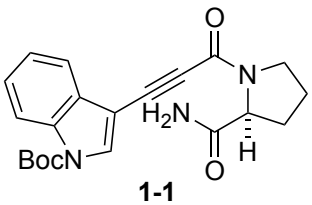
Problem session (3)

2023/04/15 Hiromu Kakizawa

Please provide mechanisms for the following reactions.
Unless otherwise noted, reactions under heated conditions were conducted in an oil bath.

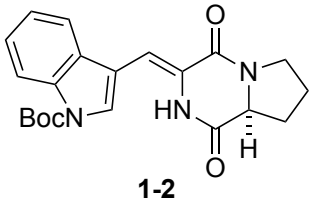
Problem 1



1-1
(optically pure)

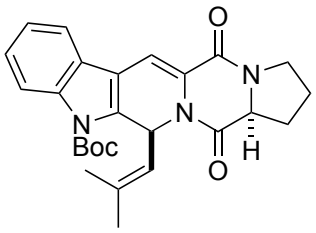
PMe_3 (10 mol%, 1.0 M in THF)
L-glutamic acid (1.0 eq), toluene/DMF (6/1, 0.090 M)
60 ºC, 81% yield, 91% ee*

*after recrystallization: 70% yield, >99% ee



1-2
+
diastereomer **1-2'**
(12%, ee was not determined)

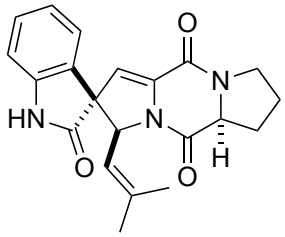
3 steps



1-3

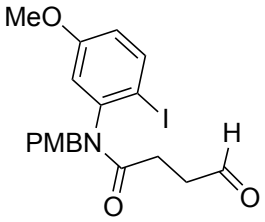
1. OsO_4 (2.7 mol%, 2.0% in H_2O)
   N-methylmorpholine-*N*-oxide (1.5 eq)
   THF/*t*-BuOH/H_2O (4/1/1, 0.040 M), 35 ºC, 80%
2. EtOH (0.028 M), 135 ºC**, 88%

**The reaction was conducted in a microwave reactor and in a sealed flask.



1-4
spirotryprostatin B

Problem 2

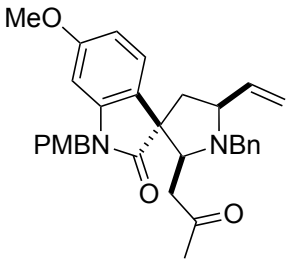


2-1

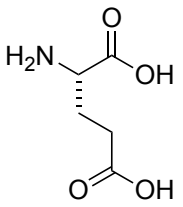
1. **A** (2.0 eq), $Ti(OEt)_4$ (2.0 eq), THF (0.40 M), 75 ºC, 90%
2. vinylmagnesium bromide (1.3 eq, 1.0 M in THF)
   CH_2Cl_2 (0.13 M), – 78 ºC, 75%
3. BnBr (1.2 eq), NaH (2.0 eq), THF (0.19 M), 0 ºC to rt, 95%
4. CuI (10 mol%), $LiN(TMS)_2$ (2.0 eq, 1.0 M in THF), 70 ºC;
   B (2.0 eq), 0 ºC to rt, **2-2a**: 60%, **2-2b**: 20%

2-2a, **2-2b**
two diastereomers

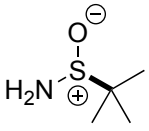
1 M aq. HCl (1.2 eq), DMSO (0.060 M), rt
from **2-2a**: 59%, from **2-2b**: 55%



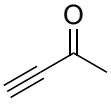
2-3



L-glutamic acid



A



B

Problem session (3) -answer-

2023/04/15 Hiromu Kakizawa

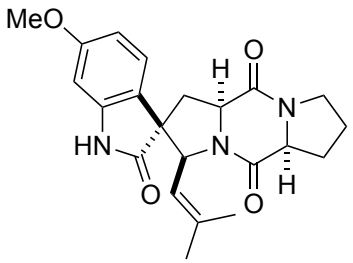
Topic: Total synthesis of spirotryprostatins

1. Introduction

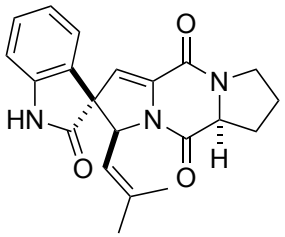
isolation: fermentation broth of *Aspergillus fumigatus*

bioactivity: cell cycle inhibitors in G2/M phase
spirotryprostatin A: IC_{50} = 197.5 μM
spirotryprostatin B: IC_{50} = 14.0 μM

structural features:
- spiroxyindole (quaternary carbon at indole C3 position)
- diketopiperadine ring
- enamide (spirotryprostatin B)



spirotryprostatin A



spirotryprostatin B

total synthesis:

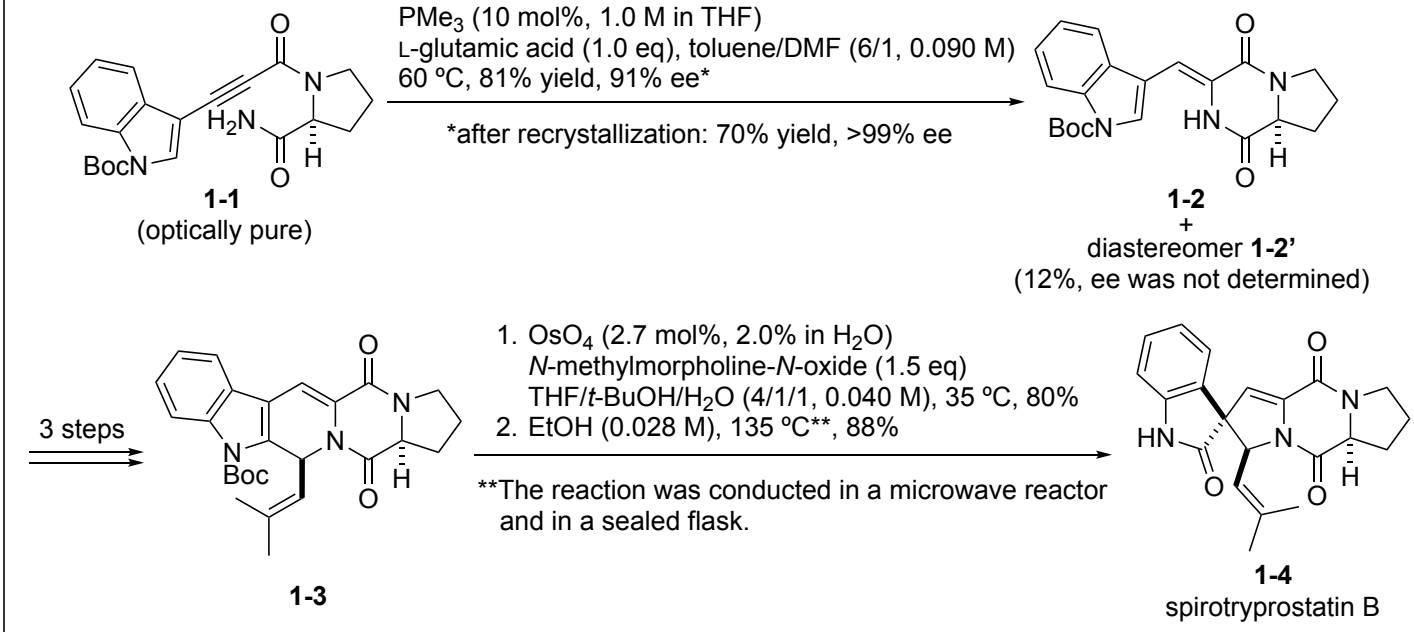
- spirotryprostatin A

Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147− 2155.
Onishi, T.; Sebahar, P. R.; Williams, R. M. *Tetrahedron* **2004**, *60*, 9503−9515.
Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 4249−4251.
Kitahara, K.; Shimokawa, J.; Fukuyama, T. *Chem. Sci.* **2014**, *5*, 904−907.
Xi, Y.-K.; Zhang, H. B.; Li, R.-X.; Kang, S.-Y.; Li, J.; Li, Y. *Chem. Eur. J.* **2019**, *25*, 3005−3009.
Peng, T.; Liu, T.; Zhao, J.; Dong, J.; Zhao, Y.; Yang, Y.; Yan, X.; Xu, W.; Shen, X. *J. Org. Chem.* **2022**, *87*, 16743. (problem 2)

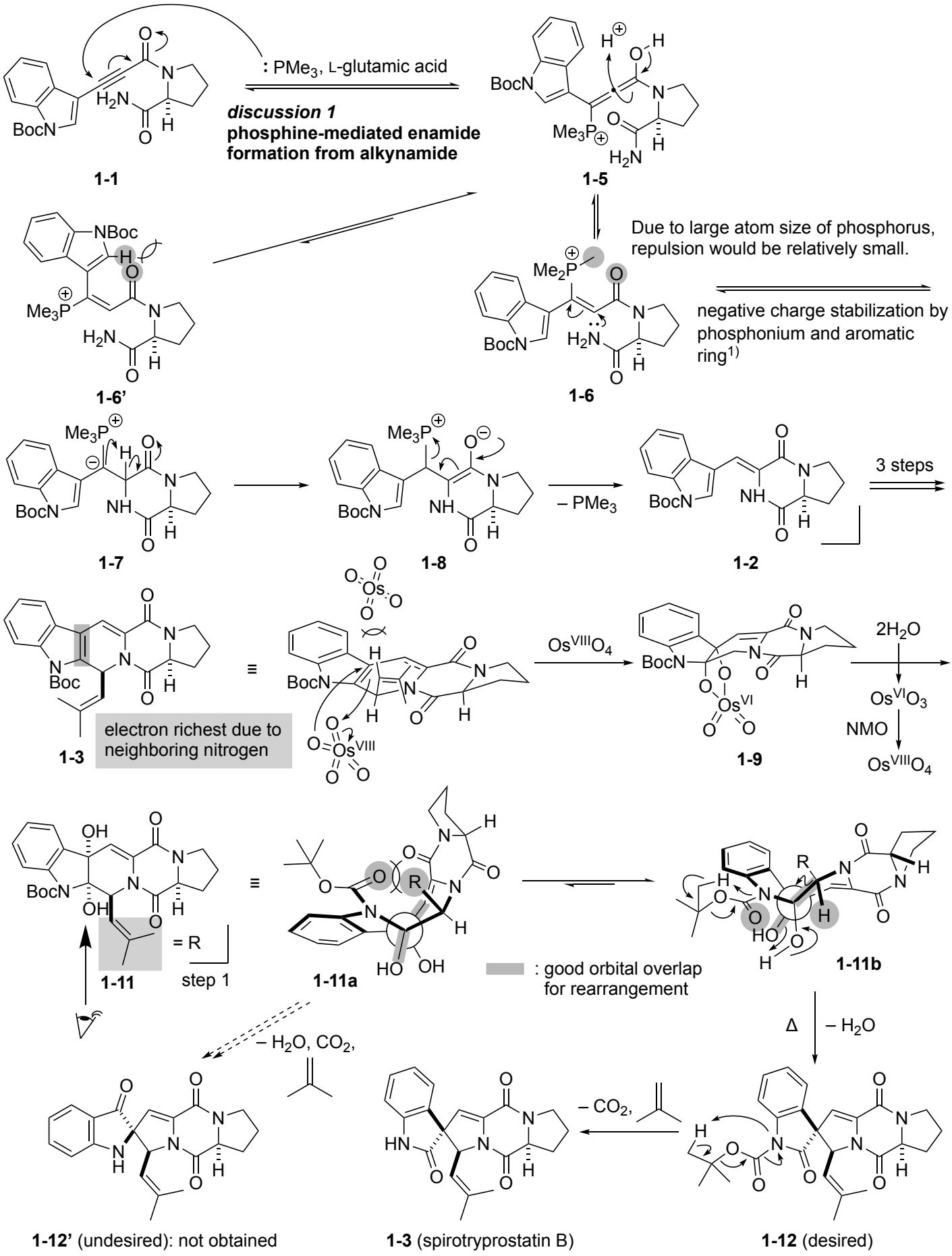
- spirotryprostatin B (many works, only five of them are shown)

Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694−696.
Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5357−5360.
Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505−11515.
Trost, B. M.; Stiles, D. T. *Org. Lett.* **2007**, *9*, 2763−2766.
Xi, Y.-K.; Zhang, H. B.; Li, R.-X.; Kang, S.-Y.; Li, J.; Li, Y. *Chem. Eur. J.* **2019**, *25*, 3005− 3009. (problem 1)

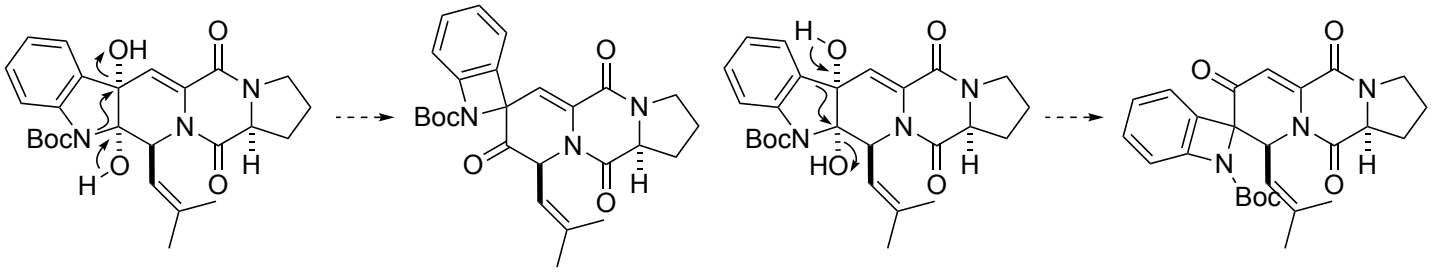
2. Problem 1 - Total synthesis of spirotryprostatin B by Li's group



Xi, Y.-K.; Zhang, H. B.; Li, R.-X.; Kang, S.-Y.; Li, J.; Li, Y. *Chem. Eur. J.* **2019**, *25*, 3005− 3009.


: PMe3, L-glutamic acid
discussion 1
phosphine-mediated enamide formation from alkynamide
1-1
1-5
Due to large atom size of phosphorus, repulsion would be relatively small.
negative charge stabilization by phosphonium and aromatic ring1)
1-6'
1-6
1-7
1-8
– PMe3
1-2
3 steps
1-3
electron richest due to neighboring nitrogen
OsVIIIO4
1-9
2H2O
OsVIO3
NMO
OsVIIIO4
1-11
= R
step 1
1-11a
: good orbital overlap for rearrangement
1-11b
Δ
– H2O
– H2O, CO2,
– CO2,
1-12' (undesired): not obtained
1-3 (spirotryprostatin B)
1-12 (desired)

Other pathways proceed very slowly because of the resultant 4-membered ring formation.

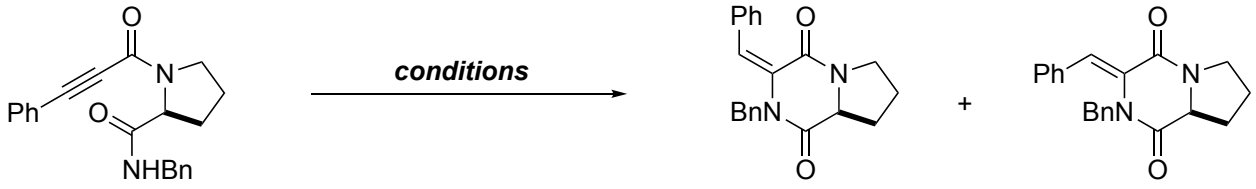


1-11 **1-13** **1-11** **1-14**

***discussion 1*: phosphine-mediated enamide formation from alkynamide**

role of L-Glu

In a reaction with another substrate, L-glutamate was found to be essential for efficient enamide formation.

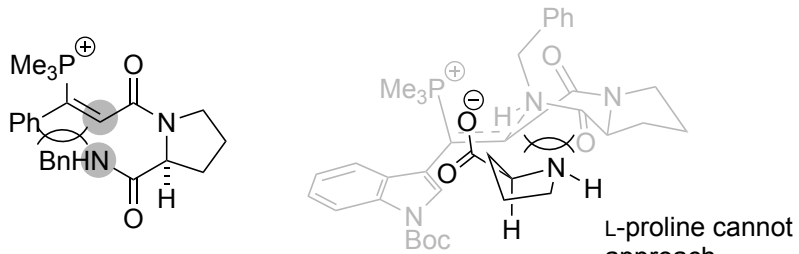


d1-1 ***conditions*** **d1-2*E*** + **d1-2*Z***

entry	***conditions***	yield of **d1-2*E*** + **d1-2*Z*** (ratio *E*/*Z*)
1	PMe_3 (10 mol%), **NaOAc** (50 mol%), **HOAc** (50 mol%) toluene*, 105 ºC	33% (6/1)
2	PMe_3 (10 mol%), **L-proline***, toluene*, 100 ºC	33% (7/1)
3	PMe_3 (10 mol%), **sodium L-glutamate*** toluene/DMF*, 100 ºC	92% (10/1)
4	PMe_3 (10 mol%), **L-glutamic acid** (1.0 eq) toluene/DMF (6/1, 0.075 M), 80 ºC	93% (10/1)

* Equivalent or concentration was not mentioned (L-proline/sodium L-glutamate: probably 50-100 mol%).

