Problem session (2)

2025.5.31 M1 Shuntaro Kawai

topic: Hydrogen atom transfer in total synthesis

Main review: Deng, M.; Wu, F.; Liu, T.; Jiang, Z.; Luo, T. *J. Am. Chem. Soc.* **2025**, *147*, 8132.

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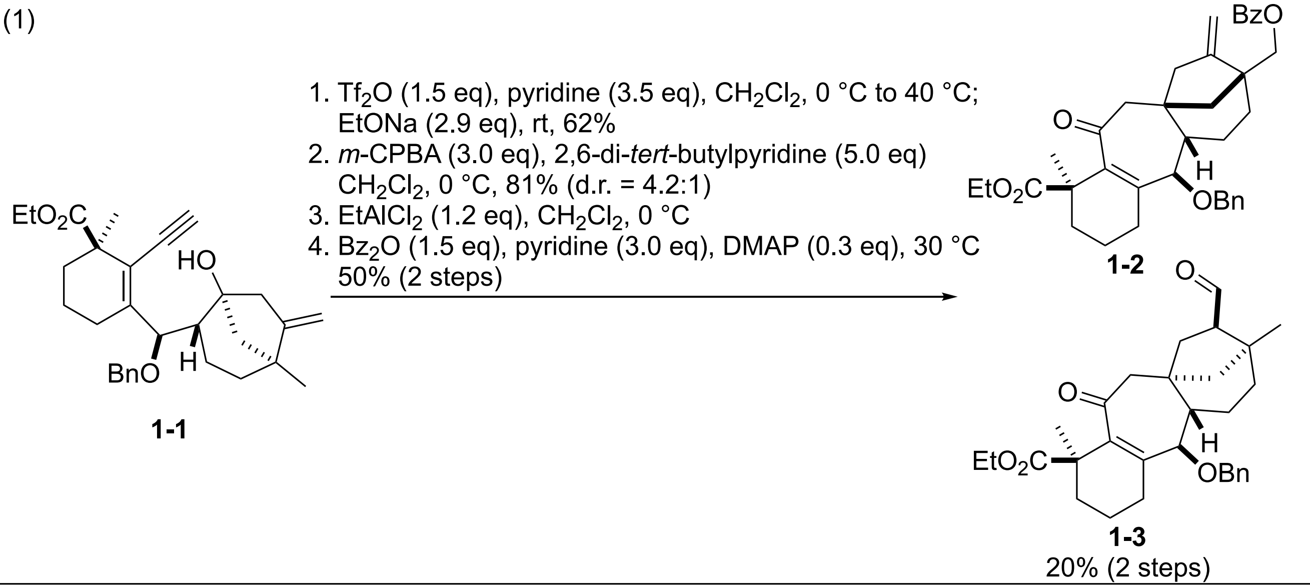
(1)



1. Tf_2O (1.5 eq), pyridine (3.5 eq), CH_2Cl_2, 0 °C to 40 °C; EtONa (2.9 eq), rt, 62%
2. *m*-CPBA (3.0 eq), 2,6-di-*tert*-butylpyridine (5.0 eq) CH_2Cl_2, 0 °C, 81% (d.r. = 4.2:1)
3. $EtAlCl_2$ (1.2 eq), CH_2Cl_2, 0 °C
4. Bz_2O (1.5 eq), pyridine (3.0 eq), DMAP (0.3 eq), 30 °C 50% (2 steps)

