### **Problem Session (1)**

Please provide the reaction mechanisms.



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# Problem Session (1) - Answer-

Topic: Construction of *cis*-hydrodibenzofuran framework and additional cycle



- 1) Balunas, M. J.; Kinghorn, A. D. Life Sciences, 2005, 78, 431–441
- 2) Patterson, C. World Alzheimer Report, Alzheimer's Disease International, 2018.
- 3) Huxtable, R. J.; Schwarz, S. K. W. Mol. Interv., 2001, 1, 189–191

4) World Health Organization Model List of Essential Medicine, 21th list, 2019

#### **Retrosynthetic analysis**

Galanthamine (by Xu's group, 2020, problem 1)



Zhang, Y.; Shen, S.; Fang, H.; Xu, T. Org. Lett. 2020, 22, 1244–1248

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Morphine (by Tu's group, 2019, problem 2)



Zhang, Y.; Shen, S.; Fang, H.; Xu, T. Org. Lett. 2020, 22, 1244–1248 \_\_\_\_\_

![](_page_3_Figure_0.jpeg)

![](_page_3_Figure_1.jpeg)

1-15

![](_page_4_Figure_0.jpeg)

1-27

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## Rhodium catalyzed "cut and sew" reaction<sup>6),7)</sup> **Discussion 1**: Stereoselectivity in oxidative addition pathway

![](_page_5_Figure_1.jpeg)

toluene)//M06/LANL2DZ-6-31G(d) level.

DFT calculation showed cleavage of C1-C8 bond kinetically favored compared with other 2 transition state. Latter 2 transition state is unfavored because of steric repulsion from rhodium ligands. This calculation also indicate that 1-31 is thermodynamically favored.

![](_page_5_Figure_4.jpeg)

Calculated at the M06/SDD-6-311+G(d,p)(SMD, toluene)//M06/LANL2DZ-6-31G(d) level.

DFT also showed that path a is favored compared with path b.

*Discussion 2:* Regioselectivity and stereoseletivity in migratory insertion 2.1. Regioselectivity in migratory insertion

![](_page_6_Figure_1.jpeg)

In migratory insertion step, olefin and Rh-C bond need to be parrallel and close.

![](_page_6_Figure_3.jpeg)

In order to proceed this reaction, orange marked atoms need to be close. However, conformation of **TS-5** is difficult because oxigen atom and carbonyl carbon atom are on the same plane and there is large rhodium group.

2.2. Stereoselectivity in migratory insertion

![](_page_6_Figure_6.jpeg)

Two diastereomer (1-20 and 1-20') can be produced in this reaction. 1-20 is from 1-19-b, 1-20 is from 1-19-a. In 1-19-b, olefin and Rh-C bond are distant due to the steric repulsion from pink marked hydrogen atom. This implicates conformation of 1-20' is difficult.

Nucleophilic attack of TMSN<sub>3</sub> Another possible pathway:

![](_page_7_Figure_1.jpeg)

In this pathway, TMSN<sub>3</sub> and FeCl<sub>3</sub> reacts first., then nucleophilic attack occurs. Nucleophilic attack may occur from both  $\alpha$  or  $\gamma$  Nitrogen atom, and finally **1-25** will be produced.

![](_page_7_Figure_3.jpeg)

Discussion 3: Regioselectivity in [3+2] cycloaddition

![](_page_7_Figure_5.jpeg)

In [3+2] cycloadditon, concerted process is possible. However, previous work by Maulide's group supports stepwise process.

Previous work by Maulide's group:

![](_page_8_Figure_1.jpeg)

![](_page_8_Figure_2.jpeg)

Maulide and co-workers produced tetrazolium salt from amide through a formal [3+2] cycloaddition. They wondered wheather [3+2] cycloaddition occurs stepwise or concerted.

To address this question, they constructed model system ( $R^1 = Et$ ,  $R^2 = R^3 = Me$ ) and performed quantum chemical study.

DFT caluculation showed that stepwise mechanism is plausible (Figure 1).

They noted that "several attempts to locate a concerted transition state did not lead to any alternative mechanism".

Possible reason to explain calculation result would be that C-N  $\sigma$  bond stabilize transition state.

Figure 1. Computed reaction profile  $(\Delta G_{298,\text{DCM}} \text{ kcal mol}^{-1})$  for the direct synthesis of tetrazoliums from nitrilium ions and azides.

#### Calculated at the RI-MP2/def2-TZVP//B3LYP-D3/6-31+G(d,p) level

Tona, V.; Maryasin, B.; Torre, A.; Sprachmann, J.; Gonzalez, L.; Maulide, N. Org. Lett. 2017, 19, 2662-2665

![](_page_8_Figure_11.jpeg)

Zhang, Q.; Zhng, F.-M.; Zhang, C.-S.; Liu, S.-Z. Tian, J.-M.; Wang, S.-H.; Zhang, X.-M., Tu, Y.-Q. *Nat. Commun.* **2019**, *10*, 2507

![](_page_9_Figure_0.jpeg)

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step 3

![](_page_10_Figure_0.jpeg)

![](_page_10_Figure_1.jpeg)

\* Sudan Red III is used as a marker of ozonolysis completion.

![](_page_10_Figure_3.jpeg)

![](_page_10_Figure_4.jpeg)

2-20'

![](_page_10_Figure_5.jpeg)

![](_page_10_Picture_6.jpeg)

![](_page_10_Figure_7.jpeg)

![](_page_10_Figure_8.jpeg)

2-20"

![](_page_10_Figure_9.jpeg)

![](_page_10_Figure_10.jpeg)

![](_page_10_Figure_11.jpeg)

![](_page_11_Figure_0.jpeg)

Discussion 1: stereoselectivity

![](_page_11_Figure_2.jpeg)

2-5-(E) is more stable comformation, so this time, we discuss stereoselectivity from 2-5-(E), not 2-5-(Z).

![](_page_11_Figure_4.jpeg)

![](_page_12_Figure_0.jpeg)

Chiral amine makes **TS-6** most stable transition state. Compared with **TS-6** and **TS-7**, steric repulsion of **TS-7** is larger because  $-(CH_2)_2OBn$  is larger than =CHCOMe. Compared with **TS-6** and **TS-8**, steric repulsion of **TS-8** is lager because pirrolidine structure is larger than hydrogen.

![](_page_12_Figure_2.jpeg)

![](_page_13_Figure_0.jpeg)

TS-10 to TS-13 is unfavored because steric hindrance from large TBDPS.