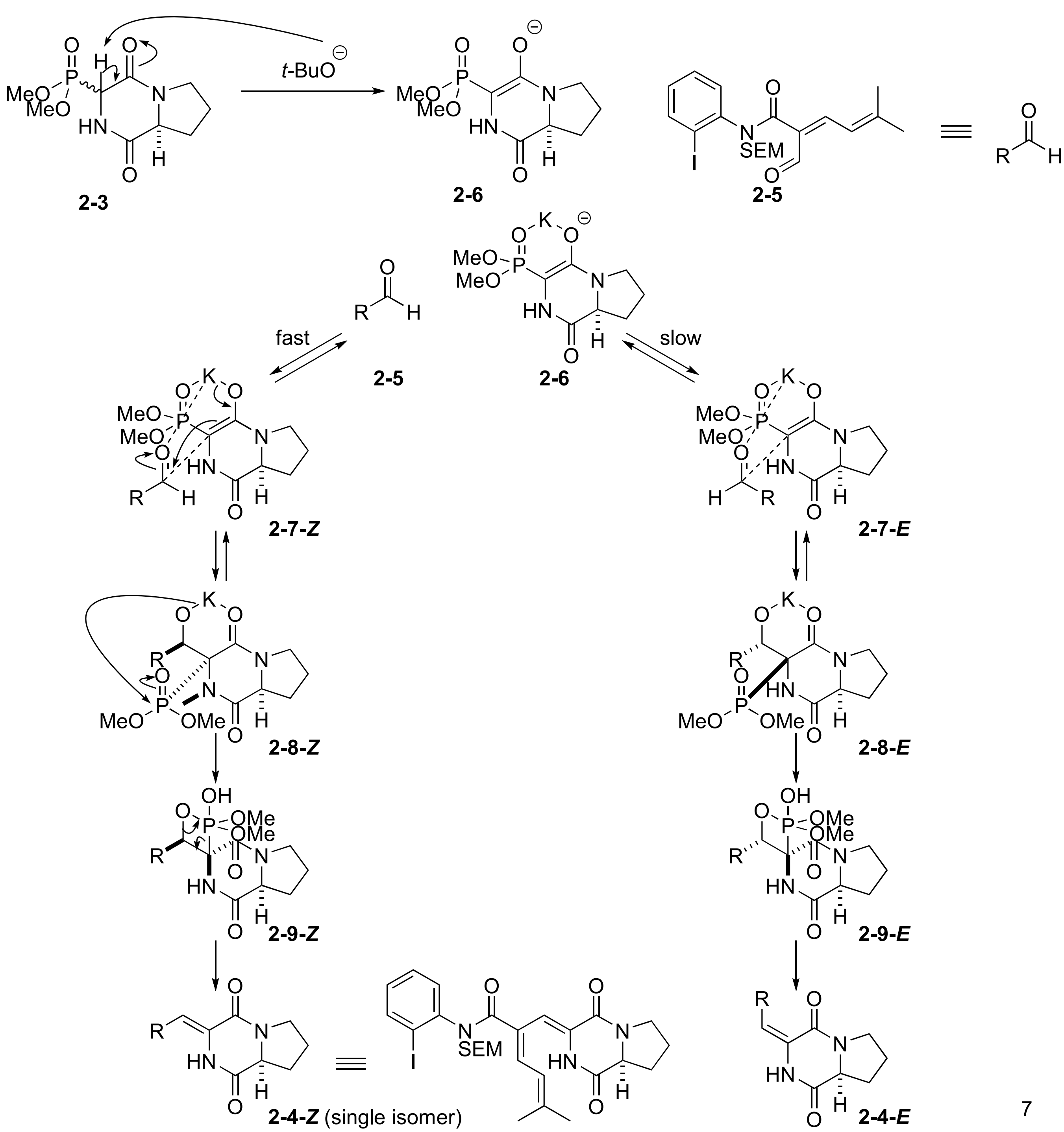


Overman, L. E. and Rosen, M. D. *Angew. Chem. Int. Ed*. **2000**, *39*, 4596.

