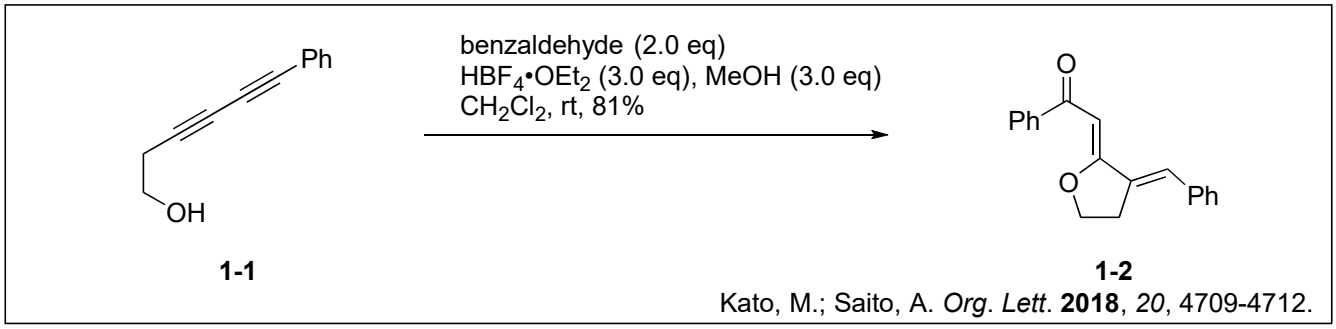
# Problem Session (5) Answer

2025/04/26 Hisahiro Morozumi

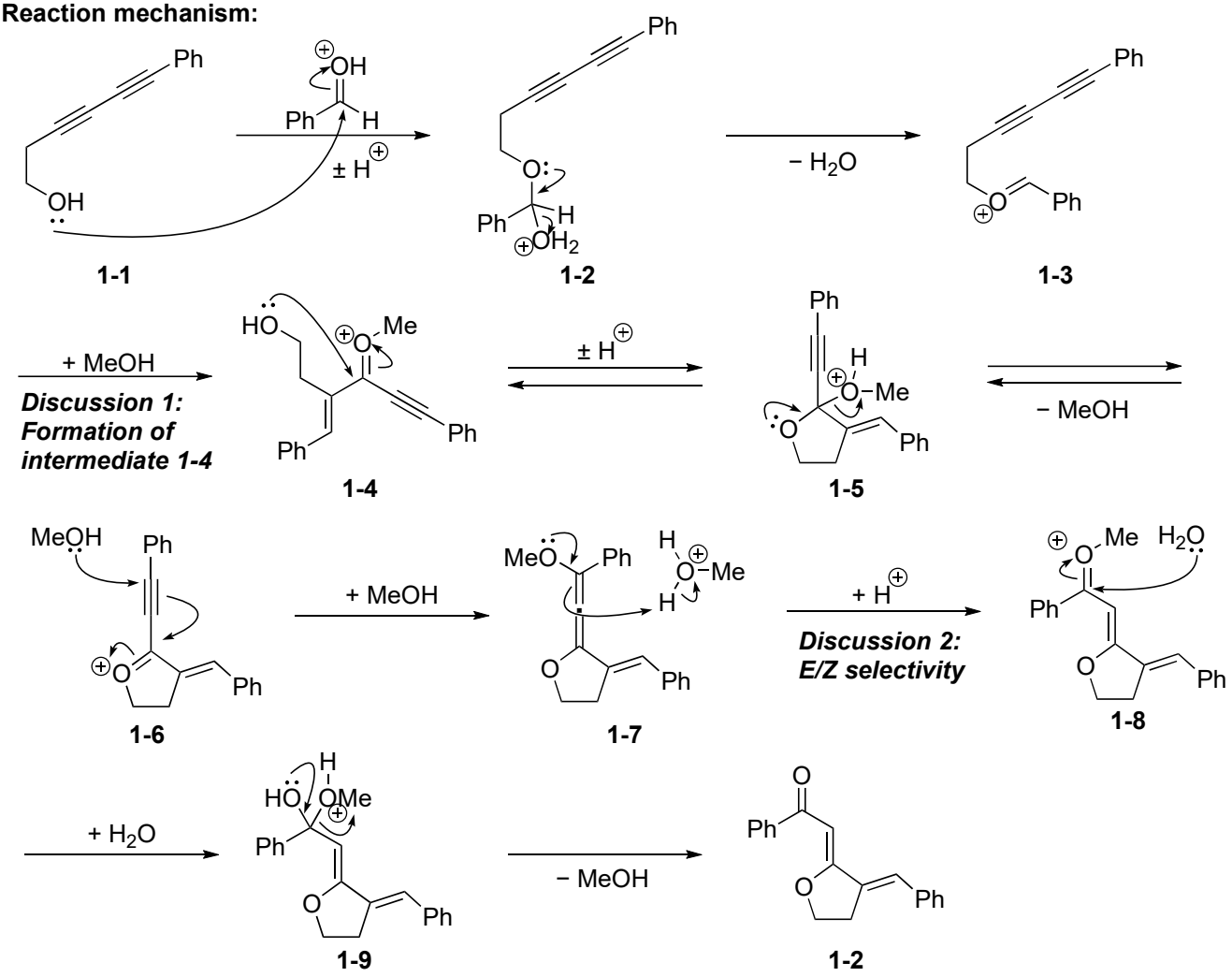
**Topic:** Tandem cyclization under acidic condition




