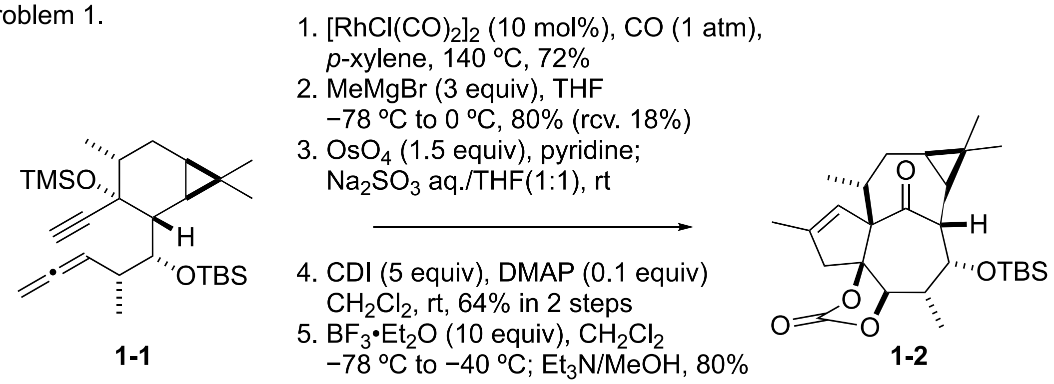
# Problem Session (2) -Problem-

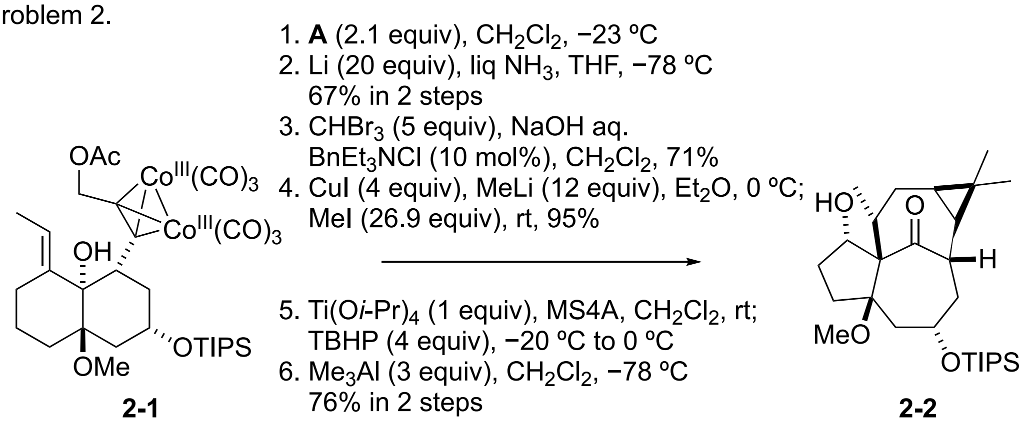
2024/11/22 Yo Matsumoto

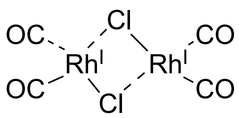
Please provide the mechanism for the following reactions.

Problem 1.

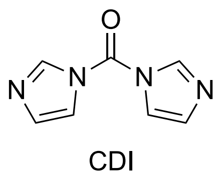



Problem 2.

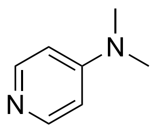


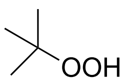

$[RhCl(CO)_2]_2$



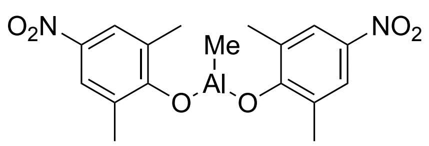

CDI




DMAP




TBHP




**A**

# Problem Session (2) -Answer-

2024/11/22 Yo Matsumoto

Topic: Total synthesis of ingenol

About ingenol

**Isolation**:

*Euphorbia ingens* (tree euphorbia)[1)]

**Structure feature**:

*in,out*-[4,4,1]bicycloundecane core (BC-ring)[2)]

Hyghly oxigenated, Cyclopropane moiety

**Bioactivity**:

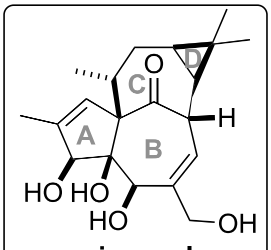
anti-cancer, anti-HIV activity[3)]

**Total synthesis**:

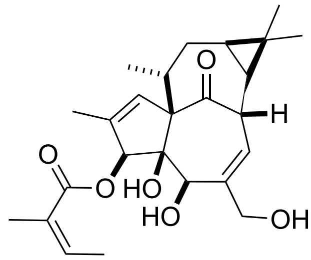
Winkler (2002, rac)[4)], Kuwajima (2003, rac)[5)]

Wood (2004, rac)[6)], Kigoshi (2004, formal synthesis, rac)[7)]

Baran (2013)[8)]




**ingenol**

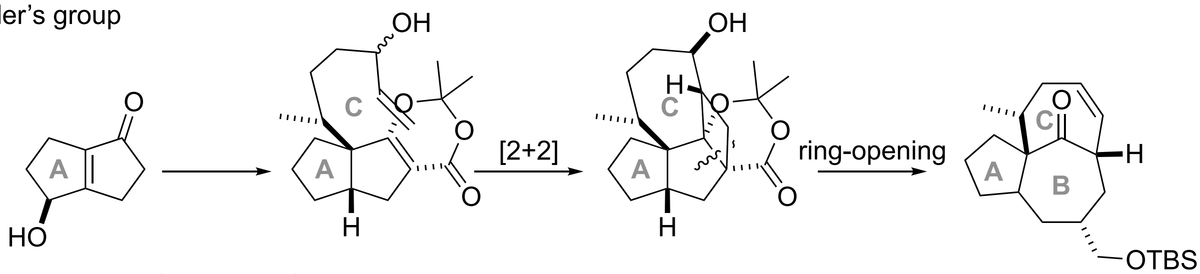



**ingenol mebute**

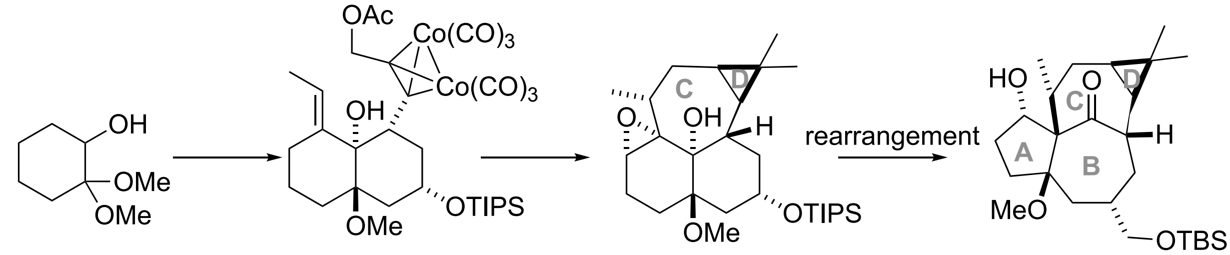
FDA approved as treatment for actinic keratosis (pre-cancerous skin condition)