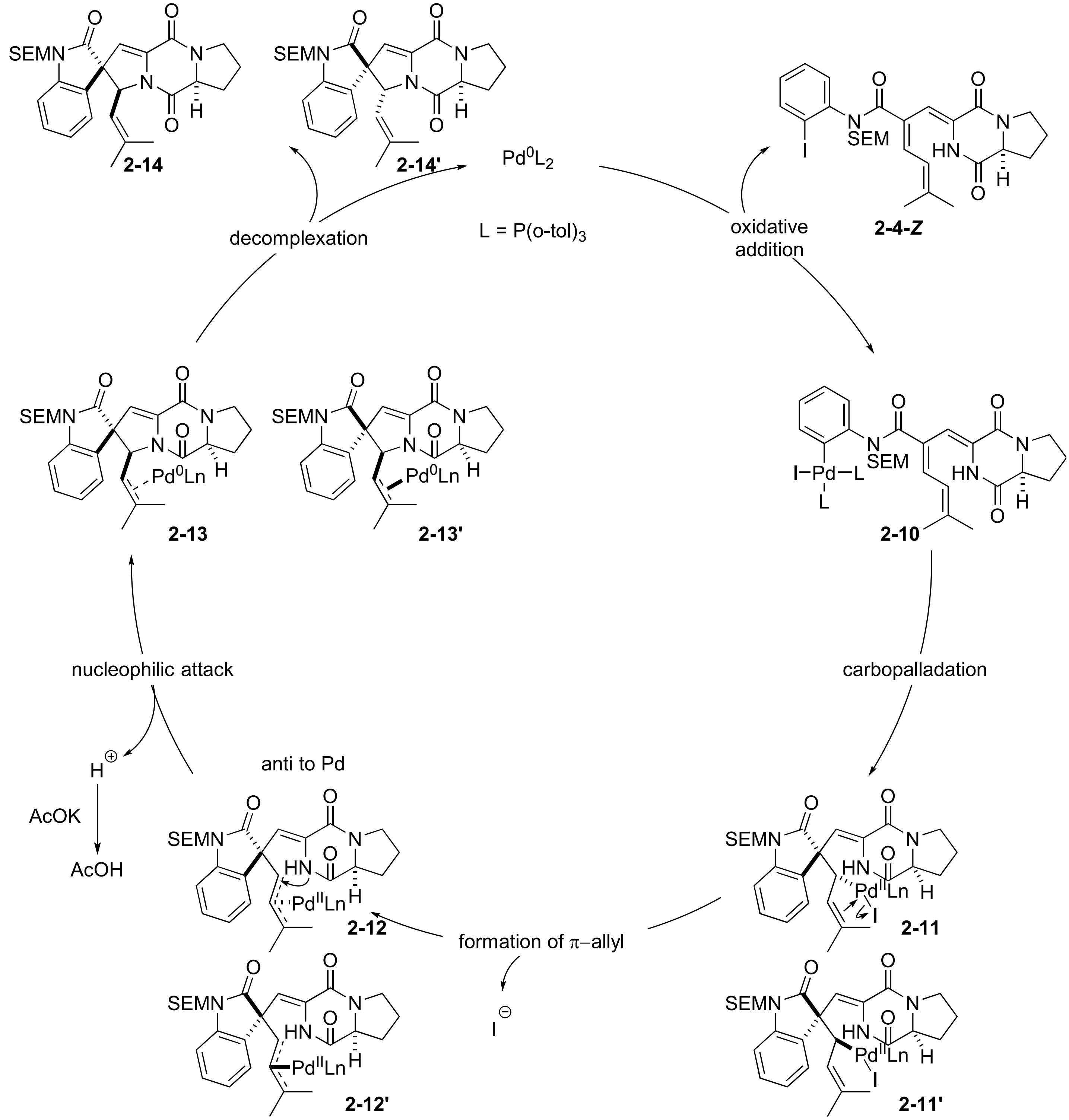
1. Dess-Martin oxidation



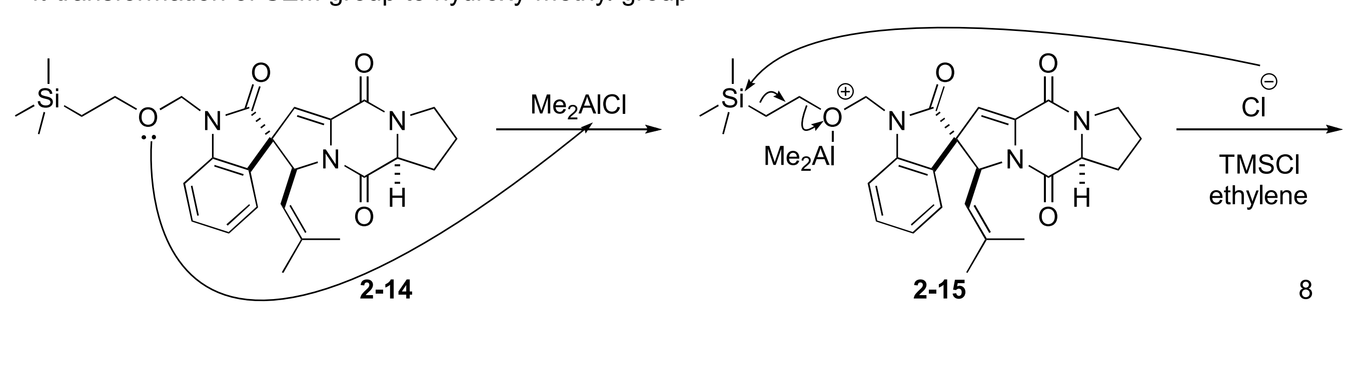
2. Horner-Wadsworth-Emmons reaction

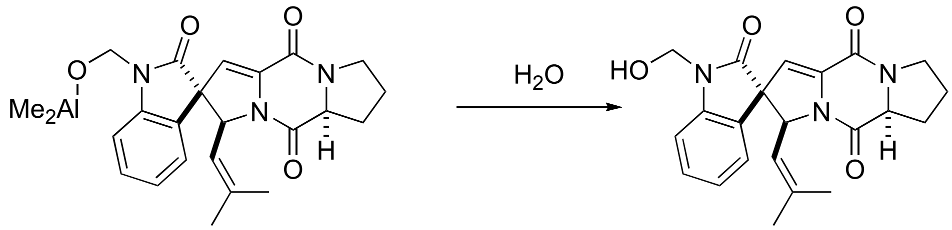


3. Heck, Tsuji-Trost cascade reaction



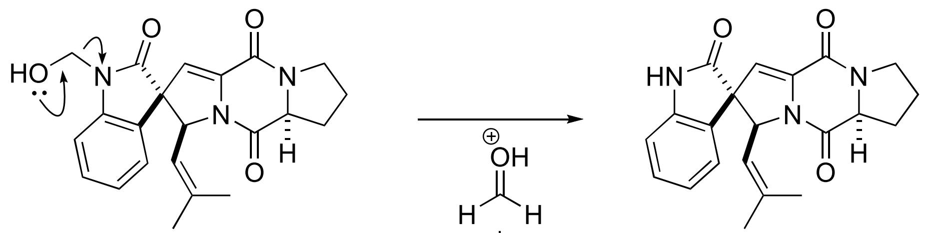
4. transformation of SEM group to hydroxy methyl group





2-16 **2-17**

5. removal of hydroxy methyl group



2-17

spirotryprostatin B (**2-2**)