**1-1** **1-2**

Kato, M.; Saito, A. *Org. Lett.* **2018**, *20*, 4709-4712.

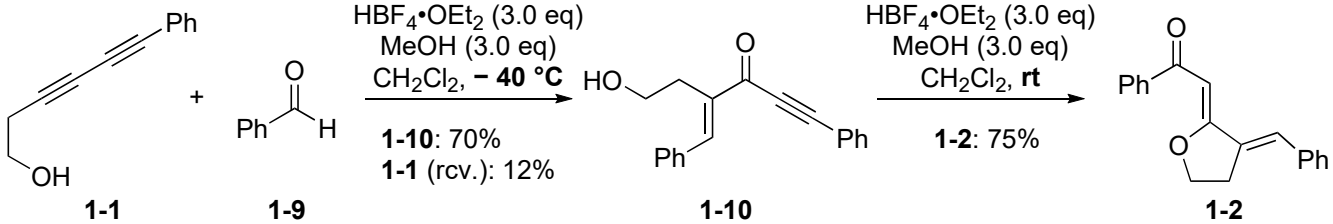
**Reaction mechanism:**




**1-1** **1-2** **1-3** **1-4** **1-5** **1-6** **1-7** **1-8** **1-9** **1-2**

***Discussion 1: Formation of intermediate 1-4***

1. Control experiments




**1-1** **1-9** **1-10** **1-2**

When the reaction was conducted at − 40 °C using the same substrate and reagents, the formation of **1-10** was confirmed. Subsequently, when the isolated **1-10** was treated with the same reagent at room temperature, the target compound **1-2** was obtained.

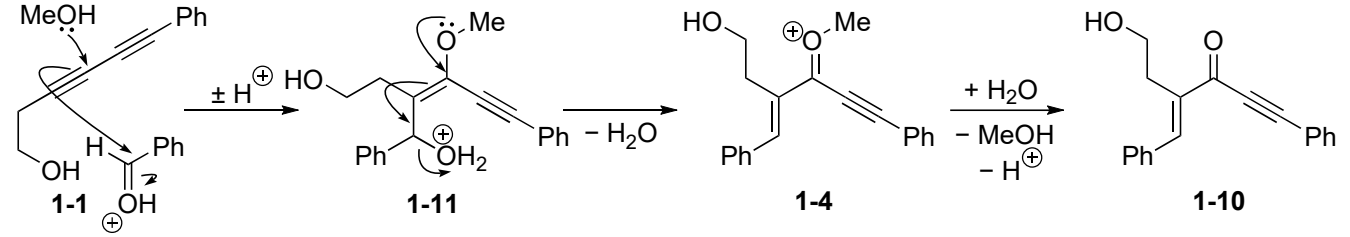
Based on these results, it is suggested that this reaction proceeds via the intermediate **1-10**.

First, I will consider the plausible mechanism of formation of **1-10**.

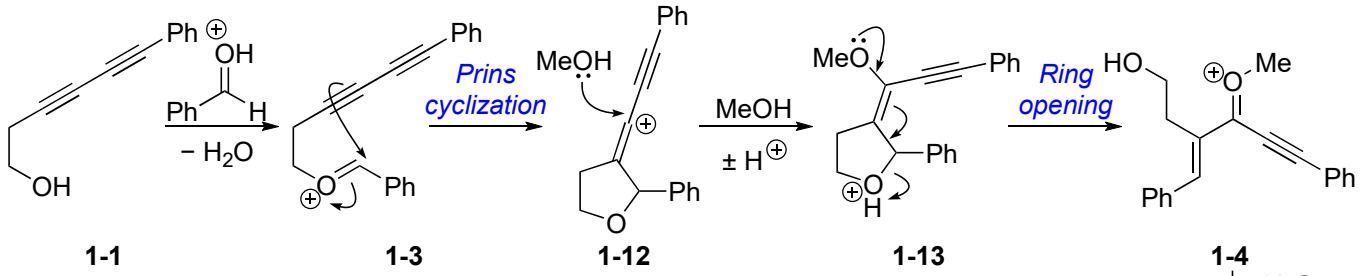
2. Plausible mechanistic pathways of formation of **1-10**