***Strategy of ring construction of ingenol***

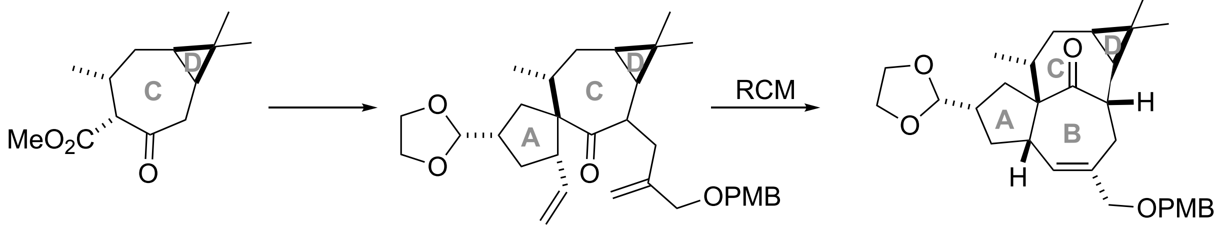
Winkler's group



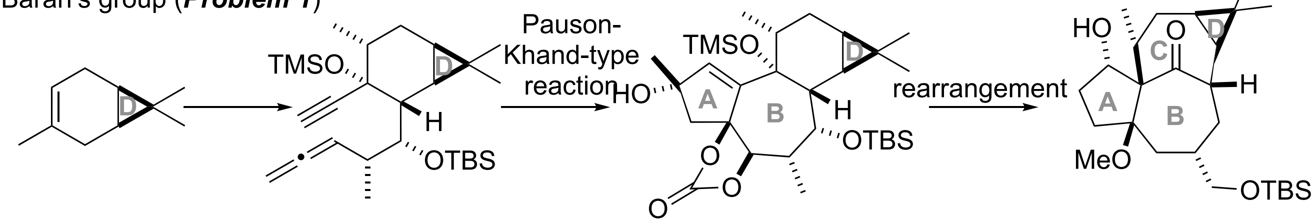

Kuwajima's group (***Problem 2***)



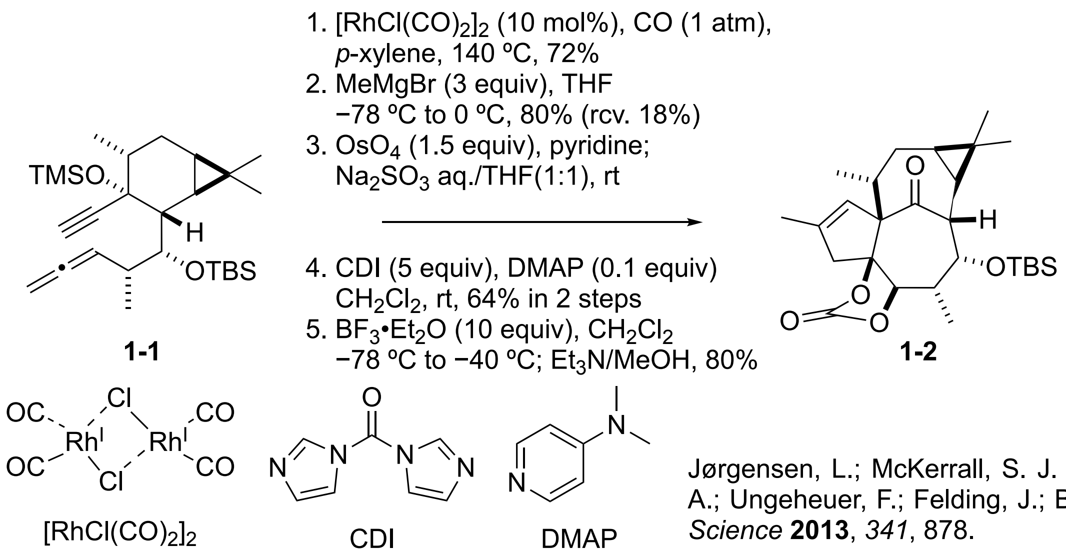

Wood's group (also Kigoshi's group used RCM for B ring construction to synthesize Winkler's intermediate.)




Baran's group (***Problem 1***)

