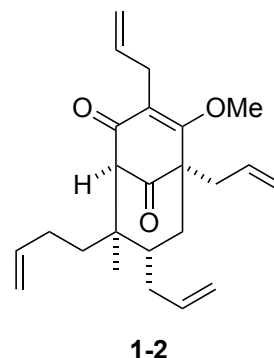
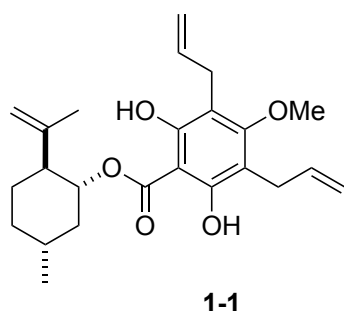


topic: Total synthesis of hyperforin

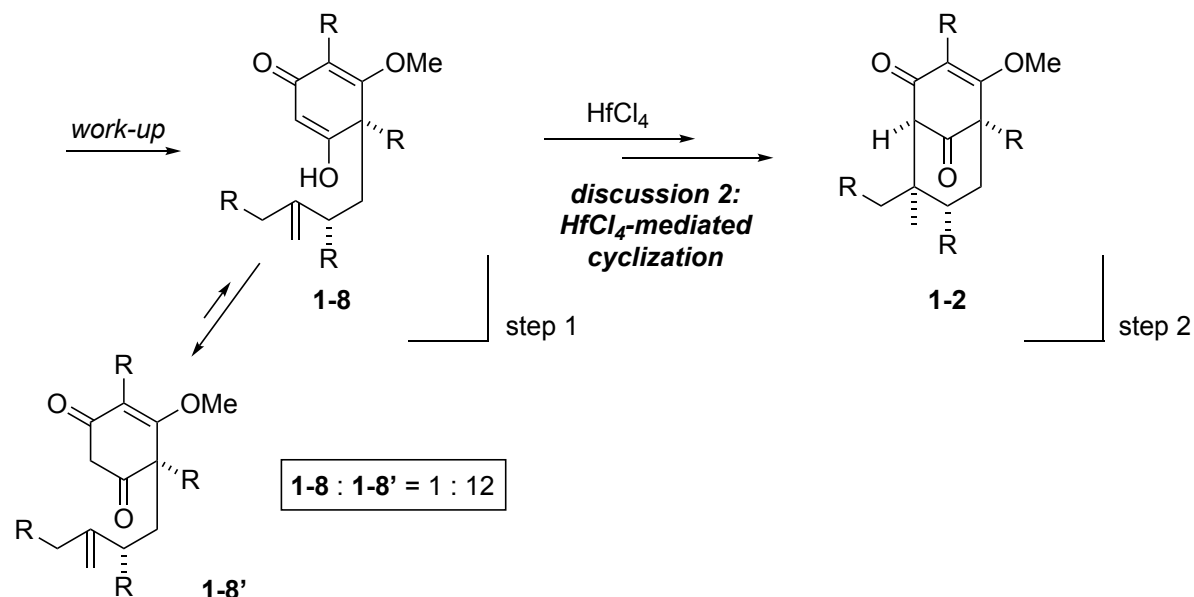
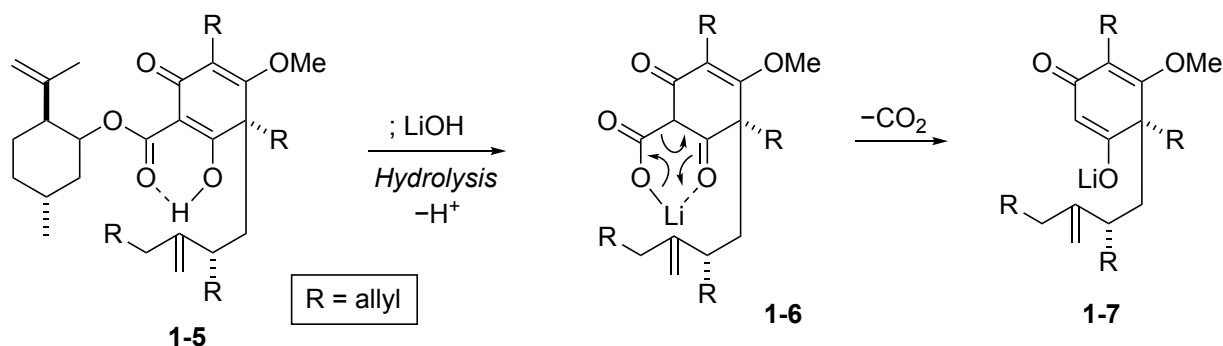
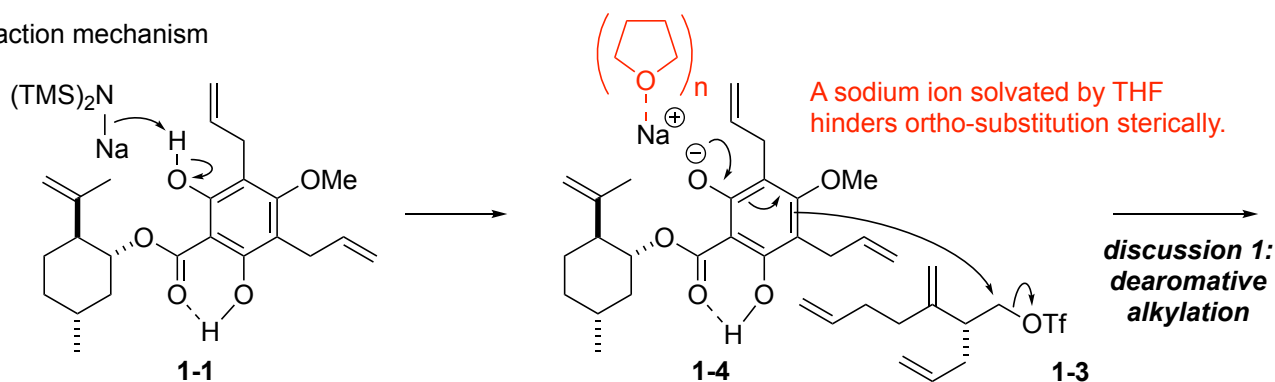
1