2-1. Plausible mechanistic pathways of formation of **1-10**

<Knoevenagel condensation (path a)>

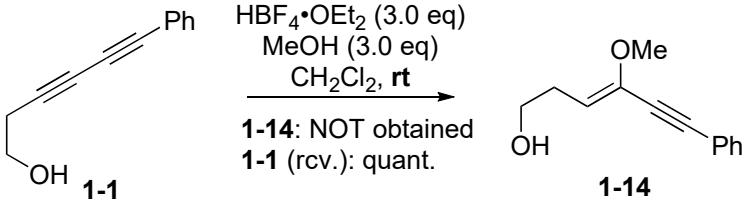



<Prins cyclization followed by ring opening (path b)>




In the path (a), hydroalkoxylation of an unactivated alkyne is required, in addition to an intermolecular reaction with an aldehyde. Therefore, this pathway is considered unlikely to proceed easily.

2-2. Experimental results by authors




In fact, even when the same reagent was applied in the absence of an aldehyde, **1-14**, which would be formed through hydroalkoxylation had not been obtained.

2-3. Prins cyclization

2-3-1. Experimental results with similar substrates[1)]

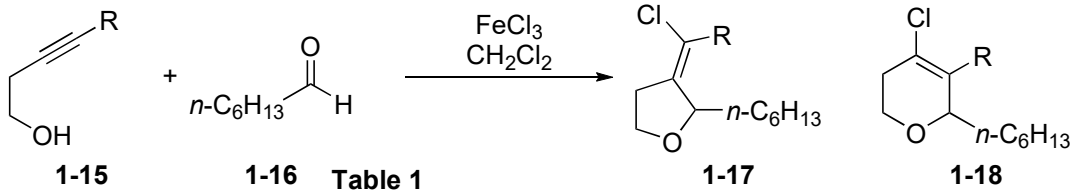
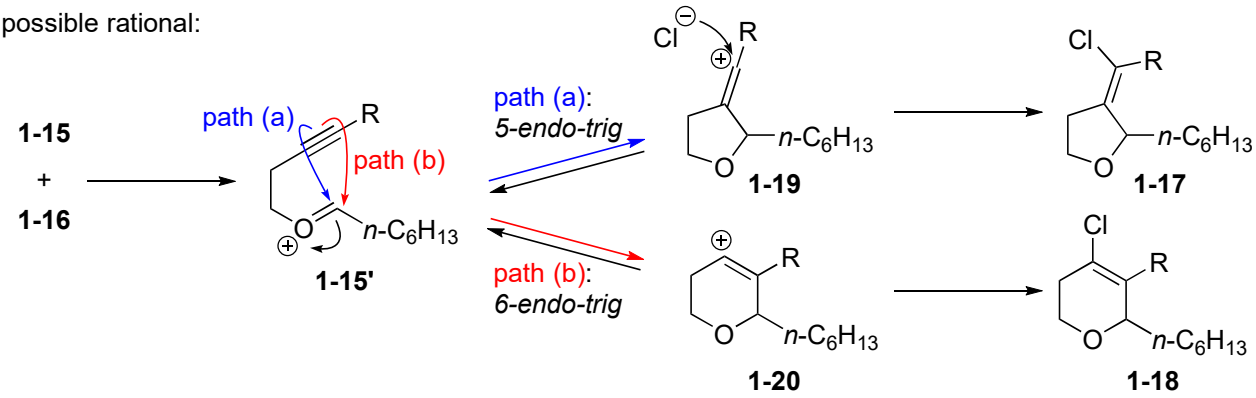