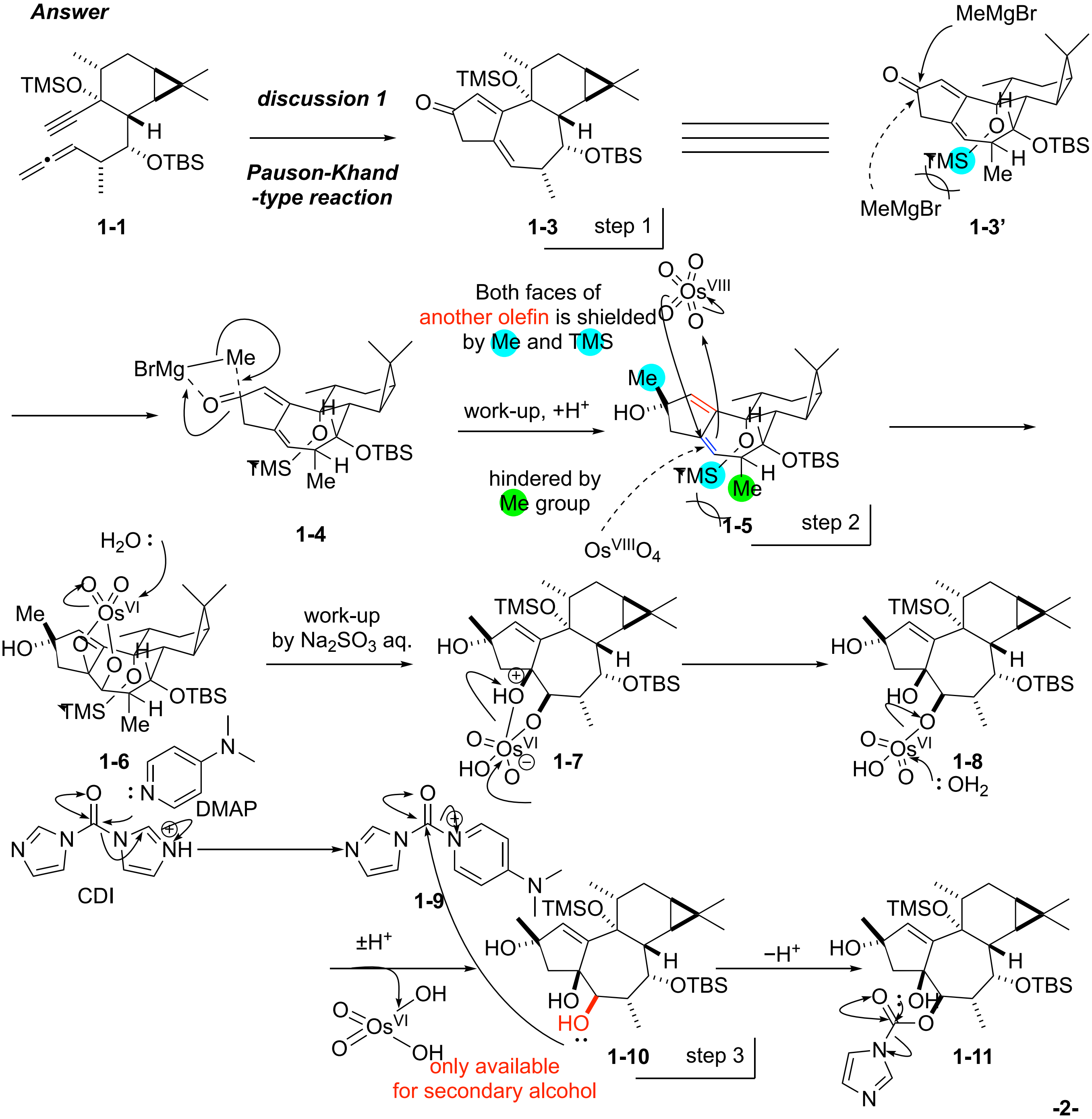


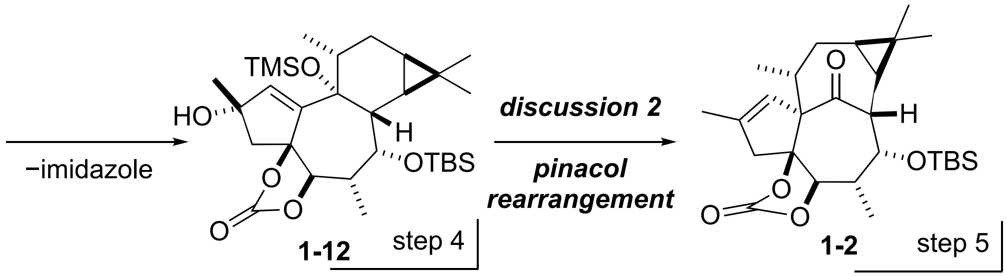
Problem 1. Total synthesis of ingenol by Baran's group.




Jørgensen, L.; McKerrall, S. J. Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878.