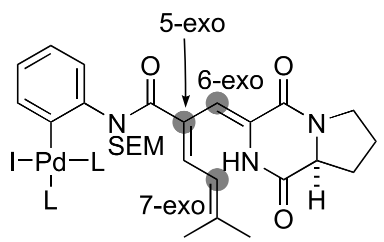
i-Pr_2NEt

HCHO

Discussion

regioselectivity of Heck reaction

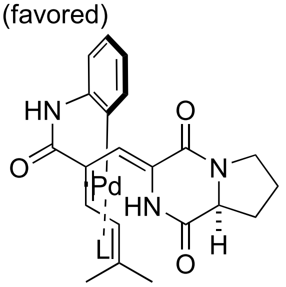
in generally, exo is favored than endo in 5, 6 or 7 membered ring formation.



2-10

7-exo: 7-membered ring containing trans olefin

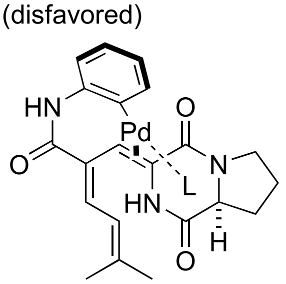
5-exo (favored)



2-18-5-exo

large ligand has steric repulsion to methyl group of prenyl group.

6-exo (disfavored)