**Table 1**

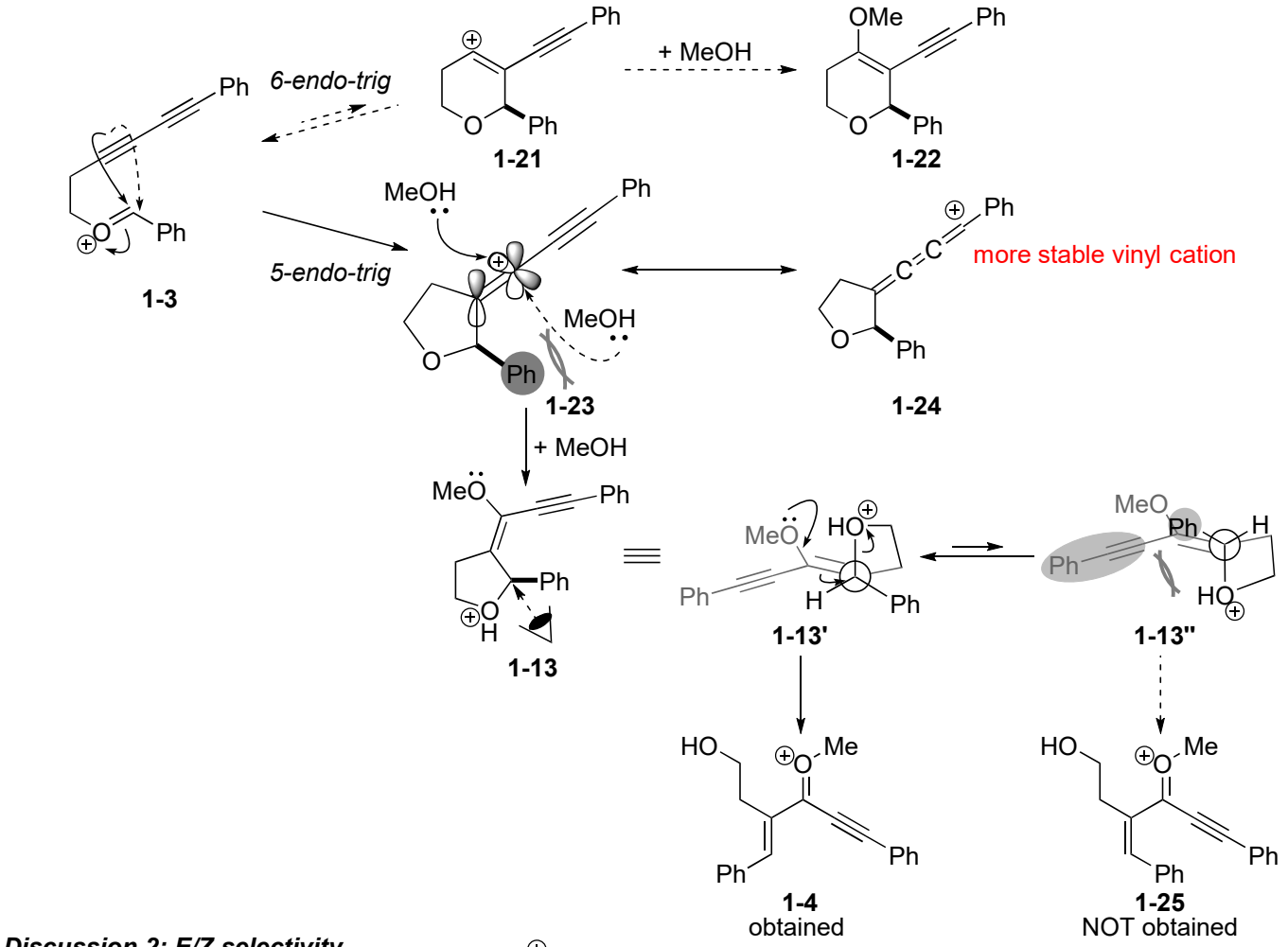
| entry | R | **1-17** : **1-18** |
|---|---|---|
| 1 | H | 1 : 100 |
| 2 | Me | 65 : 35 |

possible rational:

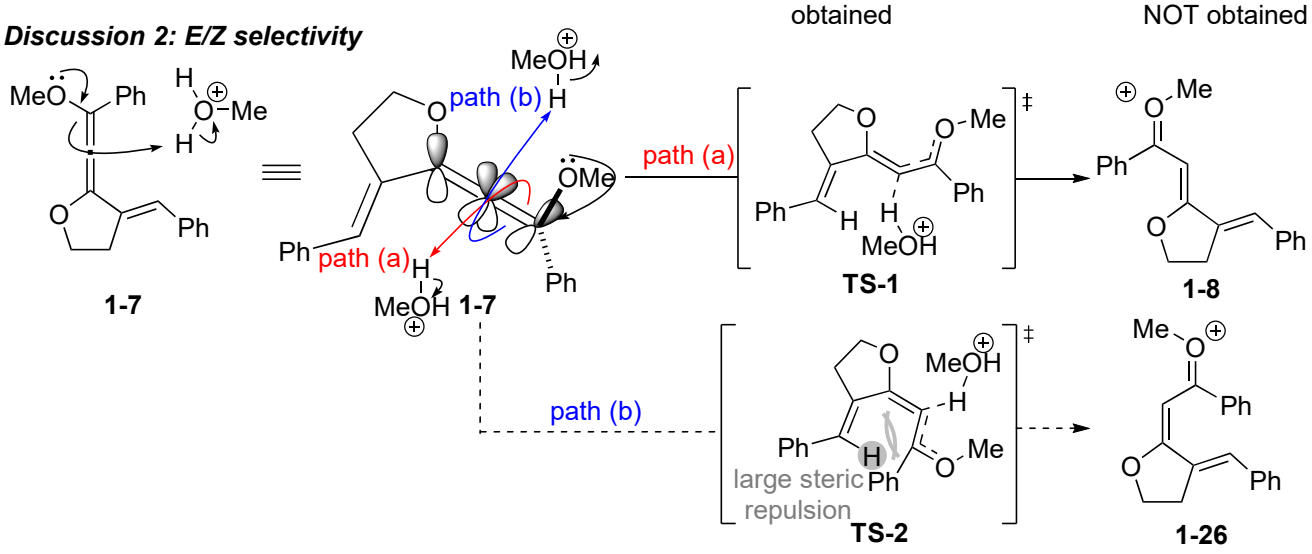


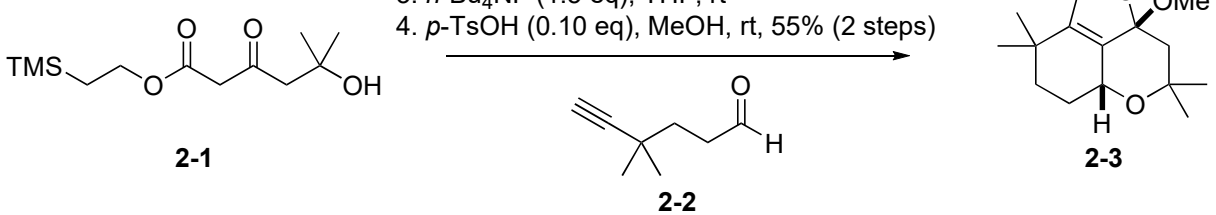

According to the Baldwin's rules[2)], *6-endo-dig* path (b) is more favorable than *5-endo-dig* path (a). However, when R is methyl group, the vinyl cation is stabilized by hyperconjugation compared to when R is a hydrogen. Therefore, **1-17** was also formed.

2-3-2. Reaction mechanism and stereoselectivity of Prins cyclization (this problem)