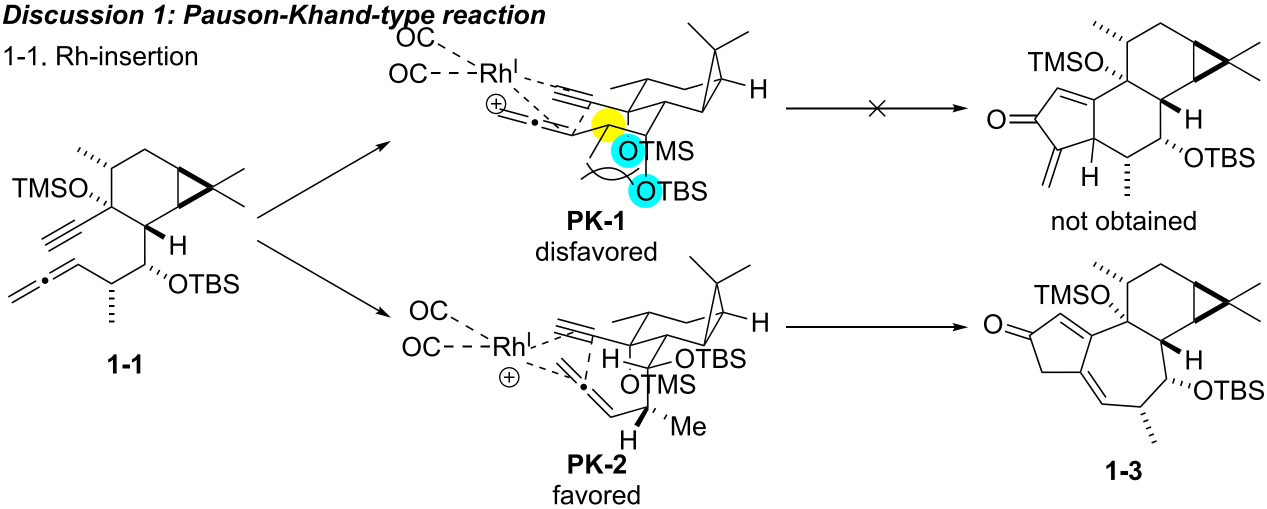
***Answer***



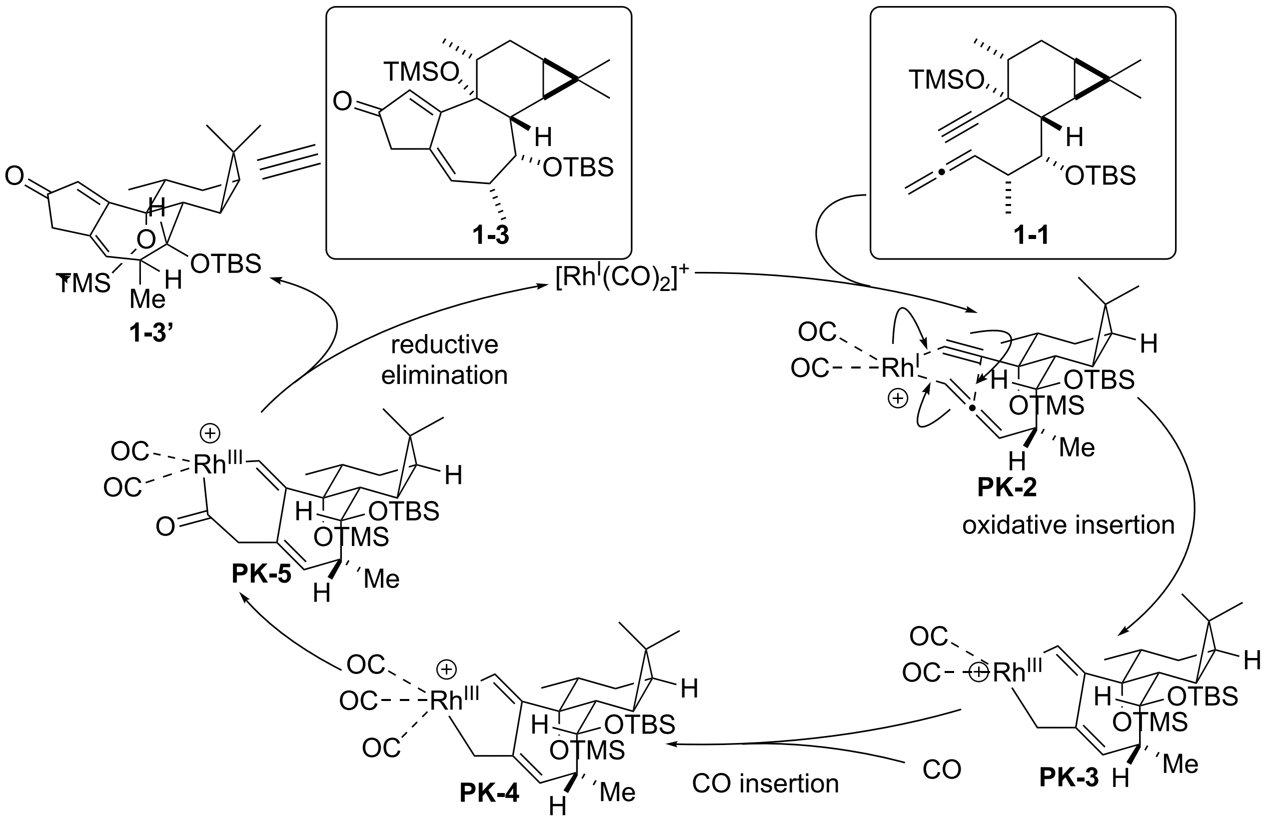



***Discussion 1: Pauson-Khand-type reaction***

1-1. Rh-insertion

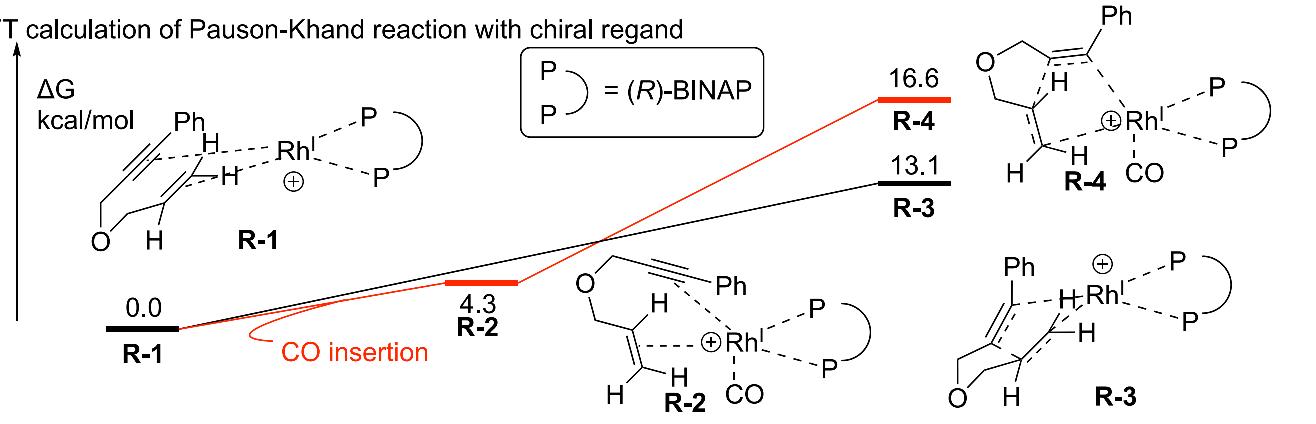



1-2. Catalytic cycle of Pauson-Khand-type reaction



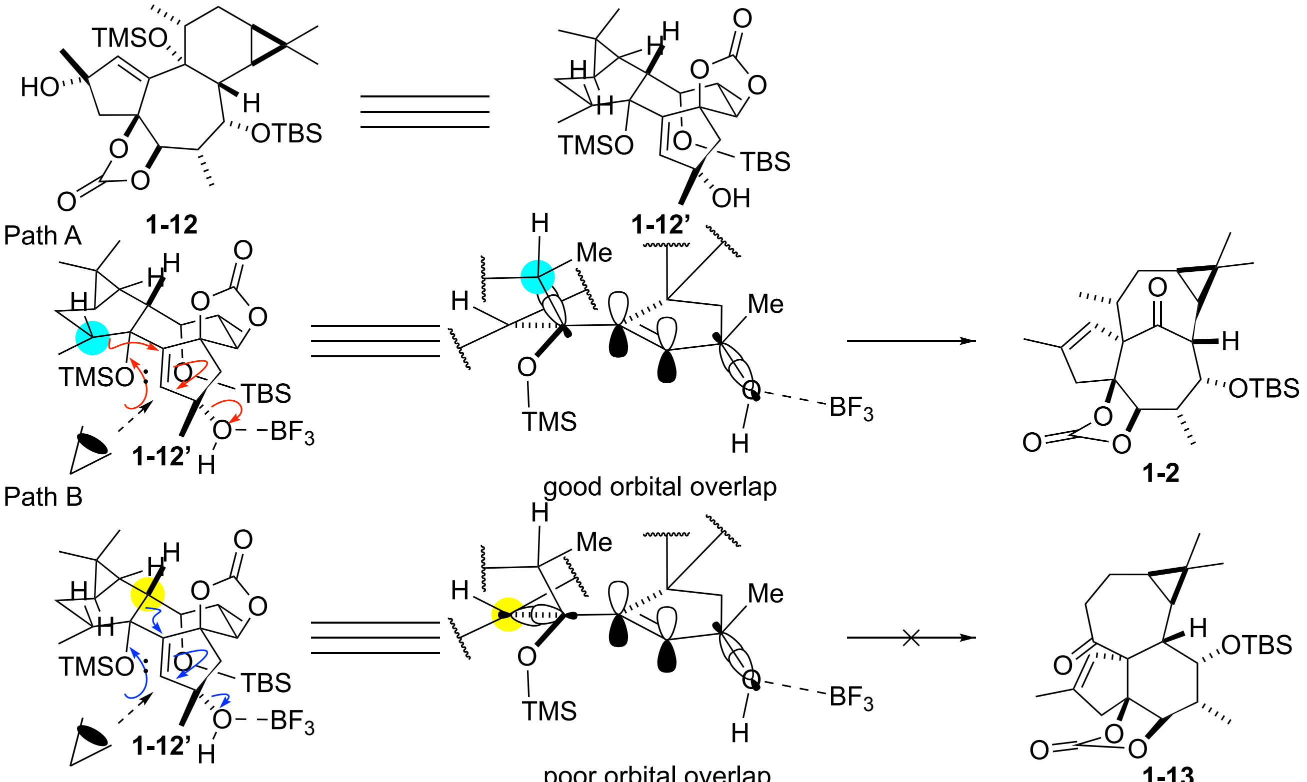

CO insertion for **PK-2** is disfavored, according to the following DFT calculation (Please see the box in the next page). 5-coodinated pathway needs higher energy than 4-coodinated pathway. I think this is because just steric repulsion increases.