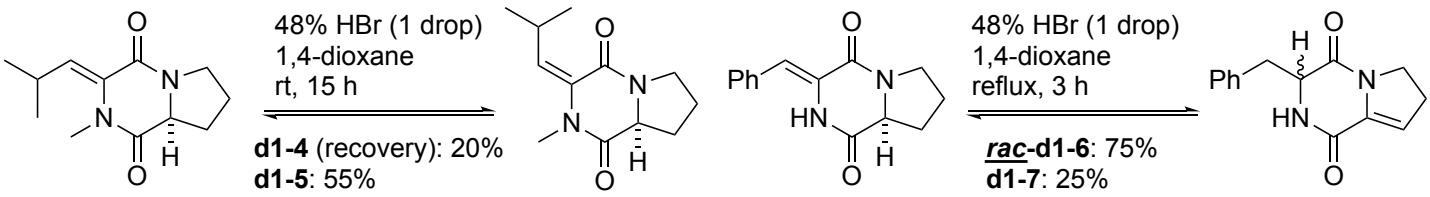
L-glutamic acid possibly works as a molecular bridge to stabilize the transition state, as well as a proton donor/acceptor. Without any additive or with the other additives, the transition state would not be stable enough for reaction progress.



d1-3 **d1-3-Pro** L-proline cannot approach. **d1-3-Glu**

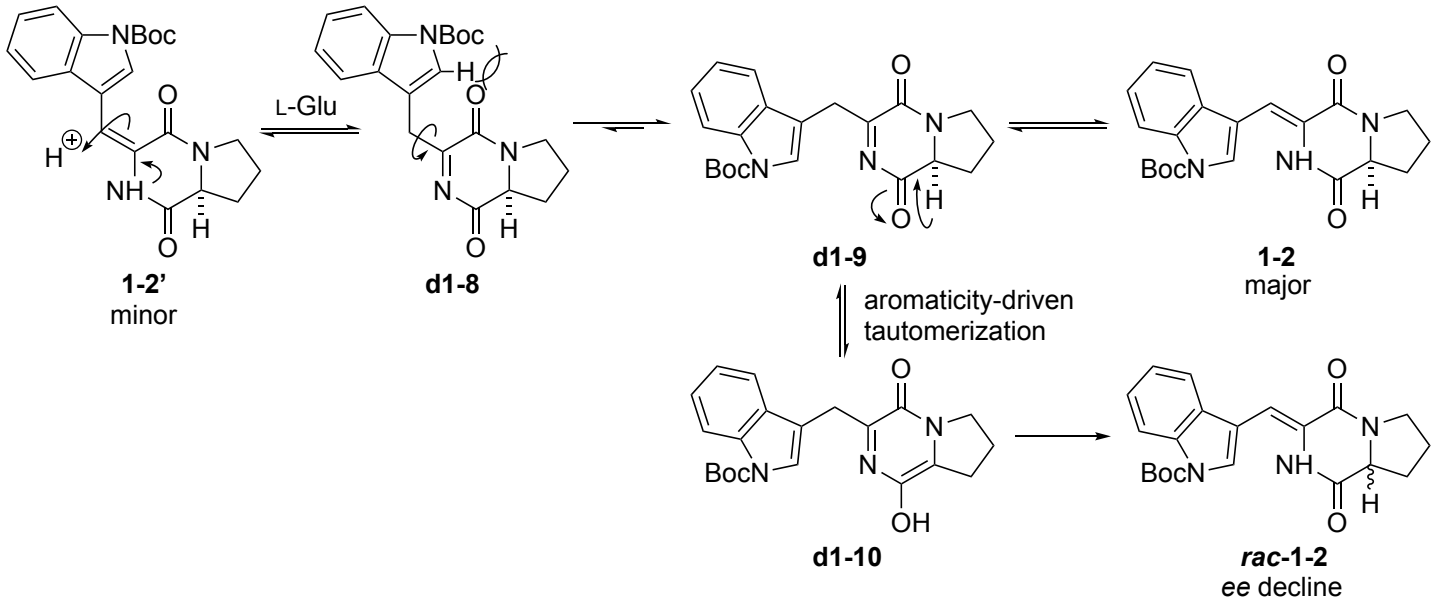
stereoselectivity

Under acidic condition, 3-alkylidene-2,5-piperazinedione structure readily isomerizes via tautomerization. experimental results[2)]:

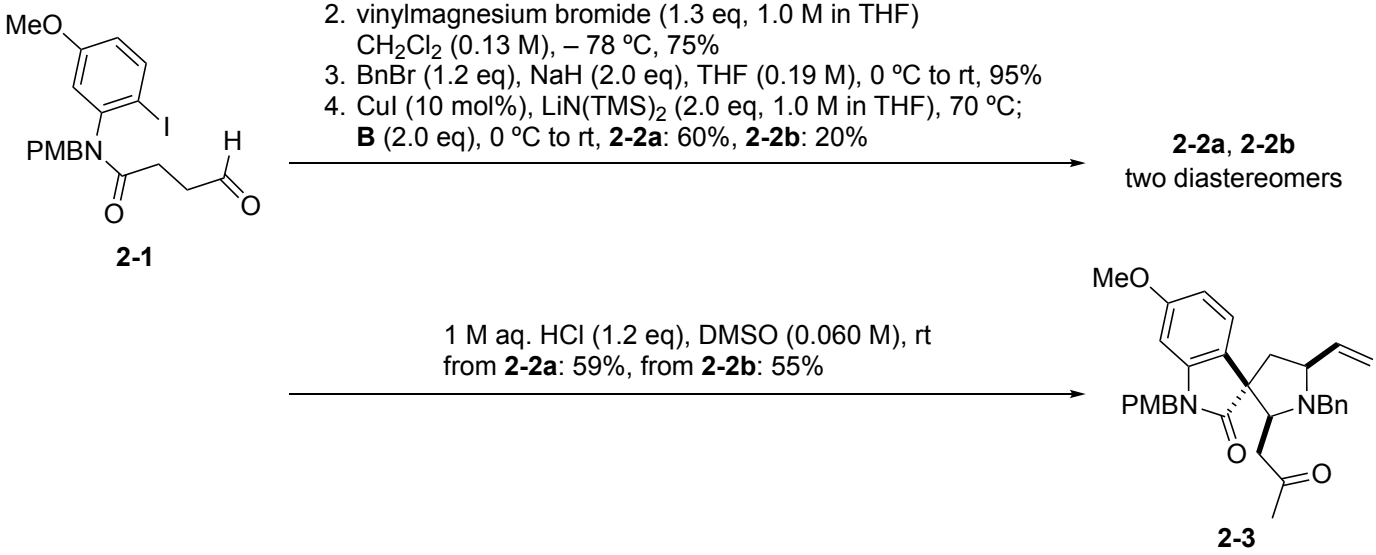


d1-4 **d1-5**: 55% **d1-5** **d1-6** ***rac*-d1-6**: 75% **d1-7**: 25% **d1-7**

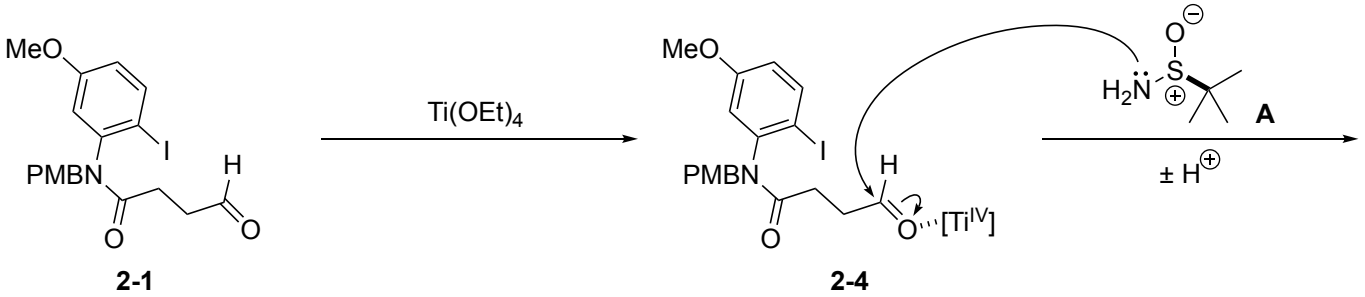
The diastereoselectivity of **1-2**/**1-2'** and partial epimerization of **1-2** probably reflects the thermodynamic stability.

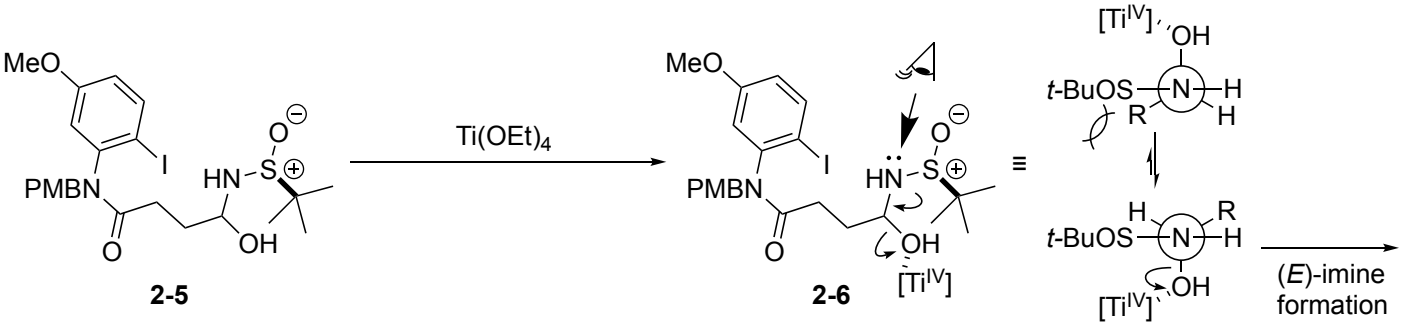


3. Problem 2-Total synthesis of spirotryprostatin A by Shen's group

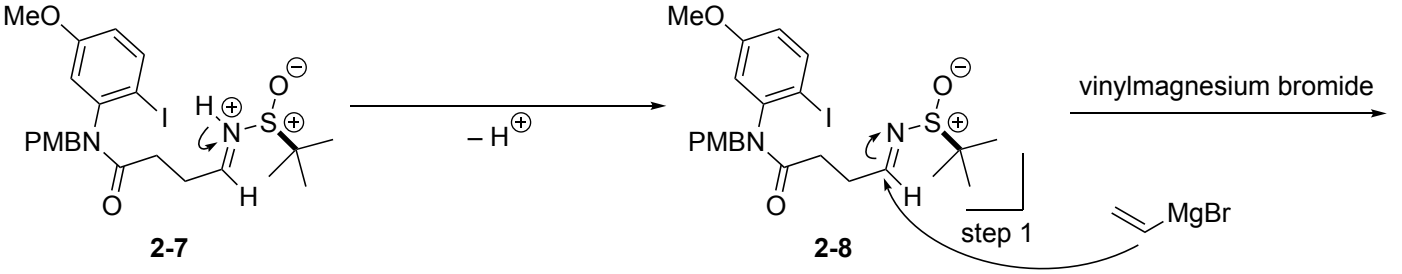


Peng, T.; Liu, T.; Zhao, J.; Dong, J.; Zhao, Y.; Yang, Y.; Yan, X.; Xu, W.; Shen, X. *J. Org. Chem.* **2022**, *87*, 16743.