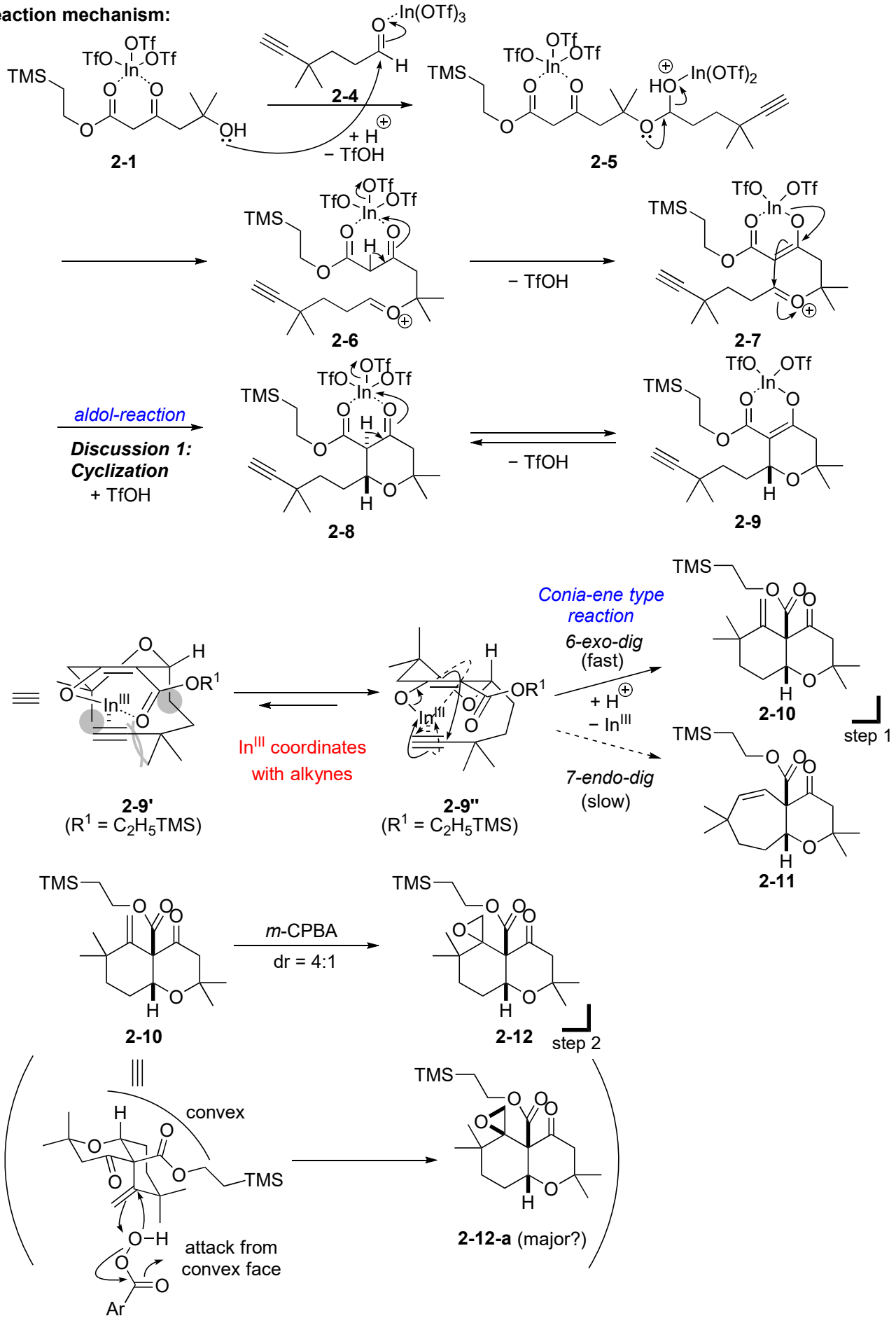

***Discussion 2: E/Z selectivity***



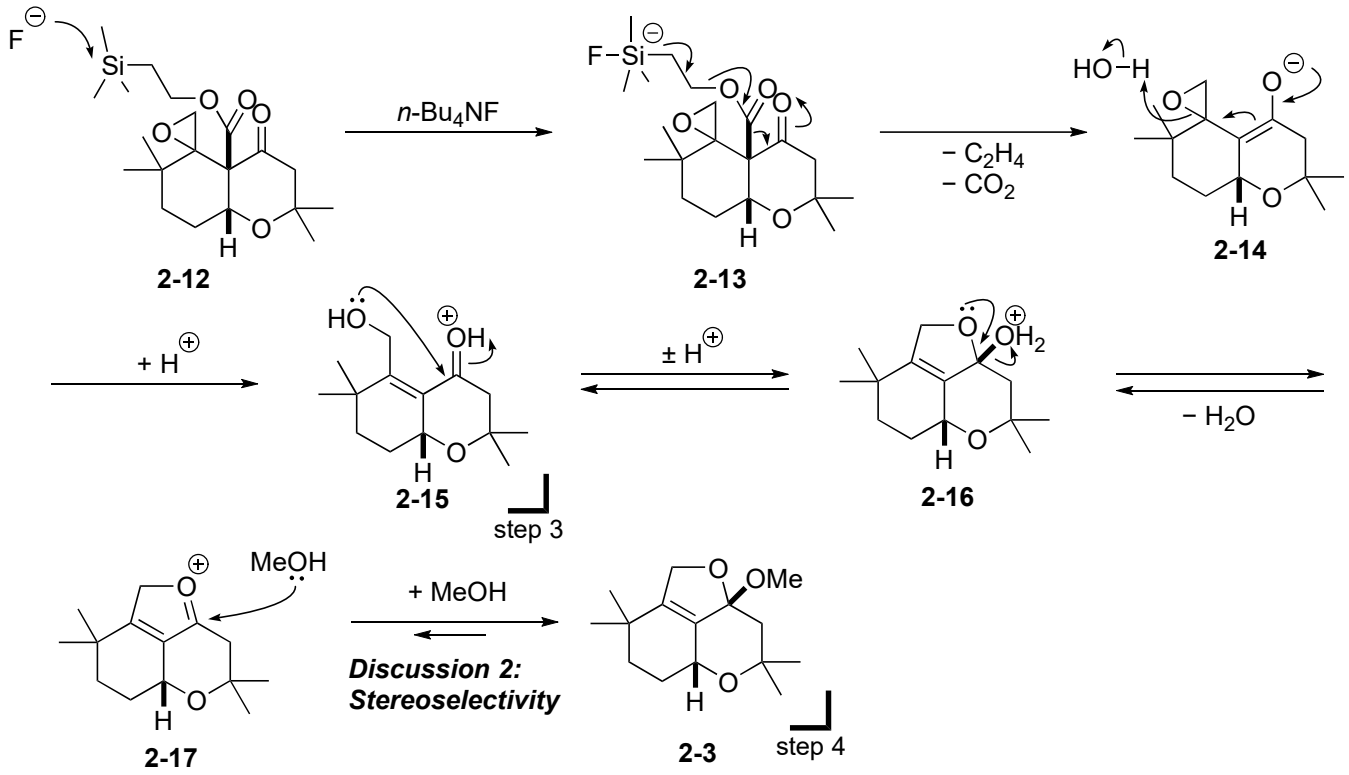




Huang, S. Du, G. Lee, C.-S. *J. Org. Chem*. **2011**, *76*, 6534-6541.