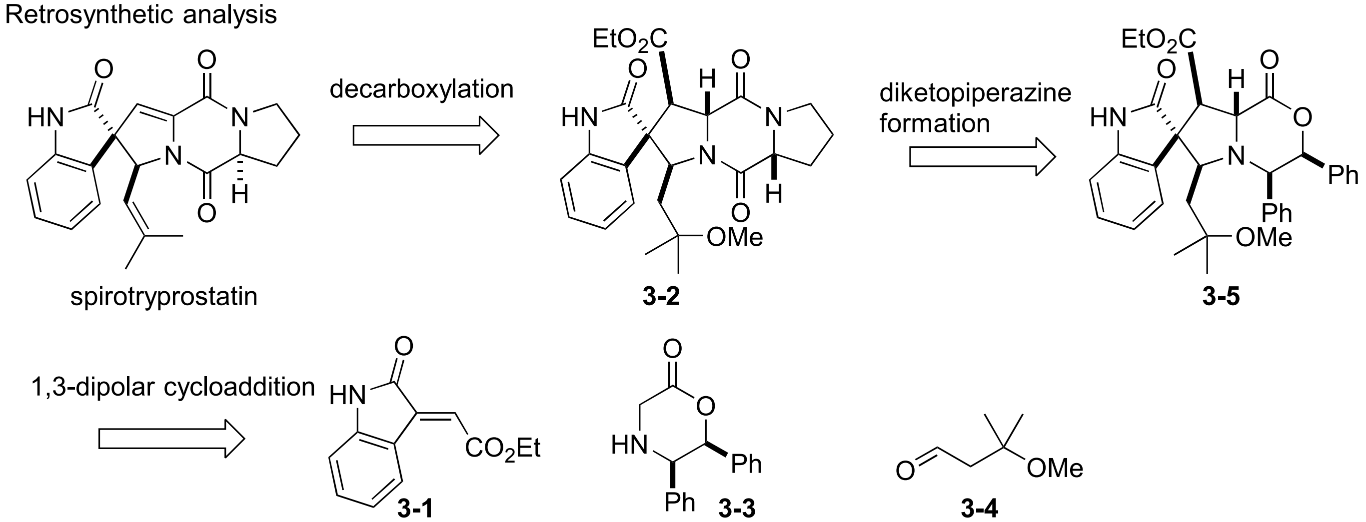


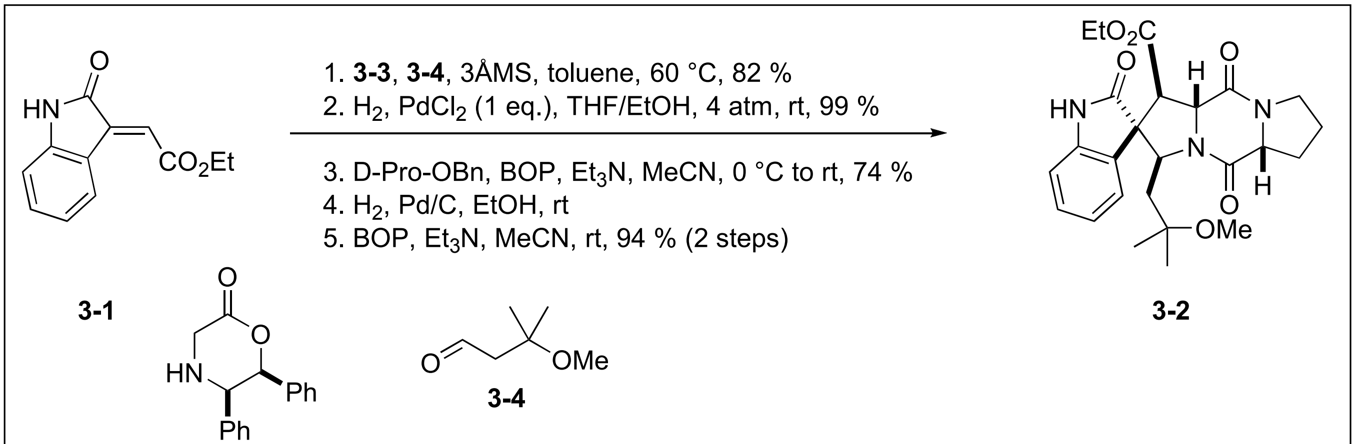
2-18-6-exo

large ligand has steric repulsion to diketopiperazine ring.

the other ligand which is located over Pd was omitted for clarity.