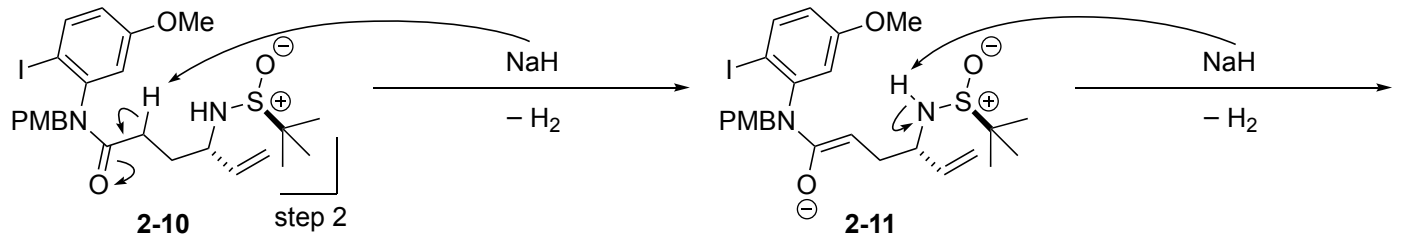
2-5 **2-6**



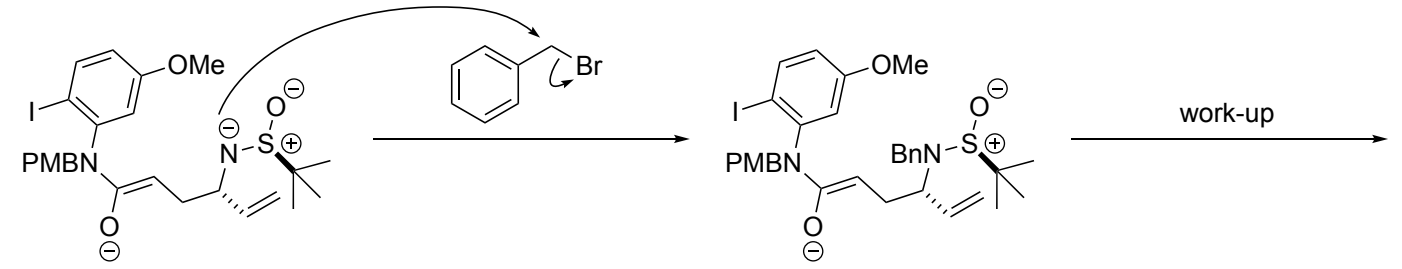
2-7 **2-8**

$Ti(OEt)_4$ worked as a drying agent as well as a Lewis acid[3], so more than catalytic amount of $Ti(OEt)_4$ was needed.

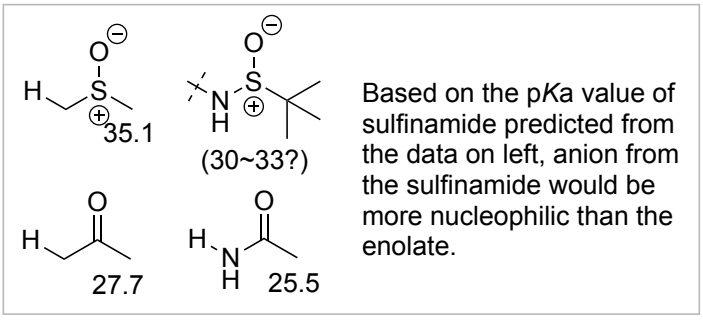
2-8TS-A unstable **2-8TS-B** **2-9**

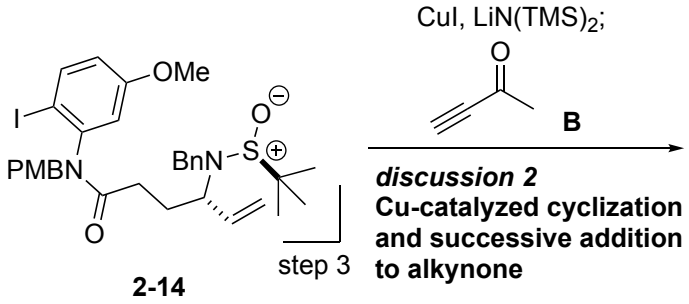


2-10 **2-11**



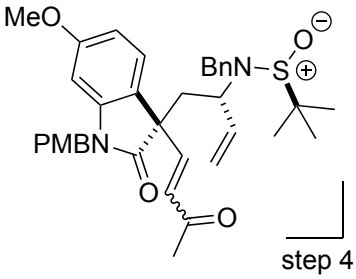
2-12 **2-13**



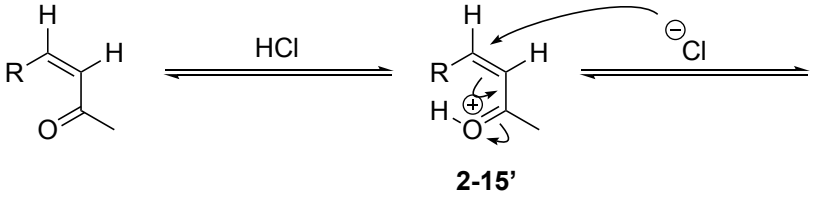


2-14

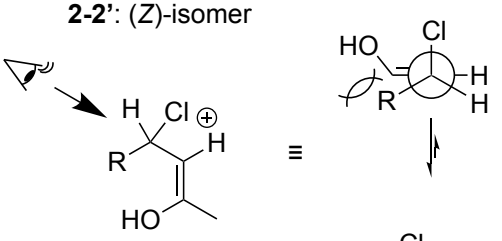
discussion 2
Cu-catalyzed cyclization and successive addition to alkynone



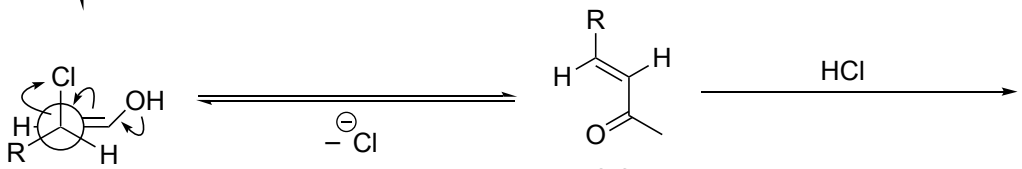
2-2: (*E*)-isomer
2-2': (*Z*)-isomer



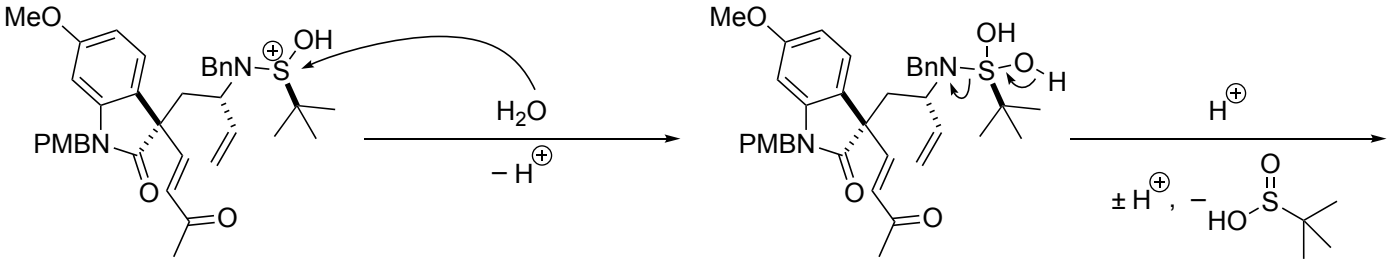
2-15'