1-1

1-2

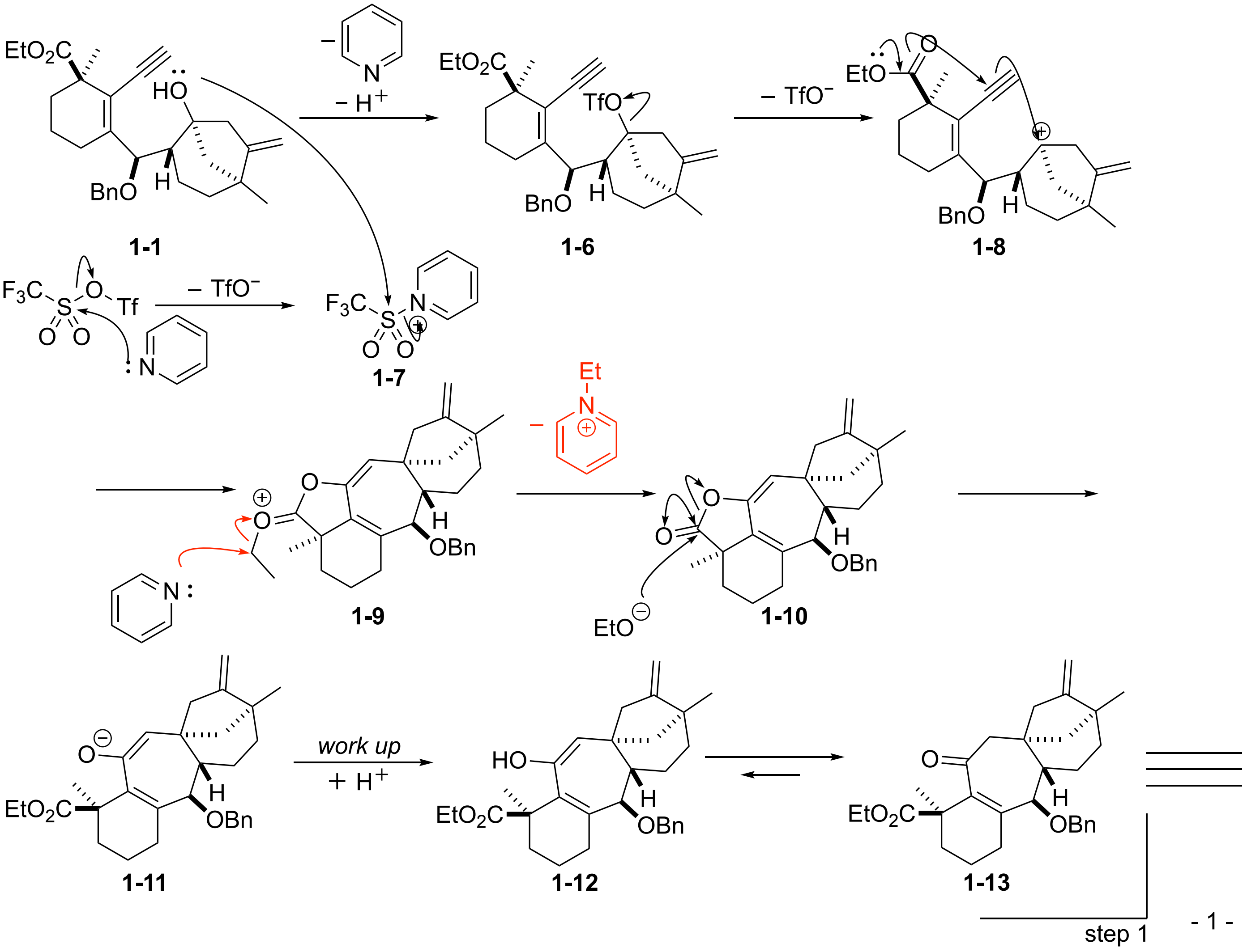
1-3

20% (2 steps)

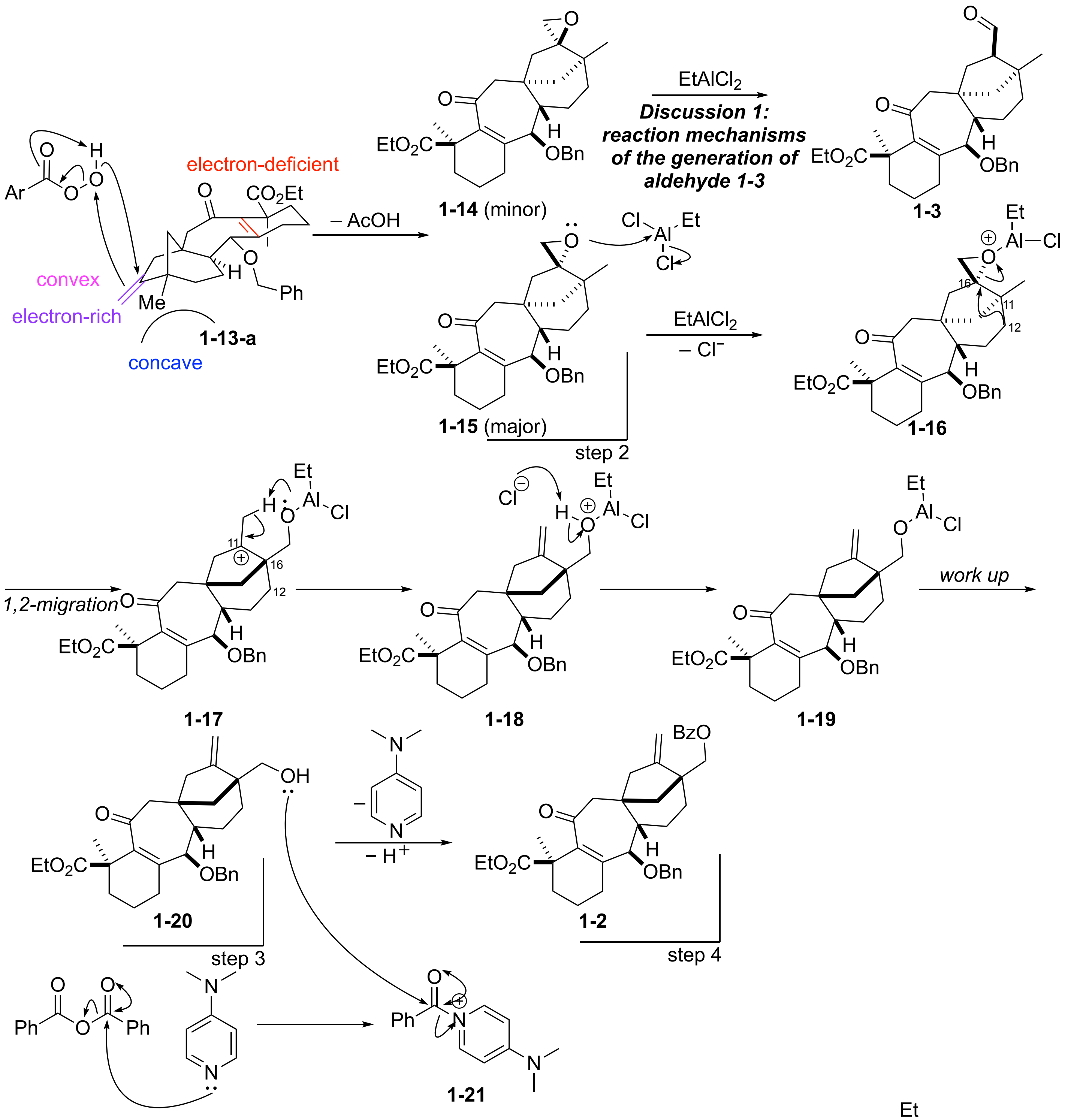
Reaction mechanisms Deng, M.; Wu, F.; Liu, T.; Jiang, Z.; Luo, T. *J. Am. Chem. Soc.* **2025**, *147*, 8132.