1. $\text{NaN}(\text{TMS})_2$ (1.0 eq), toluene/THF (1/3), $-20\text{ }^\circ\text{C}$;
1-3 (2.0 eq), $-20\text{ }^\circ\text{C}$ to rt;
 LiOH (60 eq), 1,4-dioxane/ H_2O (1/2), $100\text{ }^\circ\text{C}$
70%, dr = 1 : 1.4
2. HfCl_4 (1.0 eq), $\text{ClCH}_2\text{CH}_2\text{Cl}$, rt
43%, dr = 2.6 : 1



Ji, Y.; Hong, B.; Franzoni, I.; Wang, M.; Guan, W.; Jia, H.; Li, H. *Angew. Chem. Int. Ed.* **2022**, 61, e202116136.

1-1. Reaction mechanism



1-2. discussion 1: dearomative alkylation

1-2-0. Screening of the substrate

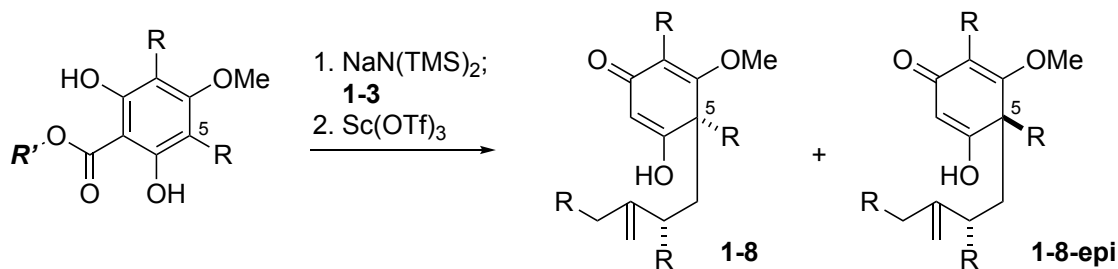


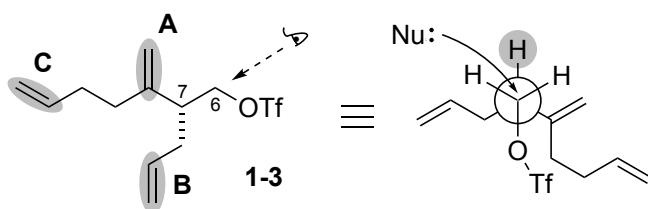
Table 1

entry	R'	yield (2 steps)	dr (1-8 : 1-8-epi)
1		30%	1 : 17
2		44%	1 : 2.8
3		36%	1 : 1.5

1-8-epi is predominantly yielded. The chiral auxiliary improved the ratio, but **1-8** remains a minor product.