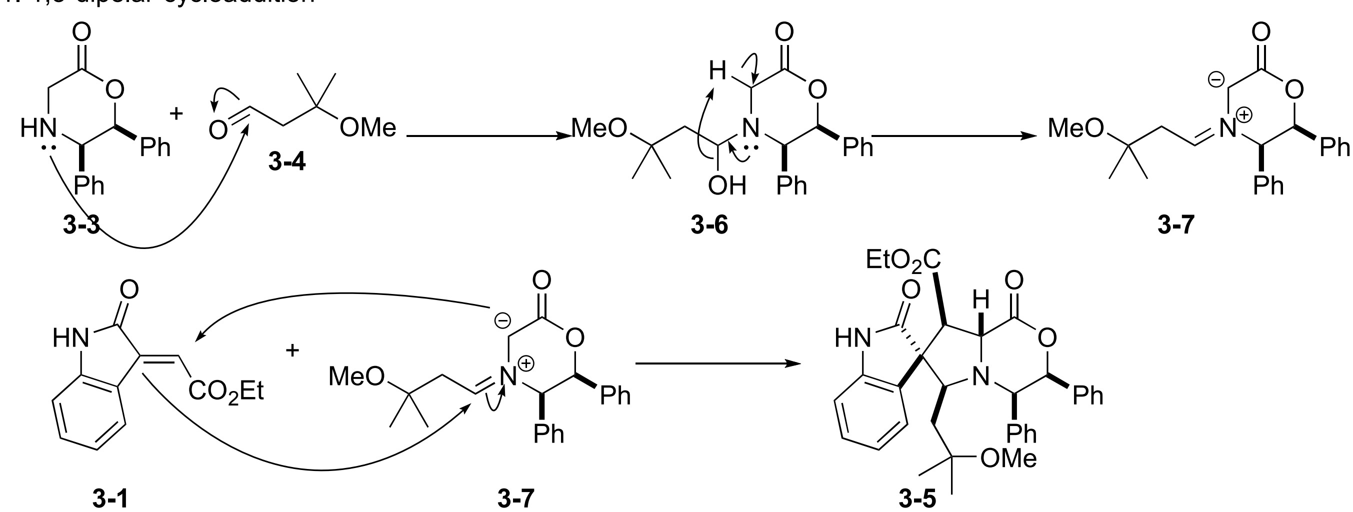
Problem 3: Williams' synthesis
Retrosynthetic analysis



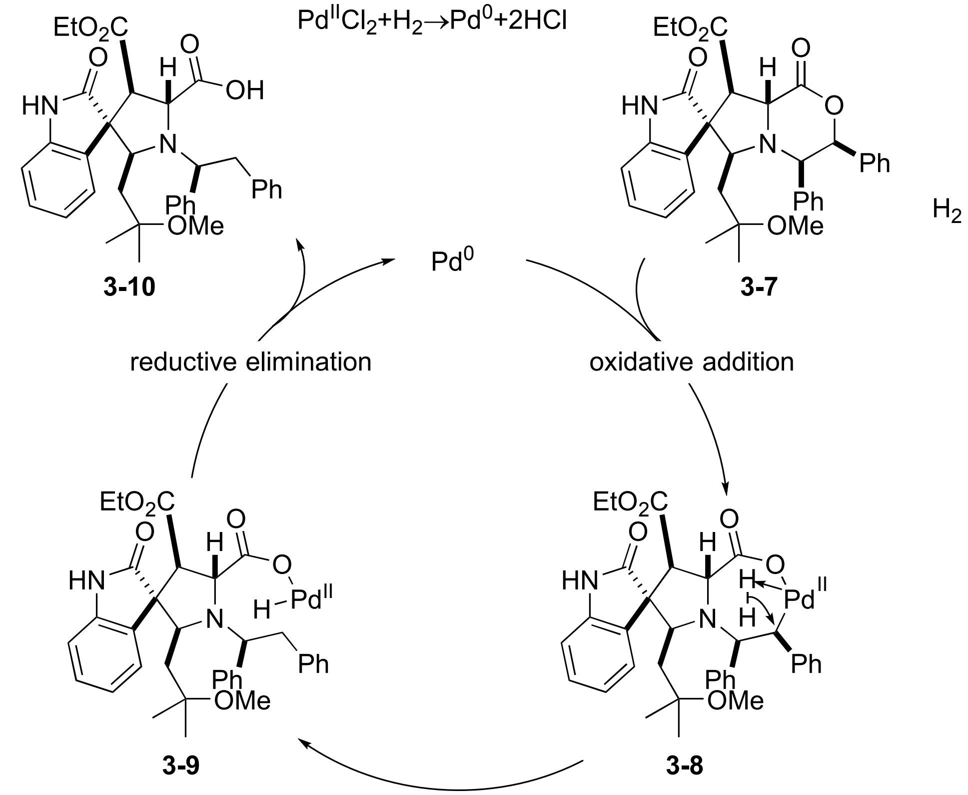


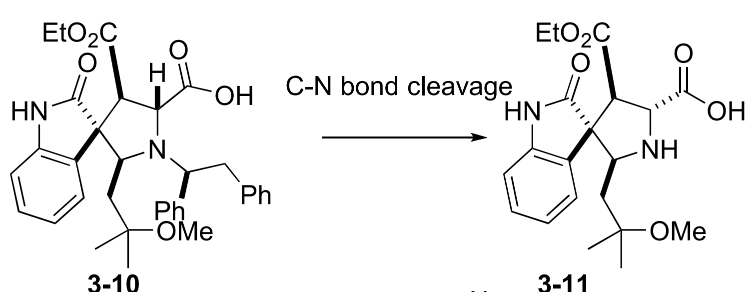
Sebahar. P. R. and Williams, R. M. *J. Am. Chem. Soc*. **2000**, *122*, 5666.