**Reaction mechanism:**

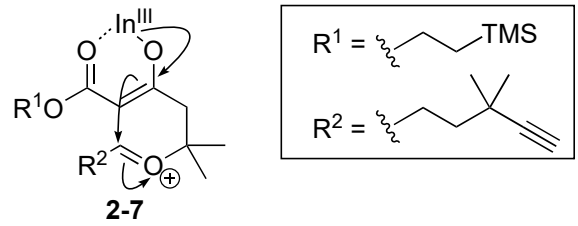



The major diastereomer of product **2-12** has not been reported. However, it is considered that *m*-CPBA approaches from the convex face of **2-10**, leading to **2-12-a** being the major diastereomer.




***Discussion 1: Cyclization***

1. Proposed stereoselectivity



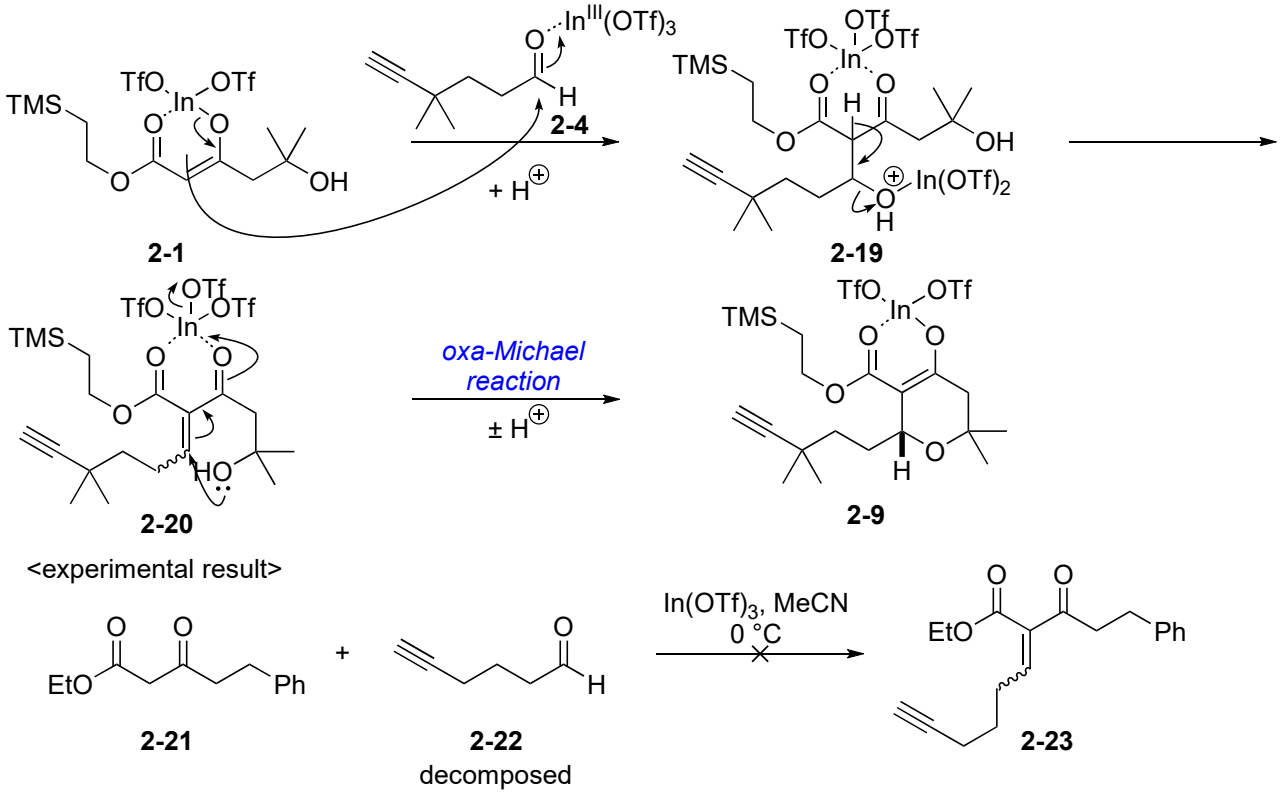

This reaction is considered to proceed via a six-membered transition state. In this case, because $R^1$ and $R^2$ are very bulky, they always adopt an equatorial position in the six-membered transition state.