DFT calculation of Pauson-Khand reaction with chiral regand

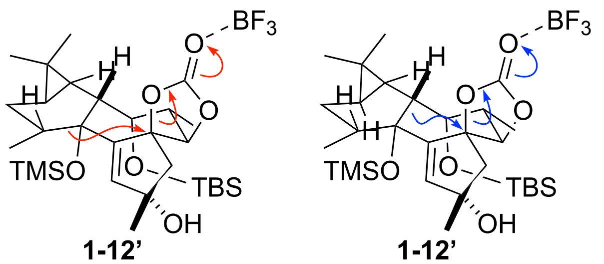



Burrows, L. C.; Jesiliewicz, L. T.; Liu, P.; Brummond, K. M. *ACS Catal.* **2021**, *1*, 323.

***Discussion 2: Pinacol rearrangement***



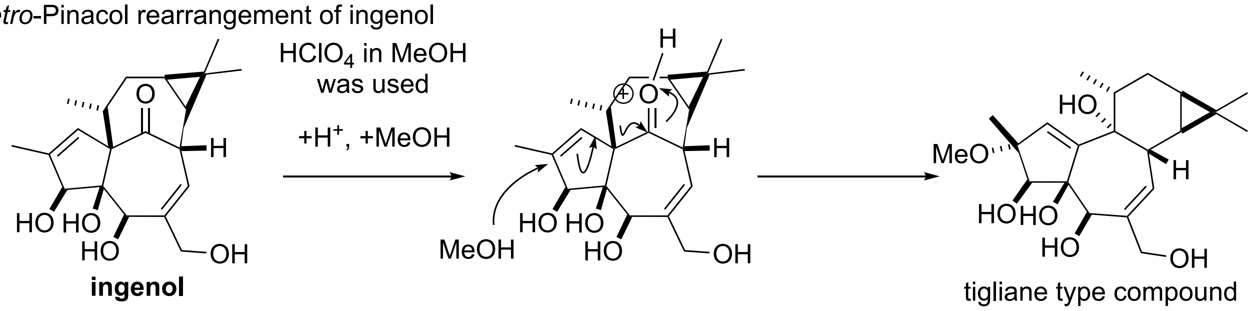

*Other pathways*




These other pathways are also considered, but its too far to react.

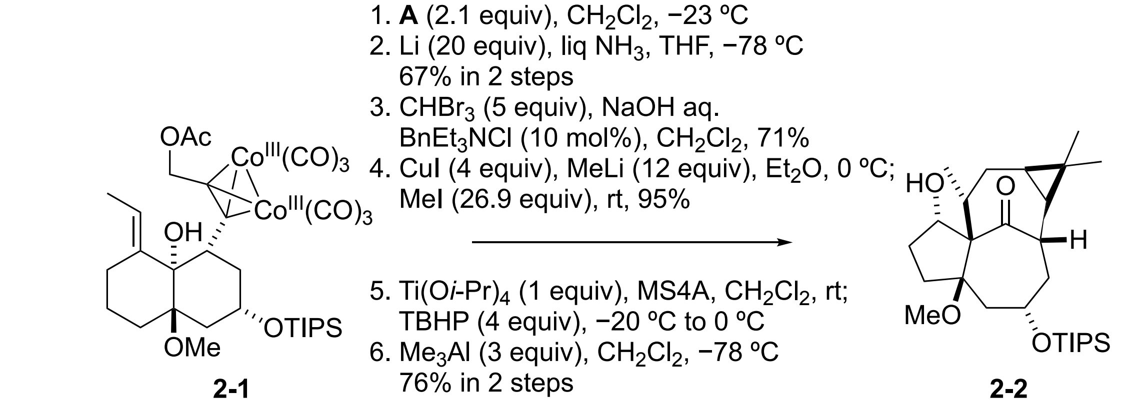
The reason of addition of $Et_3N$/MeOH before quenching by aquerious solution is to prevent reverse reaction (Author's opinion).

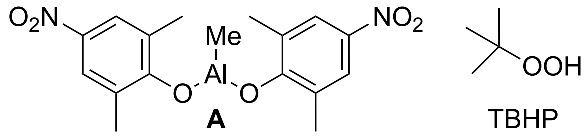
*retro*-Pinacol rearrangement of ingenol




Appendino, G.; Tron, G. C.; Cravotto, G.; Palmisano, G.; Annunziata, R.; Baj, G.; Surico, N. *Eur. J. Org. Chem.* **1999**, 3413.

Problem 2. Total synthesis of ingenol by Kuwajima's group.