About the reaction of step 1, see also: 220514_PS_jaejoong_Han

About the reaction of step 3, see also: 200613_PS_Shimizu_Shinzuke

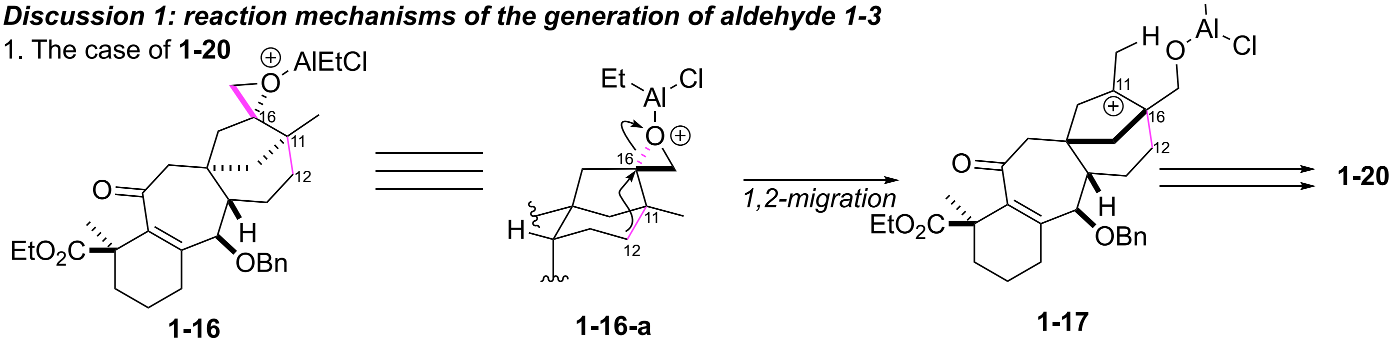


1-1 **1-6** **1-8** **1-7** **1-9** **1-10** **1-11** **1-12** **1-13**



Discussion 1: reaction mechanisms of the generation of aldehyde 1-3

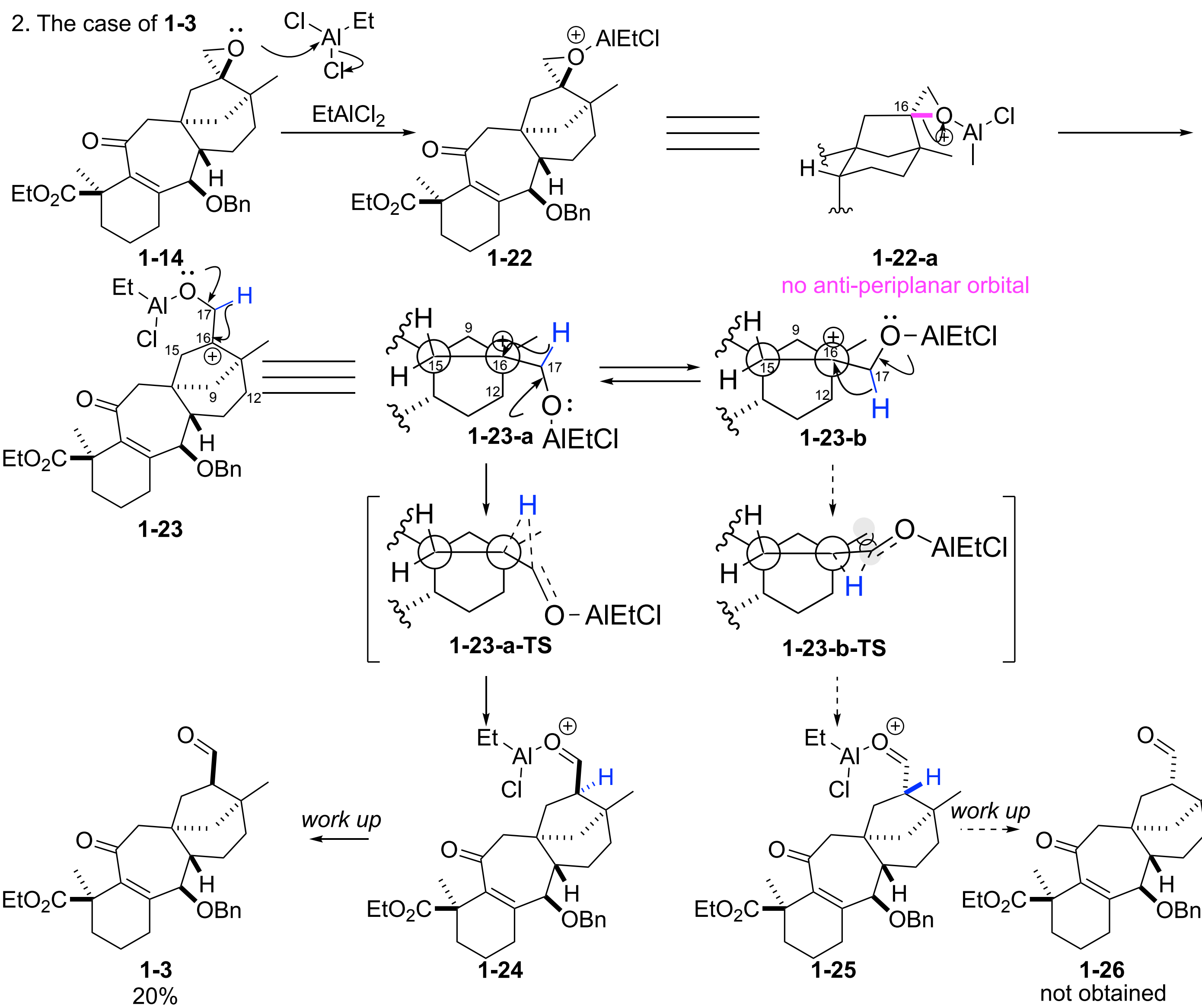
1. The case of **1-20**



The C11-C12 bond is anti-periplanar to the C16-O epoxide bond.

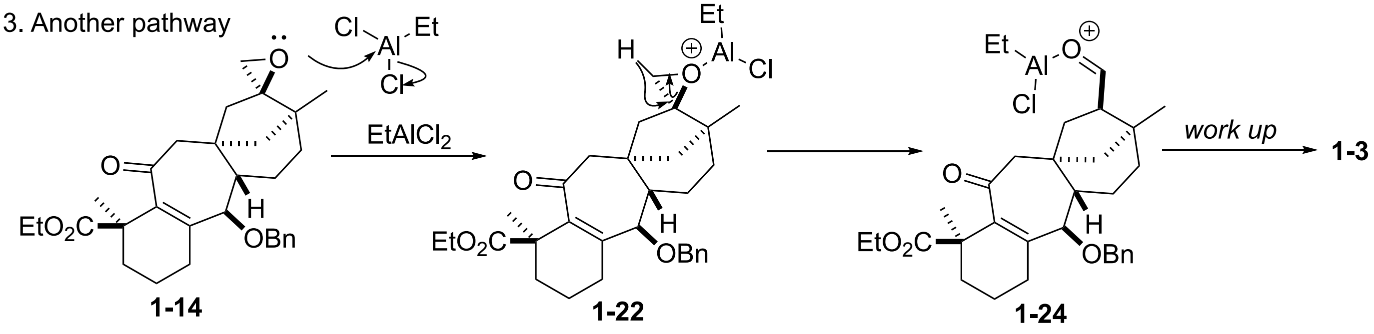
Thus, the rearrangement proceeds concertedly and yields the single diastereomer **1-20**.