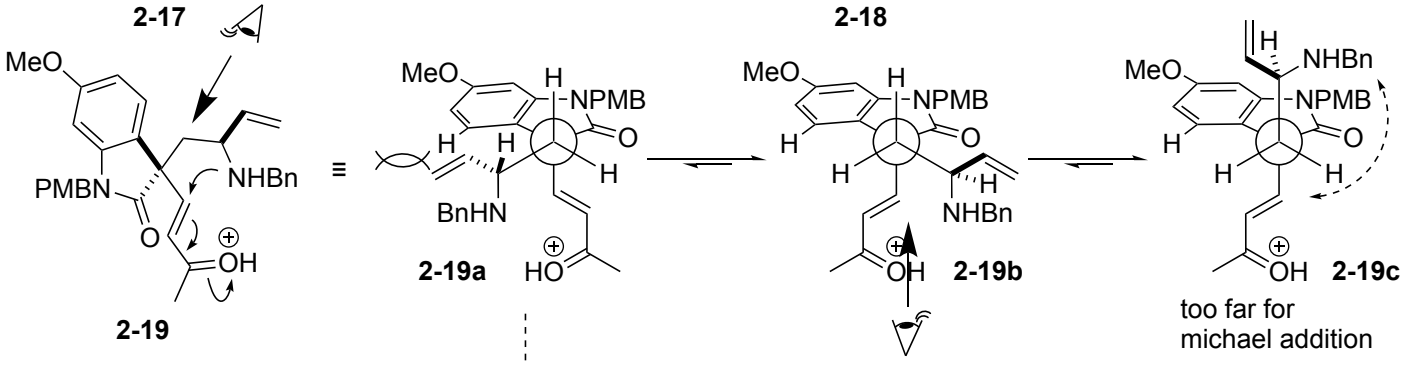
2-2' would isomerize to thermodinamically more stable **2-2** under the reaction condition.