1. 1,3-dipolar cycloaddition

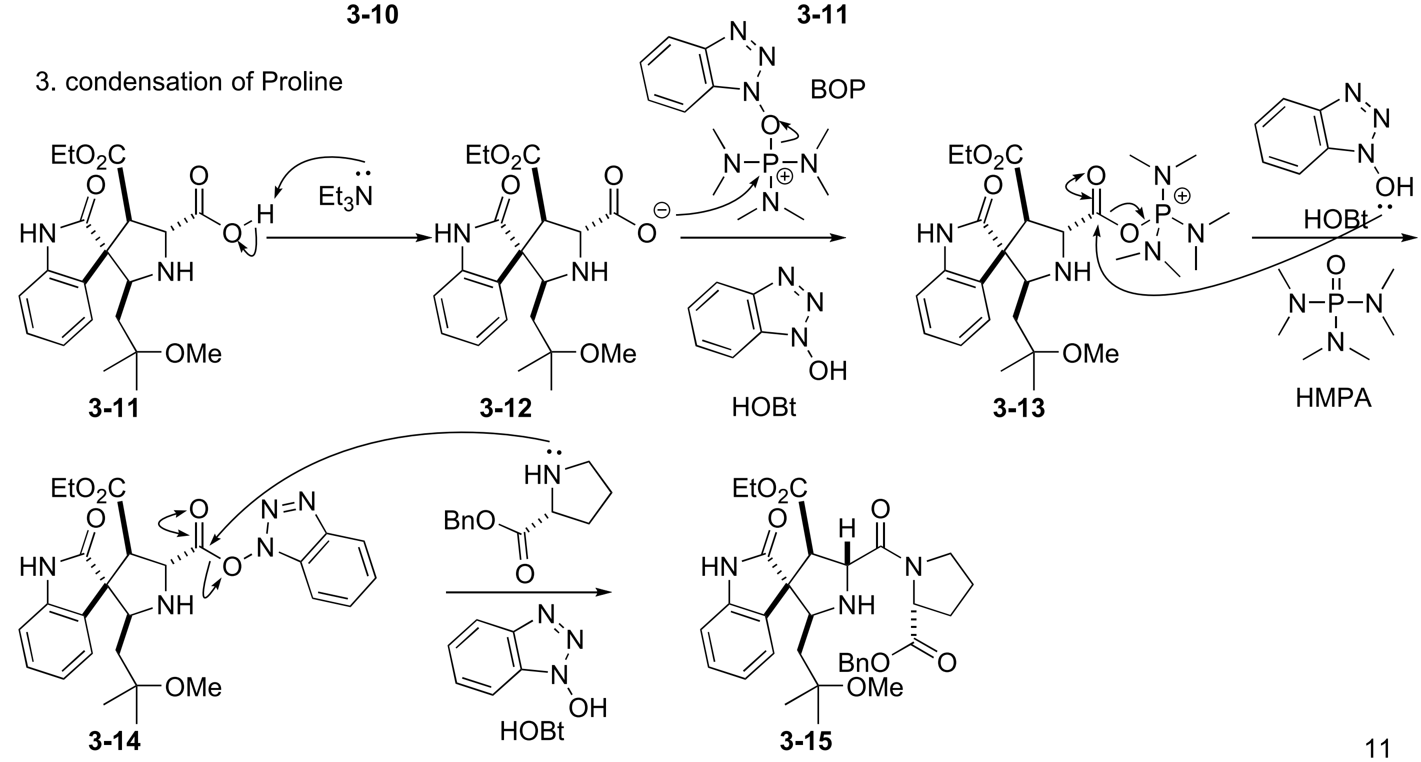


2. removal of chiral auxiliary group

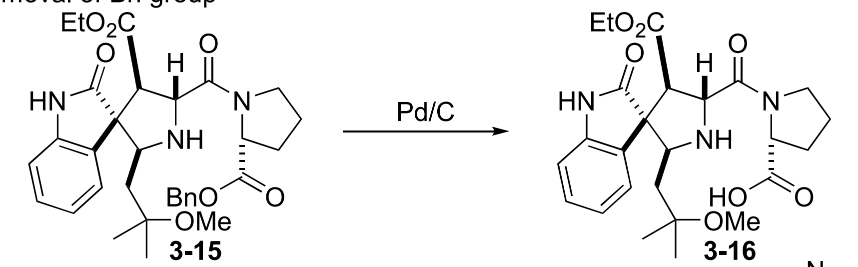




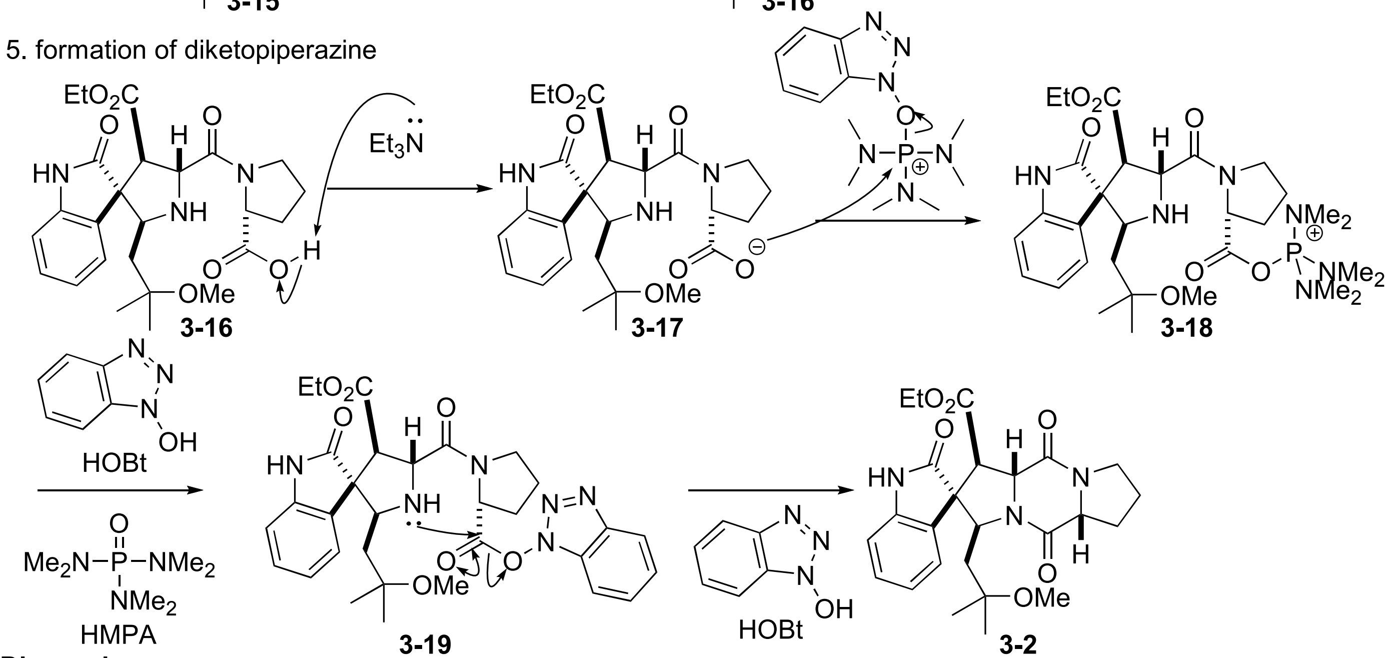
3. condensation of Proline



4. removal of Bn group



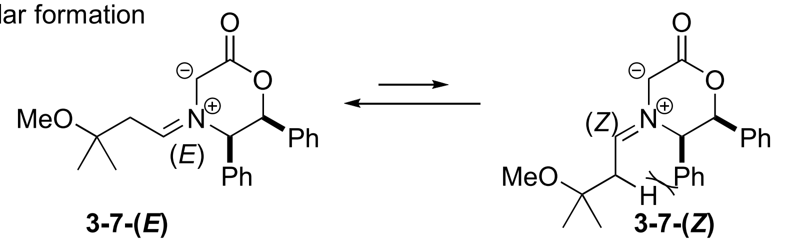
5. formation of diketopiperazine



Discussion

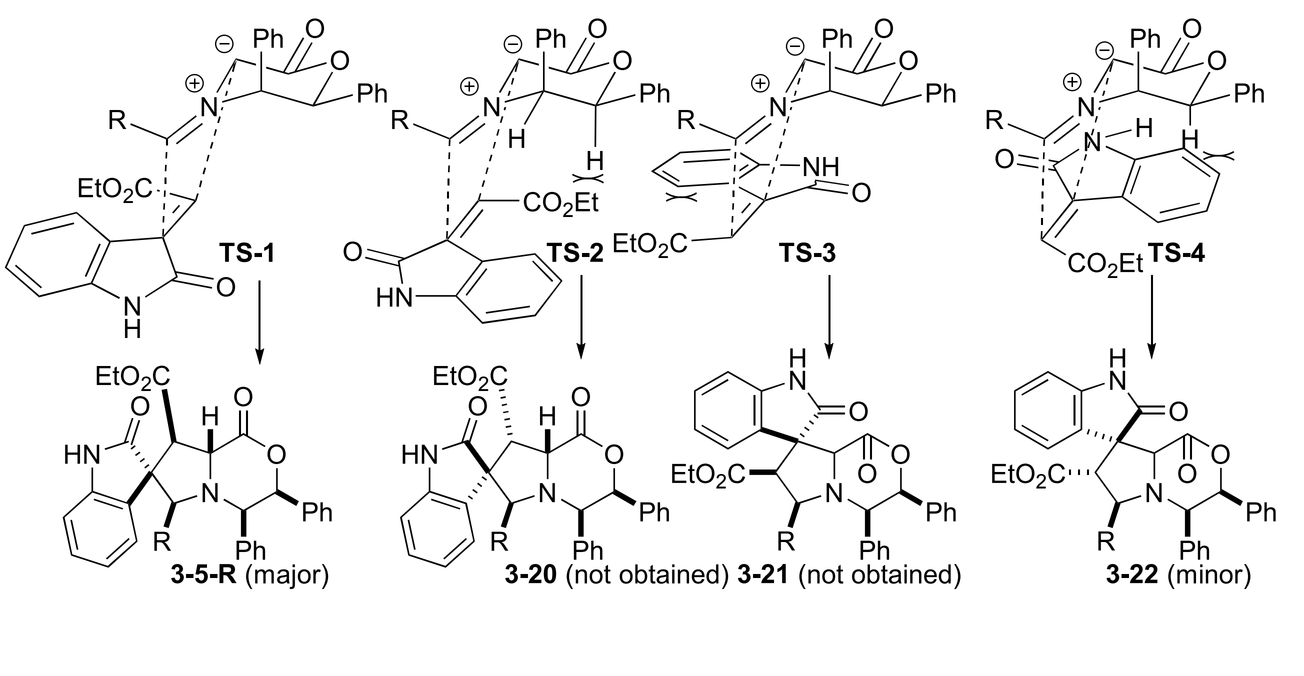
stereoselectivity of 1,3-dipolar cycloaddition

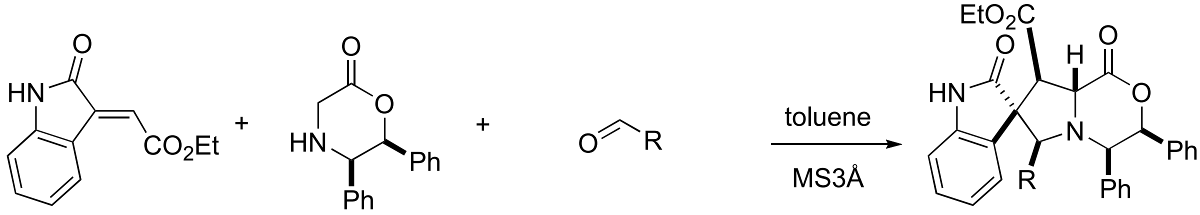