2. The case of **1-3**



1-22 has no anti-periplanar orbital.
Thus, the migration of C17 hydride occurs to generate the most stable cation, which is adjacent to the oxygen atom.
The hydride migration occurs only from **1-23-a** because the torsional strain between C17 and the methyl group is lower in **1-23-a-TS** than in **1-23-b-TS**.

3. Another pathway

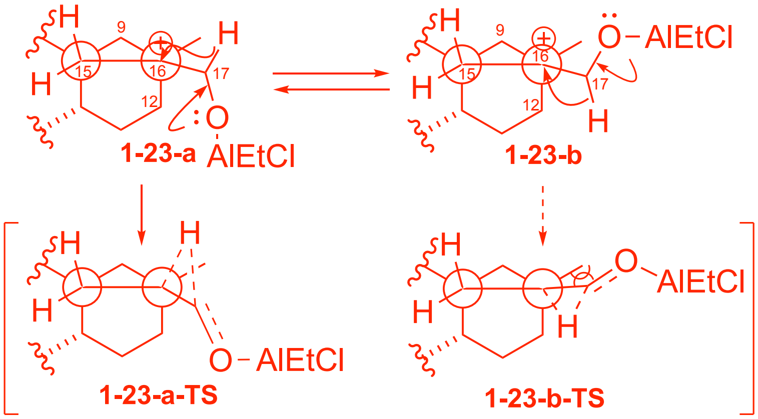


The concerted pathway of the hydride shift also can explain the stereoselectivity.

4. Consideration about pathway of **1-3**

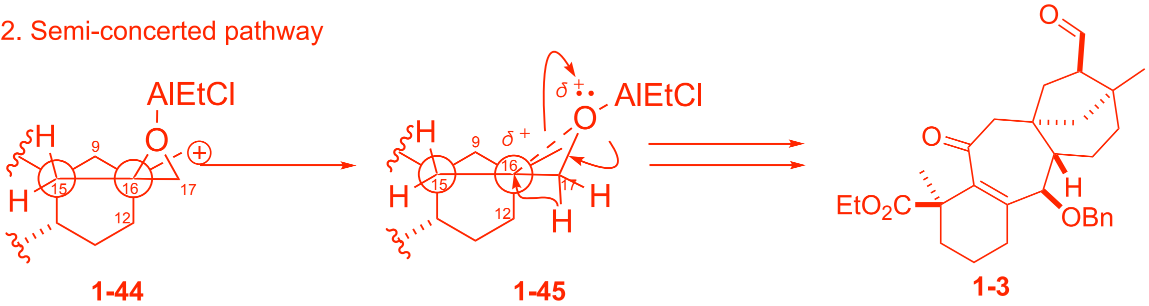
In this section, the possible accounts of the generation of **1-3** are described.

4-1. The comparison of speed between the bond rotaion and the migration



If the conversion of **1-23-a** to **1-23-a-TS** is faster than one of **1-23-a** to **1-23-b**, **1-3** can generate.

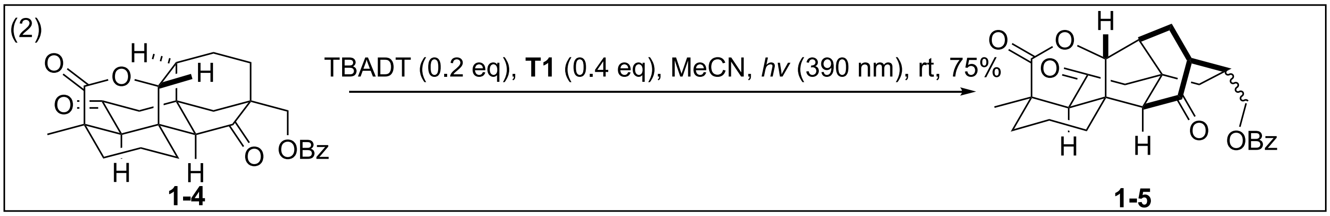
4-2. Semi-concerted pathway



When the partial cation generates at C16, the hydride migration proceeds.

1-45 maintains the stereochemical information of C16 because the cleavage of the epoxide ring does not fully proceed.

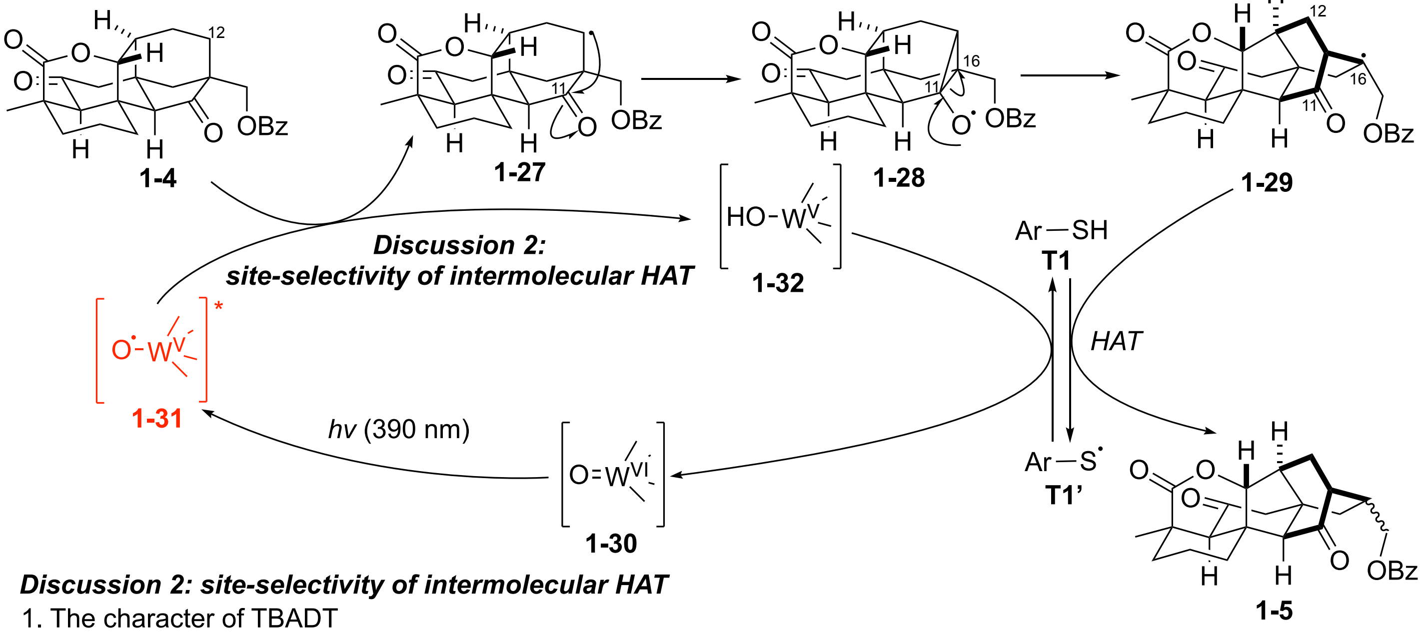
Thus, this stereochemical information and the torsional strain described in section 2 can explain the stereoselectivity at C16.