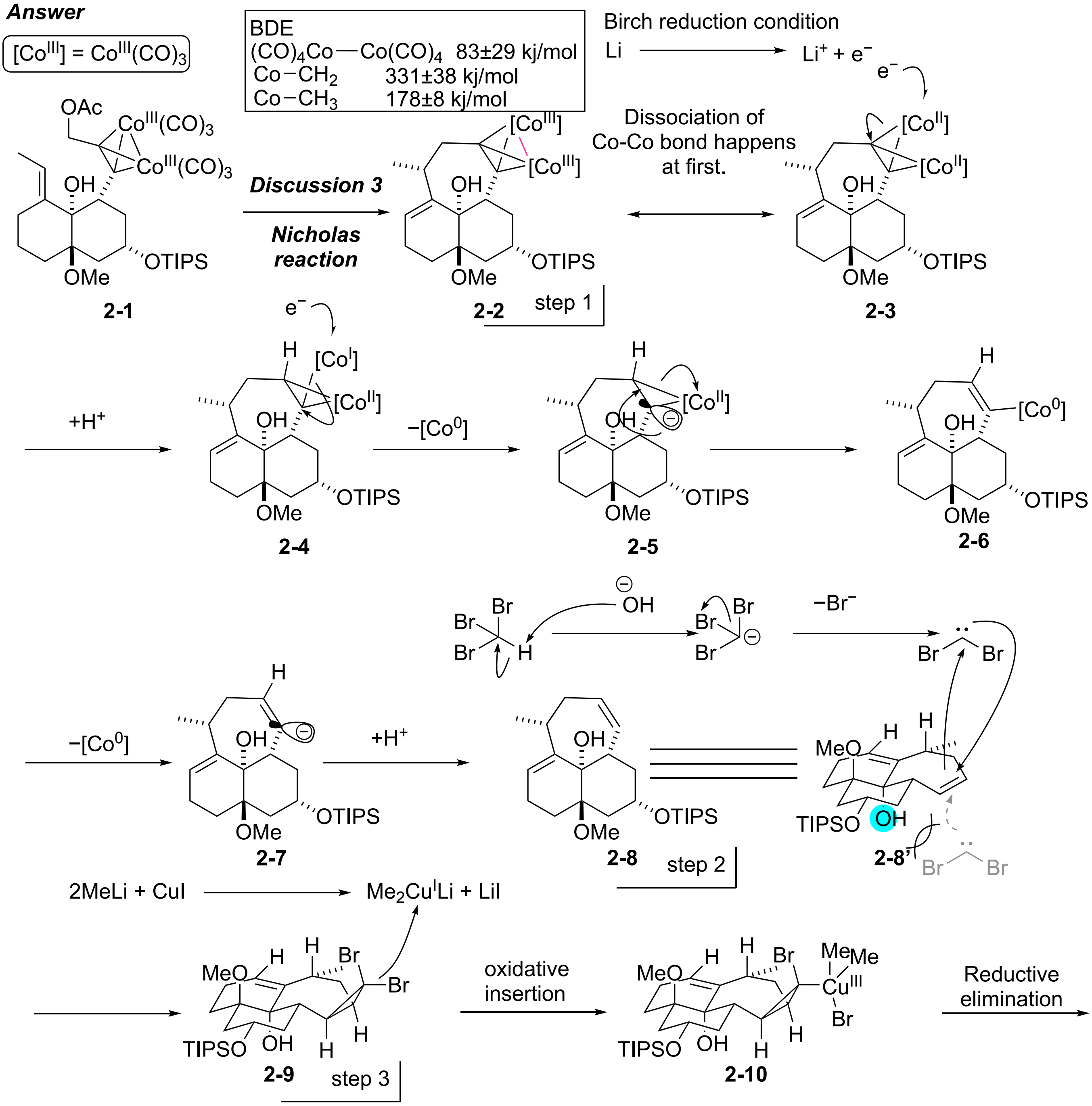



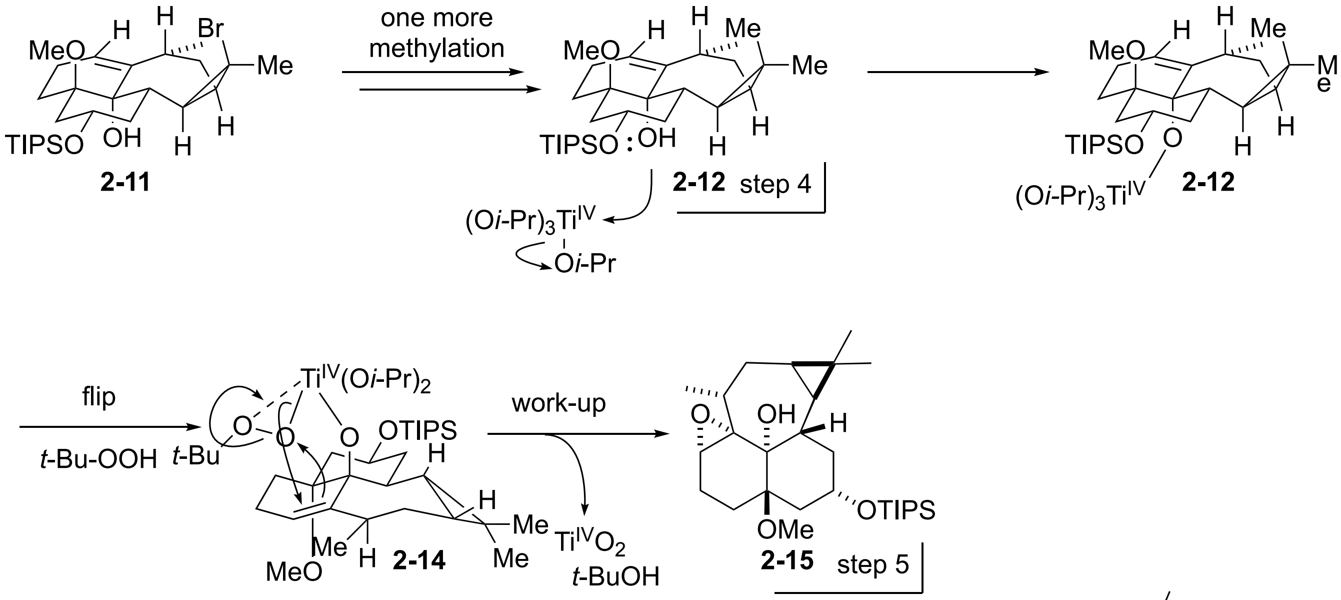

Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498.