It is considered that racemic **2-8** is obtained via a chair-like transition state. The enantiomer **2-8** will be considered in this problem.

2. Other possible mechanism

2-1. Knoevenagel condensation followed by oxa-Michael reaction

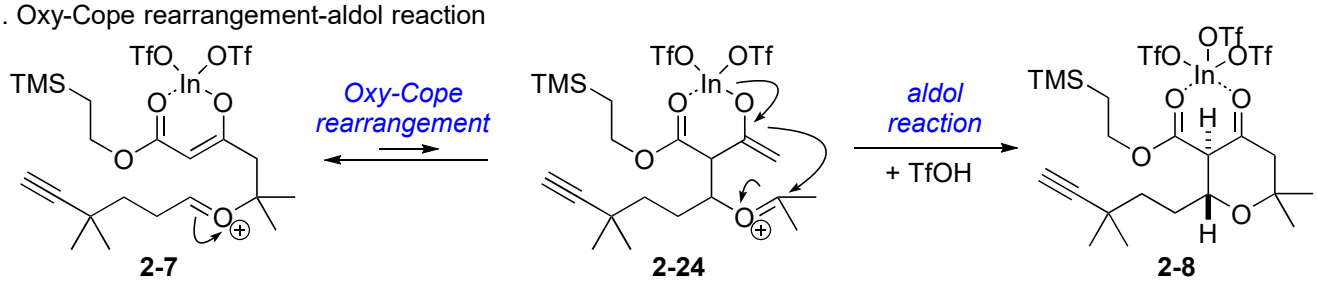



<experimental result>



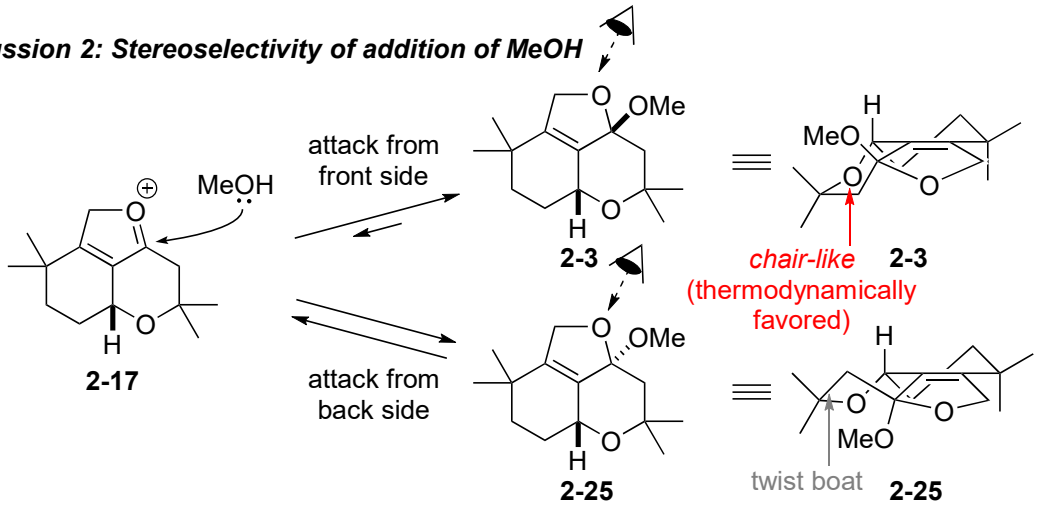

A reaction pathway can also be considered where **2-20** is formed via the Knoevenagel condensation, followed by Michael addition to form **2-8**. However, in control experiments using similar substrates, **2-23**, which would be formed from the condensation of keto ester **2-21** and aldehyde **2-22**, has not been obtained.

2-2. Oxy-Cope rearrangement-aldol reaction




A reaction pathway can also be considered where **2-7** undergoes an oxy-Cope rearrangement to form **2-24**, followed by an aldol reaction to form **2-8**. However, **2-24** has shorter conjugation compared to **2-7**, and thermodynamically, **2-7** is considered to be more stable. Therefore, this pathway less likely to proceed.

***Discussion 2: Stereoselectivity of addition of MeOH***




**References**


1) Miranda, P. O.; Diaz, D. D.; Padron, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979.

2) Gilmore, K.; Mohamed, R. K.; Alabugin, I. V. *WIREs Comput. Mol. Sci.* **2016**, *6*, 487.