TBADT (0.2 eq), **T1** (0.4 eq), MeCN, *hv* (390 nm), rt, 75%

Deng, M.; Wu, F.; Liu, T.; Jiang, Z.; Luo, T. *J. Am. Chem. Soc.* **2025**, *147*, 8132.

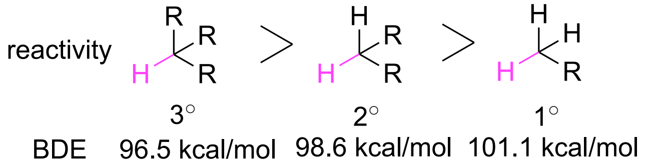
Reaction mechanisms



Discussion 2: site-selectivity of intermolecular HAT

1. The character of TBADT

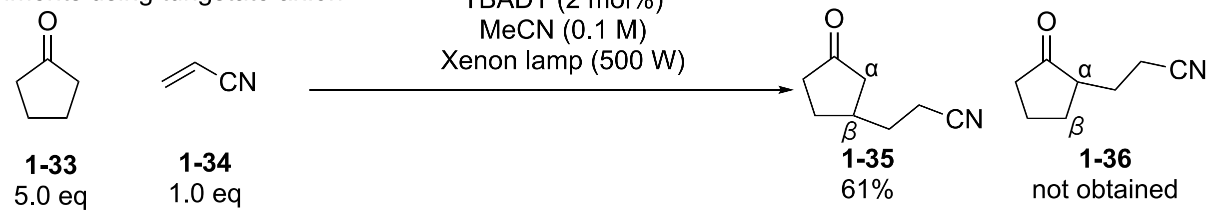
1-1. General features oh HAT



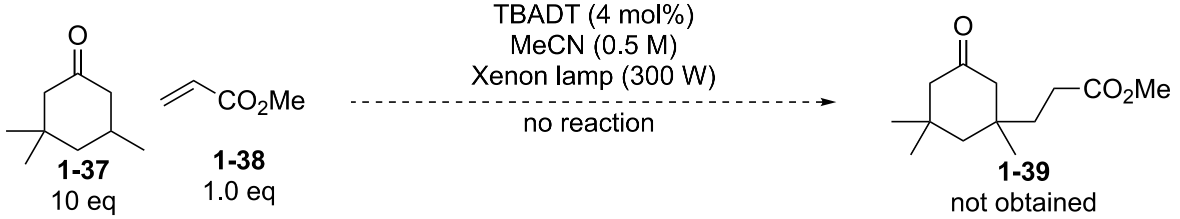
In general, HAT occurs more readily at tertiary alkanes than secondary or primary alkanes because of the lower bond dissociation energy (BDE).

1-2. The character of tungstate anion ($(W_{10}O_{32})^{4-}$)