dipolar formation



allylic strain would make (*E*)-ylide

oxindole approaches to iminiumcation from α face to avoid Ph groups.



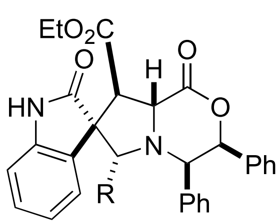


3-1 **3-3** **3-4-R** **3-5-R**

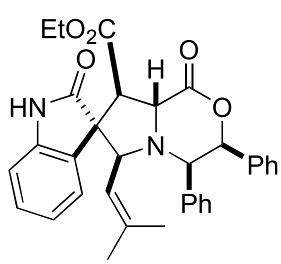
entry	R	temp.	**3-5-R**	**3-22**	**3-23**
1[a)]	H	reflux	28	11	0
2	$BzOCH_2$	reflux	44	14	0
3	$BzOCH_2$	60 °C	54	8	0
4	*i*-Pr	reflux	43	11	5
5	*i*-Pr	60 °C	74	6	trace
6	*i*-Bu	reflux	84	1	0
7	*i*-Bu	60 °C	86	0	0
8[b)]	$(Me)_2(OMe)CCH_2$	reflux	29	0	0
9[c)]	$(Me)_2(OMe)CCH_2$	60 °C	82	1	0
10	*p*-MeOPh	reflux	60	0	0

a) **3-21** was obtained (9 %)
b) **3-24** was obtained (59 %)
c) **3-24** was obtained (6 %)

Sebahar, P. R. and Williams, R. M. *Heterocycles*, **2002**, *58*, 563.



3-23 (generate from **3-7-(*Z*)**)



3-24

bulkiness of R dominantly influenced on regioselectivity
→steric repulsion between CO_2Et and R would be dominant.