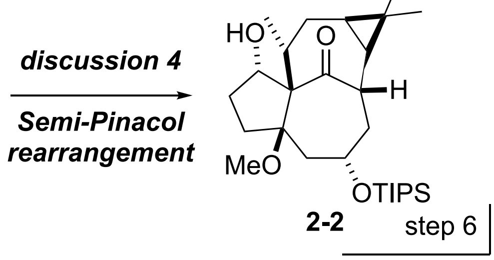
***Answer***

$[Co^{III}] = Co^{III}(CO)_3$

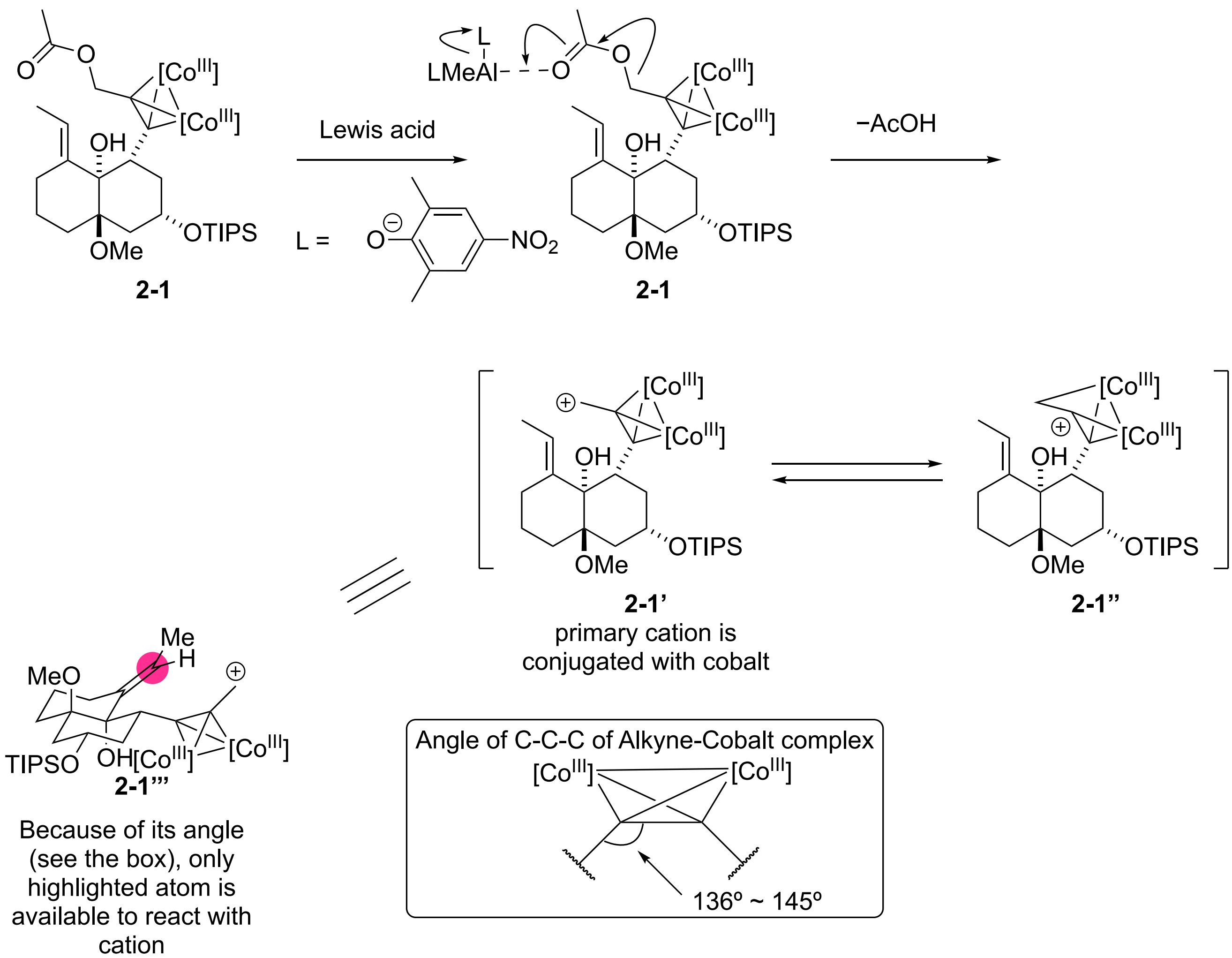
| BDE | |
|---|---|
| $(CO)_4Co—Co(CO)_4$ | 83±29 kj/mol |
| $Co-CH_2$ | 331±38 kj/mol |
| $Co-CH_3$ | 178±8 kj/mol |