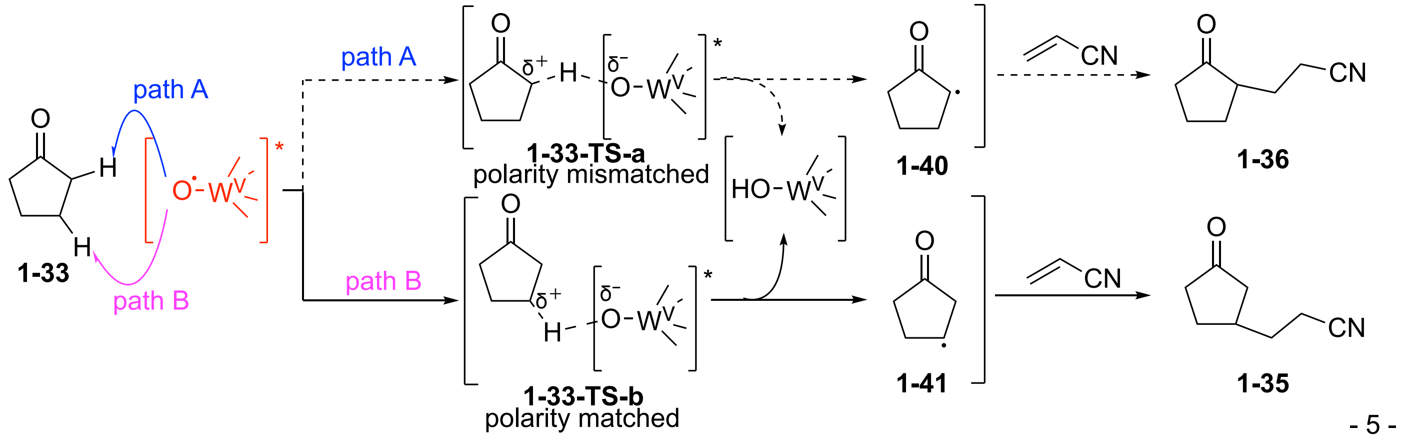
Experiments using tungstate anion



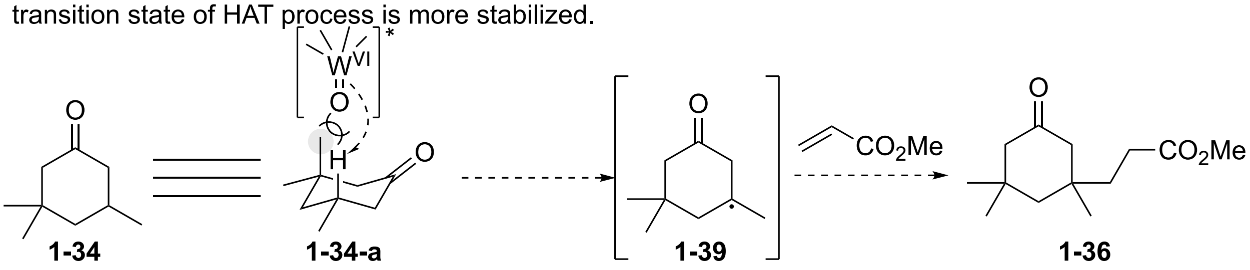
Okada, M.; Fukuyama, T.; Yamada, K.; Ryu, I.; Ravelli, D.; Fagnoni, M. *Chem. Sci.* **2014**, *5*, 2893.



Yamada, K.; Fukuyama, T.; Fujii, S.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Chem. Eur. J.* **2017**, *23*, 8615.

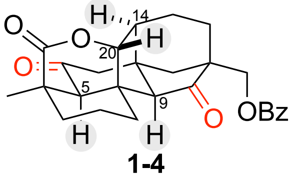


TBADT has an electrophilic oxygen center, so a partial positive charge (δ^{+}) generates at the corresponding carbon in the transition state of HAT process.
Thus, TBADT exhibits **higher reactivity at electronegative carbons** such as a β-positions of a ketone because the transition state of HAT process is more stabilized.



TBADT is **highly sensitive to steric effect** due to its large molecular size.

2. The possibility of HAT at 3° carbon of **1-4**



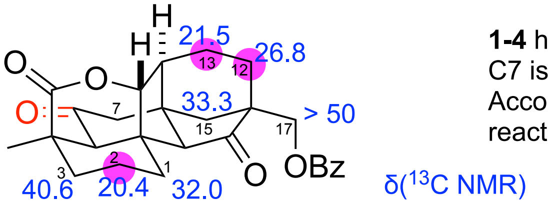
1-4

C5, C9 ⟶ They are located at the α-position of a ketone, and the transition states of HAT are unstable due to their mismatching polarity.

C14, C20 ⟶ They are highly hindered because the hydrogen atoms are located on the inner side of fused rings. Also, C20 is deactivated by the neighboring

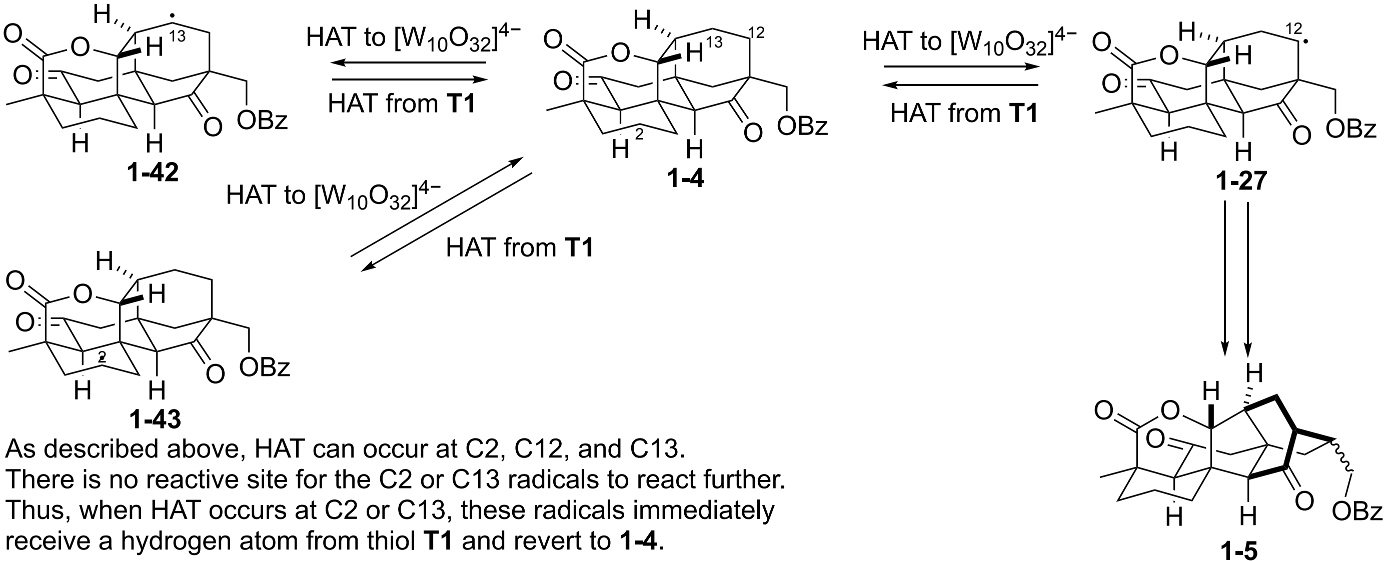
Therefore, there is little possibility of HAT at 3° carbon of **1-4.**

3. The possibility of 2° carbon of **1-4**



1-4 has eight 2° carbon (C1, C2, C3, C7, C12, C13, C15, and C17).
C7 is α-position of the ketone highlighted, so it is not reactive.
According to the 13C NMR, C2, C12, and C13 were considered to be reactive due to their electron-rich trend.

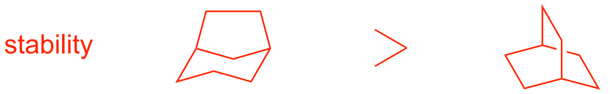
4. Site-selectivity of the reaction by reversible HAT



As described above, HAT can occur at C2, C12, and C13.
There is no reactive site for the C2 or C13 radicals to react further.
Thus, when HAT occurs at C2 or C13, these radicals immediately receive a hydrogen atom from thiol **T1** and revert to **1-4**.
Eventually, **1-4** is converted to **1-5**.