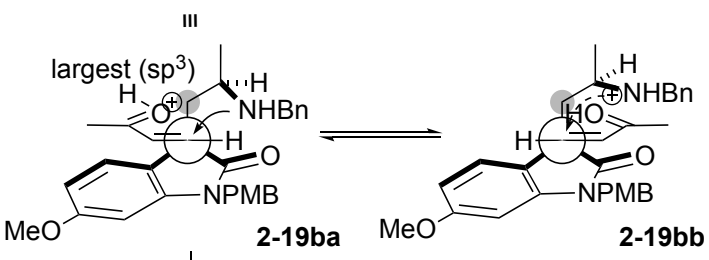
2-2



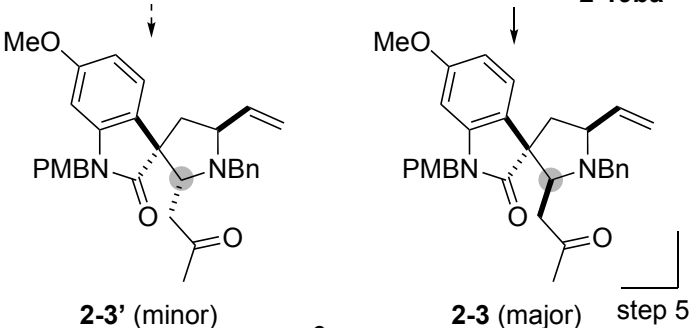
2-17 **2-18**



too far for michael addition

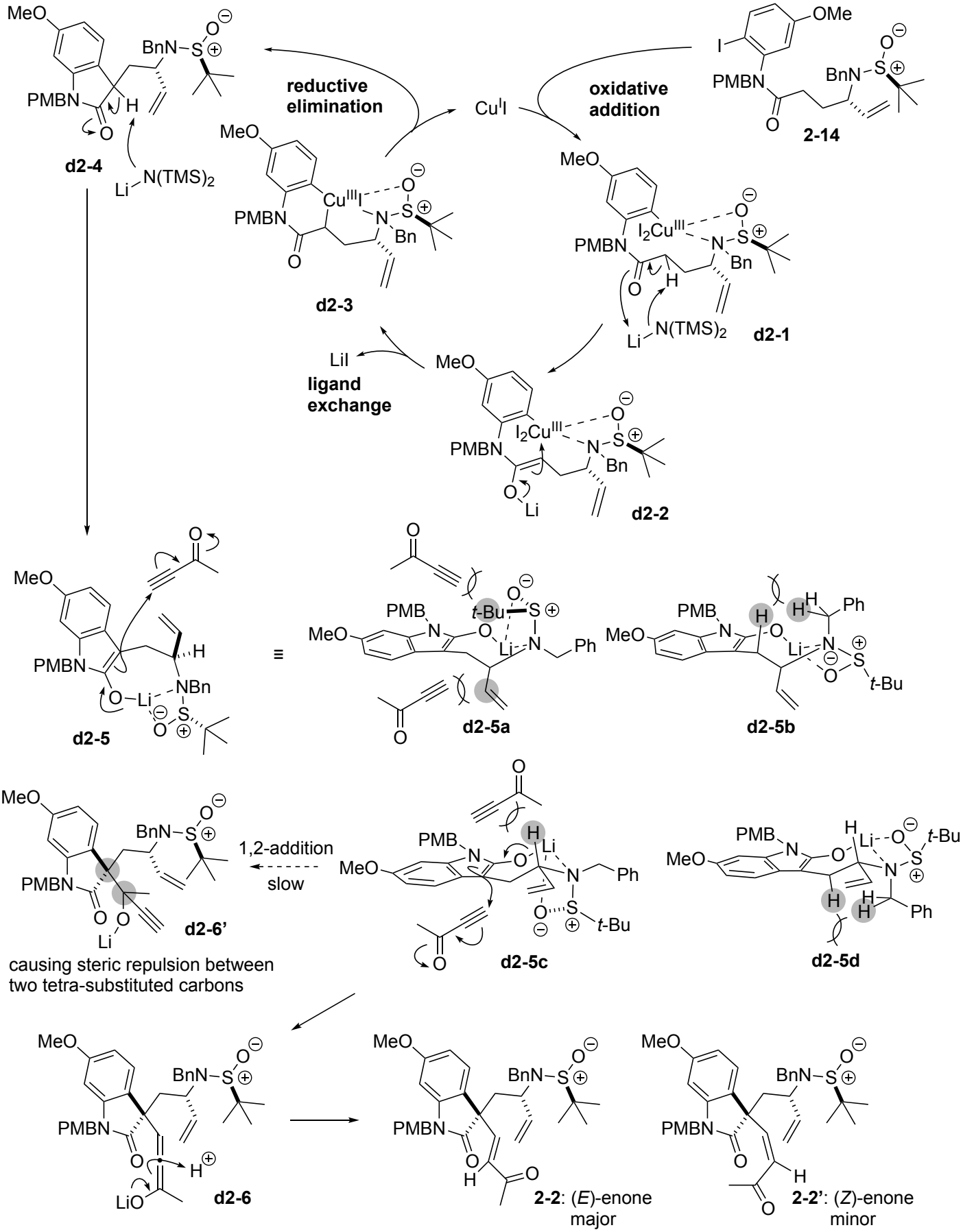


Amine cannot approach in Bürgi-Dunitz angle.



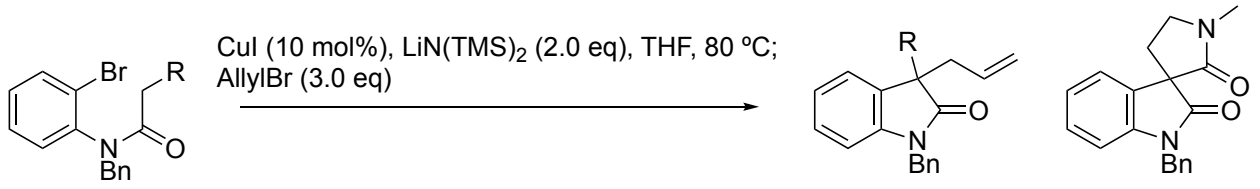
***discussion 2*: Cu-catalyzed cyclization and successive addition to alkynone**

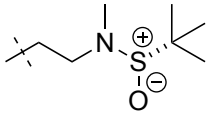
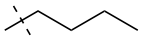
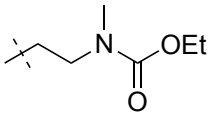
reaction mechanisms and stereoselectivity



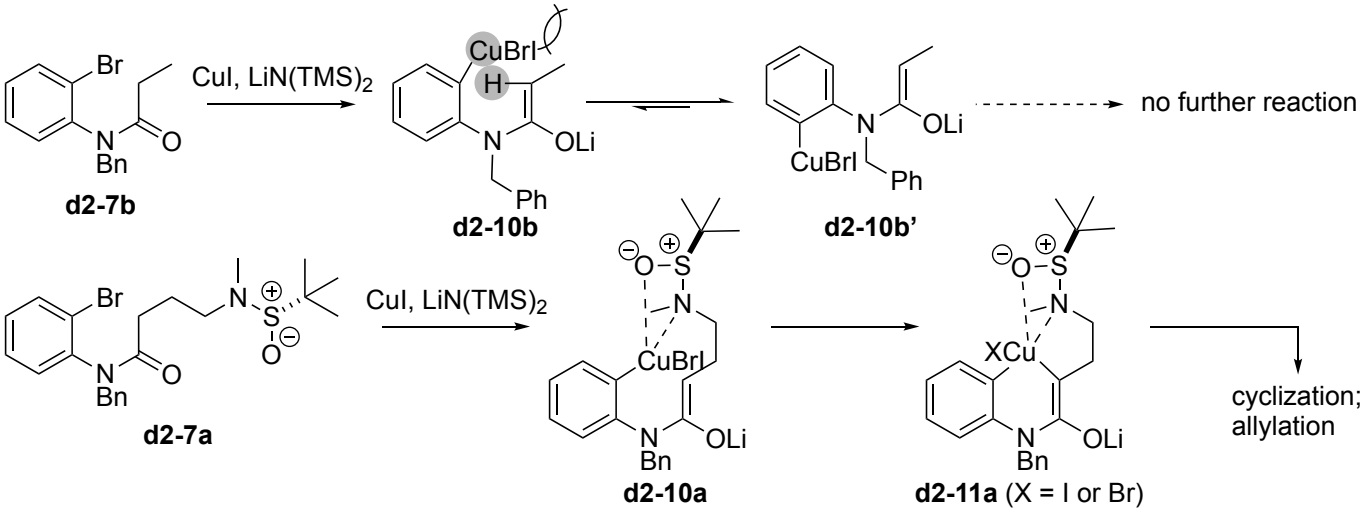
chelation effect of sulfinamide

Sulfinamide (or chelating moiety) was essential for desired copper-catalyzed reaction[5].



	R	result
d2-7a:		**d2-8a**: 72%
d2-7b:		**d2-8b**: not obtained
d2-7c:		**d2-8c**: not obtained
d2-7d:	 *AllylBr was not added.	**d2-9d**: 90% (generated via intramolecular addition to carbamate)

Chelating moiety would be necessary for the proper orientation of Cu^{III}-inserted bromoaryl ring.



references

1) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595.
2) Jin, S.; Wessig, P.; Liebscher, J. *Eur. J. Org. Chem.* **2000**, 1993.
3) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P. Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.
4) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.
5) Zhou, Y.; Xi, Y.; Zhao, J.; Sheng, X.; Zhang, S.; Zhang, H. *Org. Lett.* **2012**, *14*, 3116.