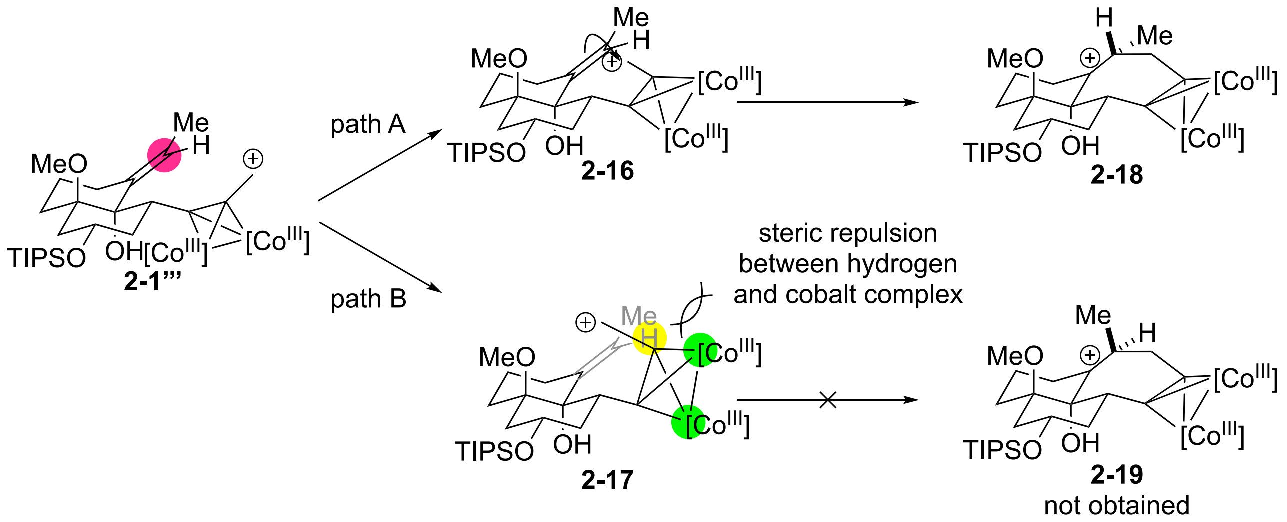




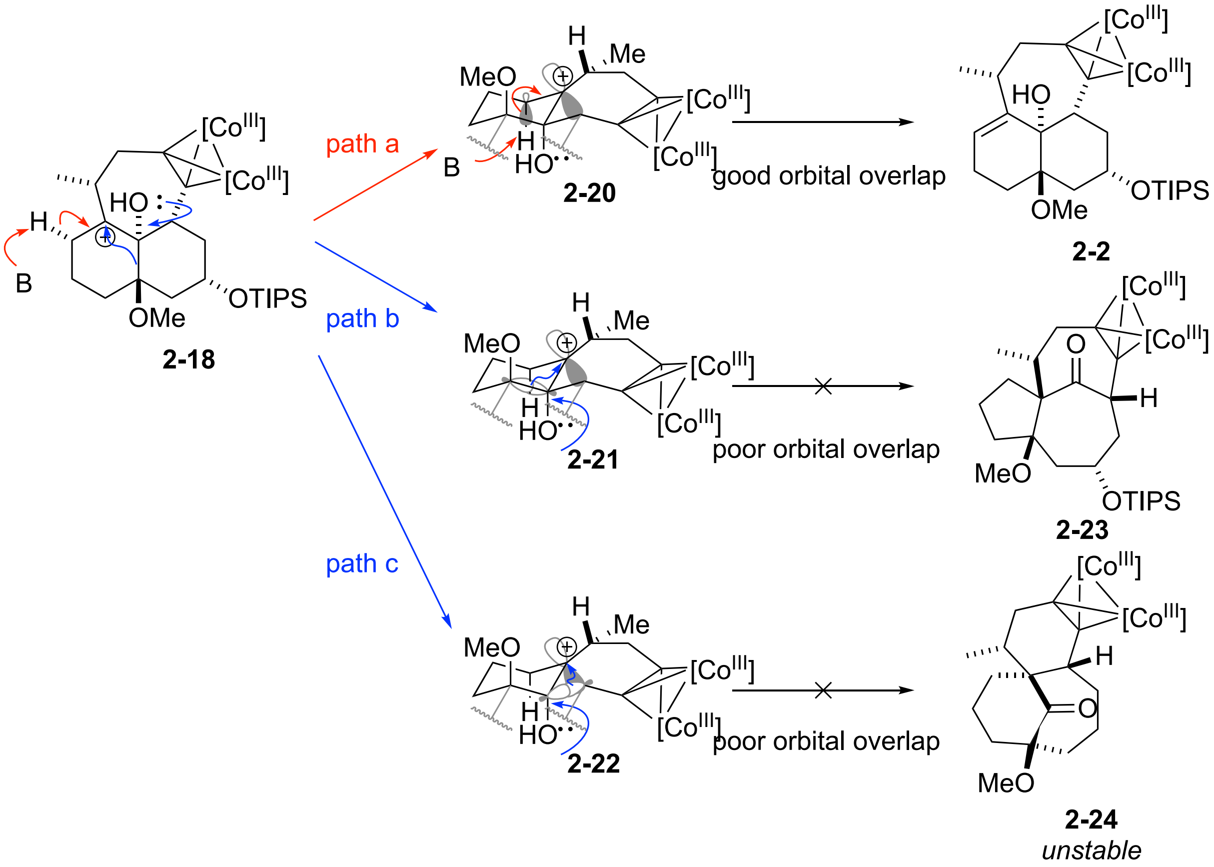




***Discussion 3: Nicholas reaction***





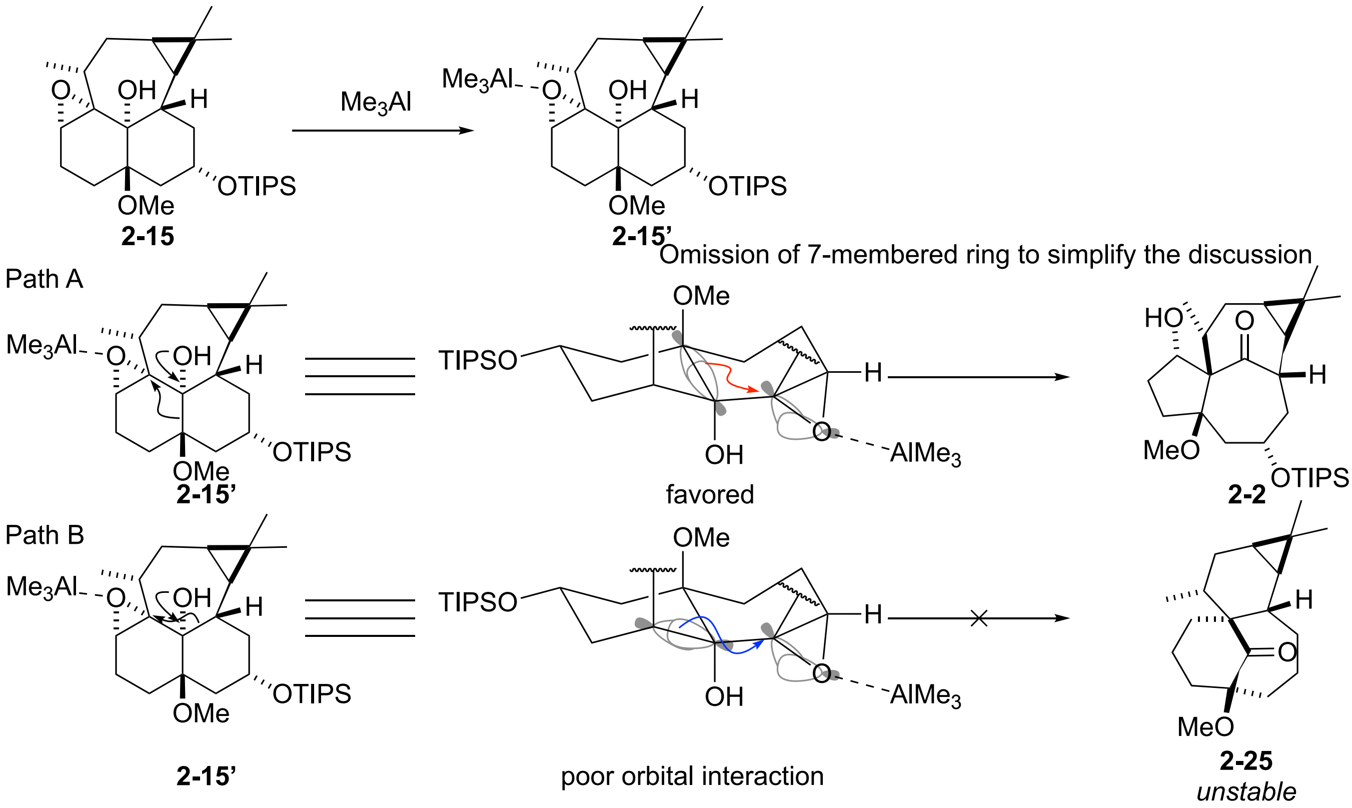

After the generation of tertiary cation.




σ-orbital of axial hydrogen has good orbital overlap with tertiary cation. Therefore, deprotonation of this position happened instantly.
Also, because of this bad orbital overlap, moreover rearrangement did not happen in compound **2-18**.

### *Discussion 4: Semi-Pinacol rearrangement*

According to the result of discussion 3, I think $S_N2$-like mechanism is better in this reaction.




The pathway having best orbital overlap is A.
Other pathways are not good at this point and also their products are unstable.


**Reference**

1. Hecker, E. *Cancer Res.* **1968**, *28*, 2338.
2. Zechmeister, K.; Brandl, F.; Hoppe, W.; Hecker, E.; Opferkuch, H. J.; Adolf, W. *Tetrahedron Lett.* **1970**, *11*, 4075.
3. Vasas, A.; Rédei, D.; Csupor, D.; Molnár, J.; Hohmann, J. *Eur. J. Org. Chem.* **2012**, *2012*, 5115.
4. Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726.
5. Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498.
6. Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300.
7. Watanabe, K.; Suzuki, Y.; Aoki, K.; Sakakura, A.; Suenaga, K.; Kigoshi, H. *J. Org. Chem.* **2004**, *69*, 7802.
8. Jørgensen, L.; McKerrall, S. J. Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878.
9. Burrows, L. C.; Jesiliewicz, L. T.; Liu, P.; Brummond, K. M. *ACS Catal.* **2021**, *1*, 323.
10. Appendino, G.; Tron, G. C.; Cravotto, G.; Palmisano, G.; Annunziata, R.; Baj, G.; Surico, N. *Eur. J. Org. Chem.* **1999**, 3413.