5. Reasons of the generation of **1-5**

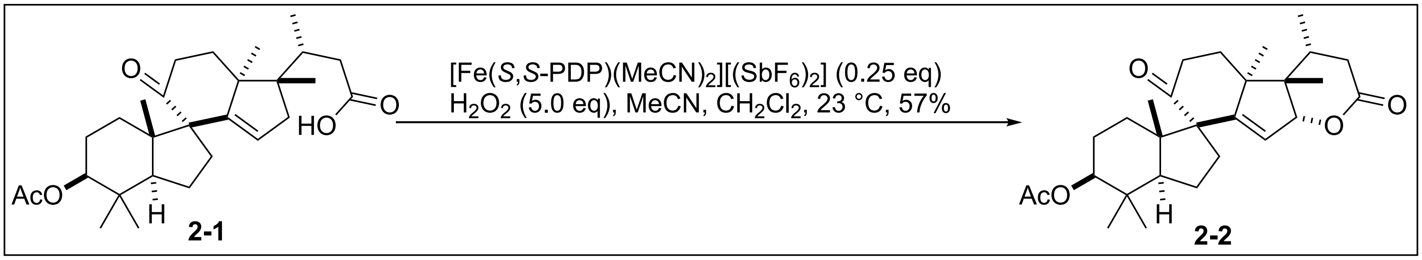
1-5 is especially stable because of its bicyclo[2,2,2] skeleton.



bicyclo[3,2,1] skeleton bicyclo[2,2,2] skeleton

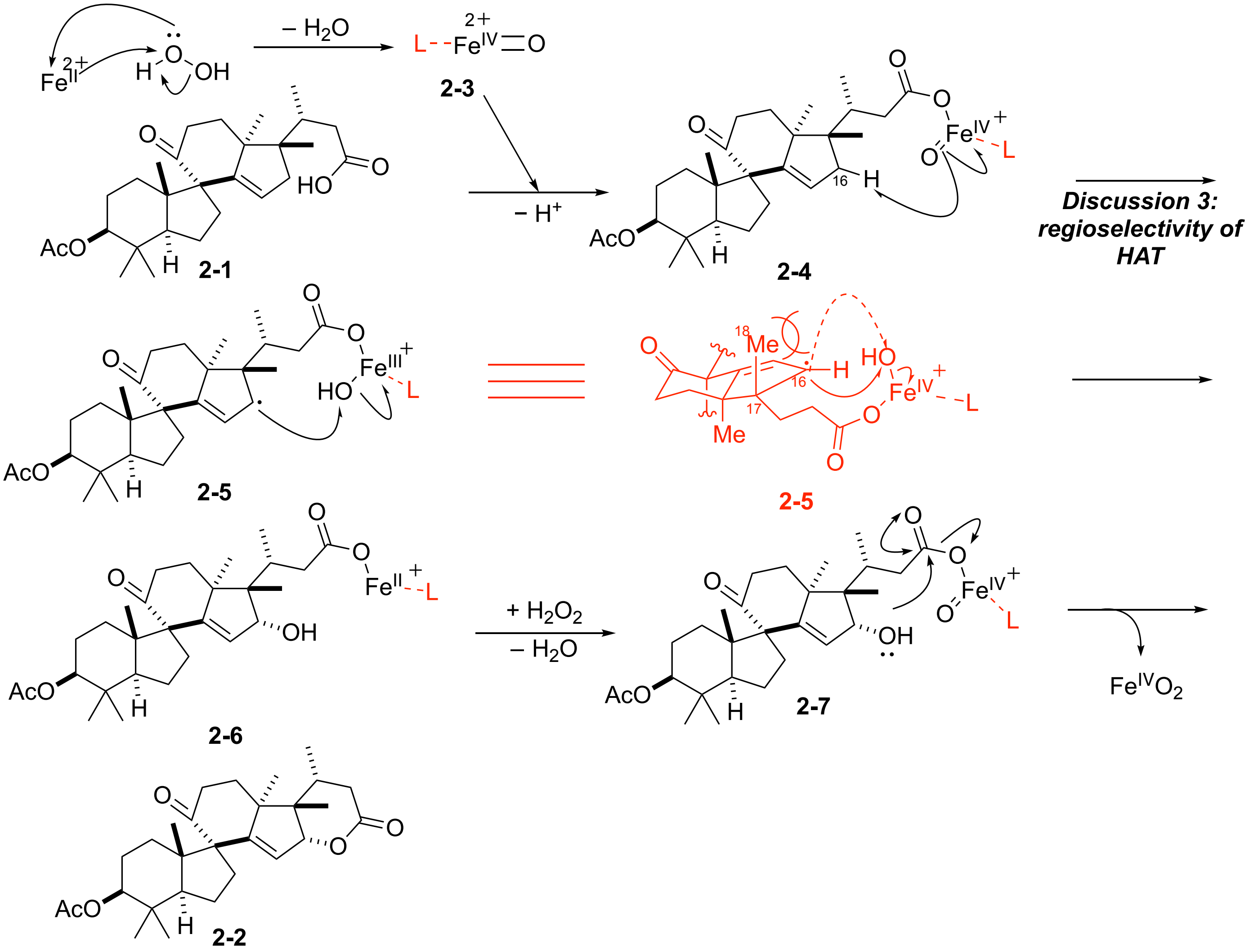
The 5-membered ring of bicyclo[3,2,1] skeleton is highly distorted, which increase the instability of the skeleton.
Thus, the bicyclo[2,2,2] skeleton is more stable.

2



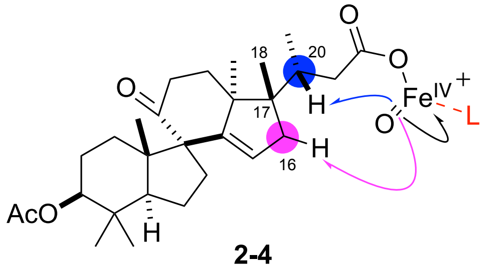
Alekseychuk, M.; Adrian, S.; Heinze, R. C.; Heretsch, P. *J. Am. Chem. Soc.* **2022**, *144*, 11574.

Reaction mechanisms



Discussion 3: regioselectivity of HAT

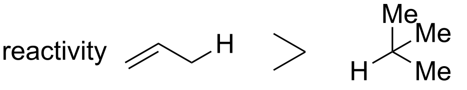
1. Possible positions of HAT



2-4

HAT can occur at C16 or C20.
The other positions are too far or the corresponding radicals are not stable enough to generate.

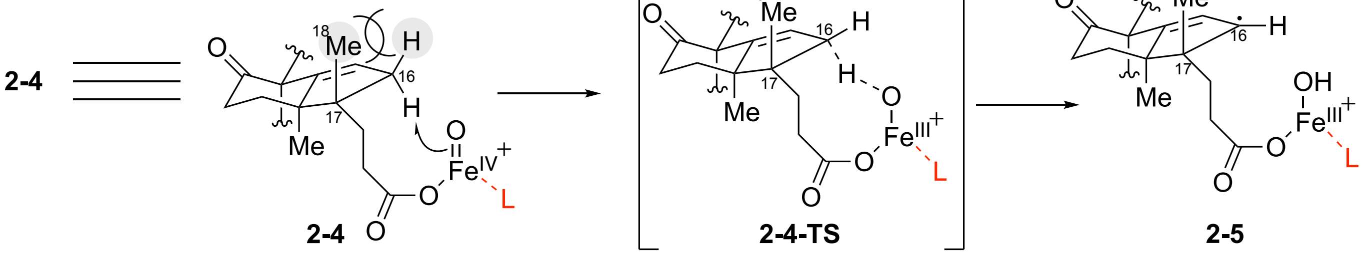
2. BDE comparison of C16 with C20



BDE 88.8 kcal/mol 96.5 kcal/mol

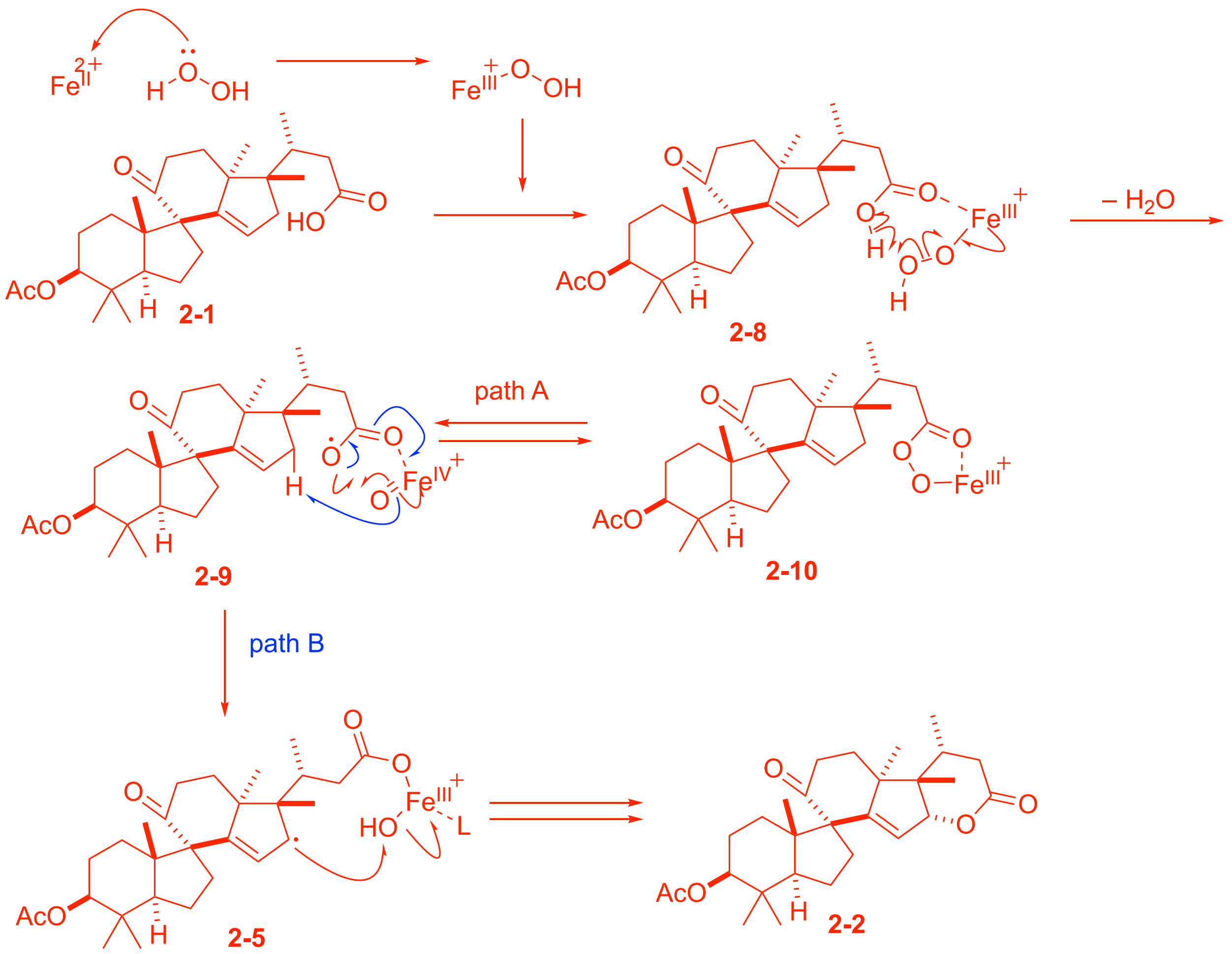
The BDE of C-H bond at the allylic position is lower than one at 3° carbon.
Hence, the former is more reactive toward HAT.

3. Steric repulsion (my proposal)



There is steric repulsion between the hydrogen atom at C16 and the methyl group at C18.
This steric repulsion may be decreased in the transition state of HAT process, making the C-H bond at C16 more reactive than one at C20.

4. Another pathway



References
1) Deng, M.; Wu, F.; Liu, T.; Jiang, Z.; Luo, T. *J. Am. Chem. Soc.* **2025**, *147*, 8132.
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3) Okada, M.; Fukuyama, T.; Yamada, K.; Ryu, I.; Ravelli, D.; Fagnoni, M. *Chem. Sci.* **2014**, *5*, 2893.
4) Yamada, K.; Fukuyama, T.; Fujii, S.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Chem. Eur. J.* **2017**, *23*, 8615.
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