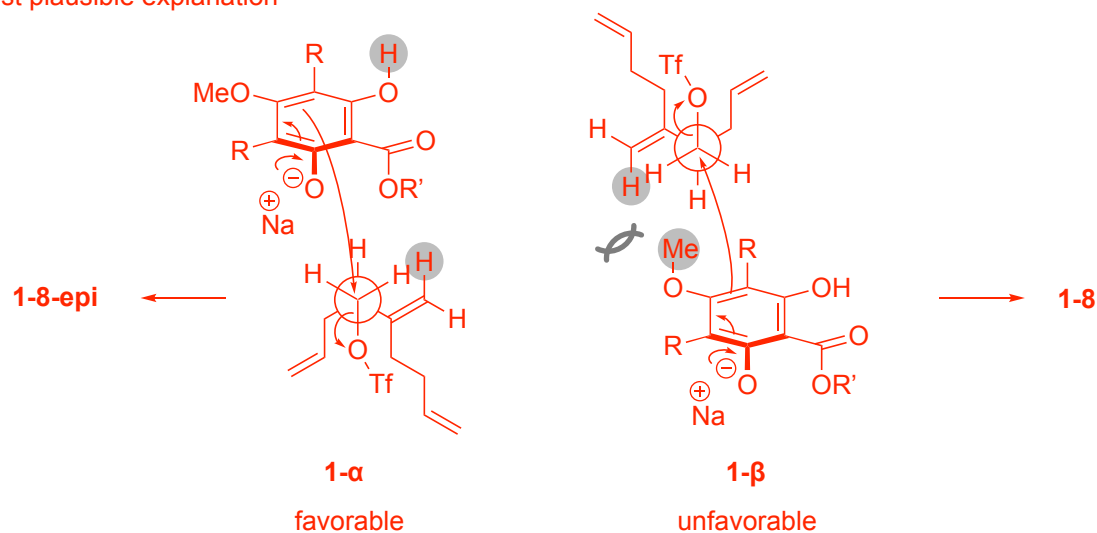
The asymmetric electrophile **1-3** appears to contribute to the preferential generation of **1-8-epi** when comparing entries 1 with 2.

1-2-1. Asymmetric induction by electrophile



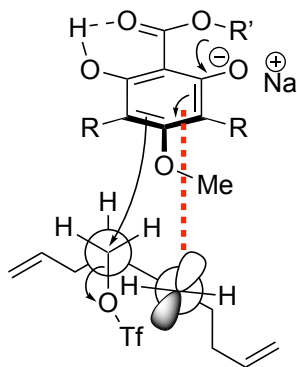
The C6-C7 bond is fixed to minimize the steric repulsion with the approaching nucleophile.

1-2-1-1. The most plausible explanation

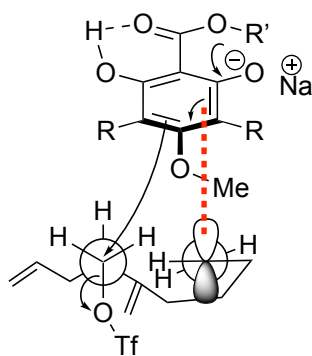


The nucleophile presumably approaches the electrophile from its tail to diminish steric repulsion.

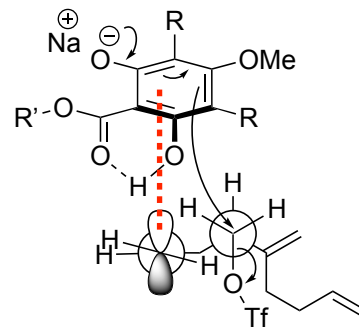
1-2-1-2. Another explanation



A: insufficient orbital overlap

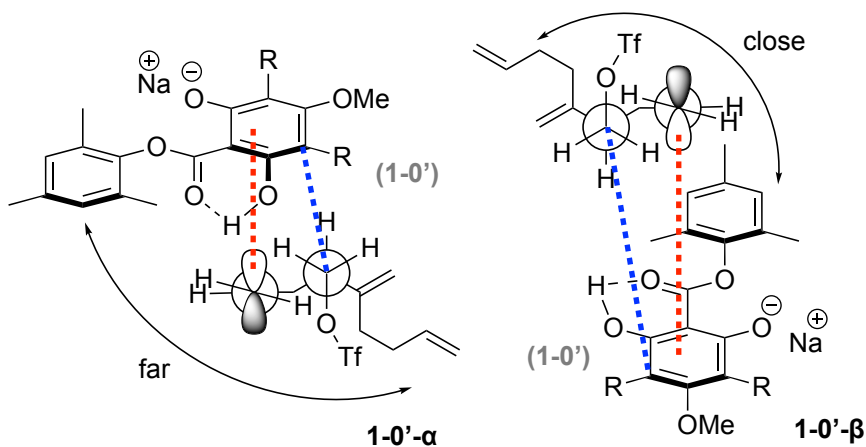


C: good alignment
rotation of the long aliphatic
chain is highly restricted



B: ideal alignment

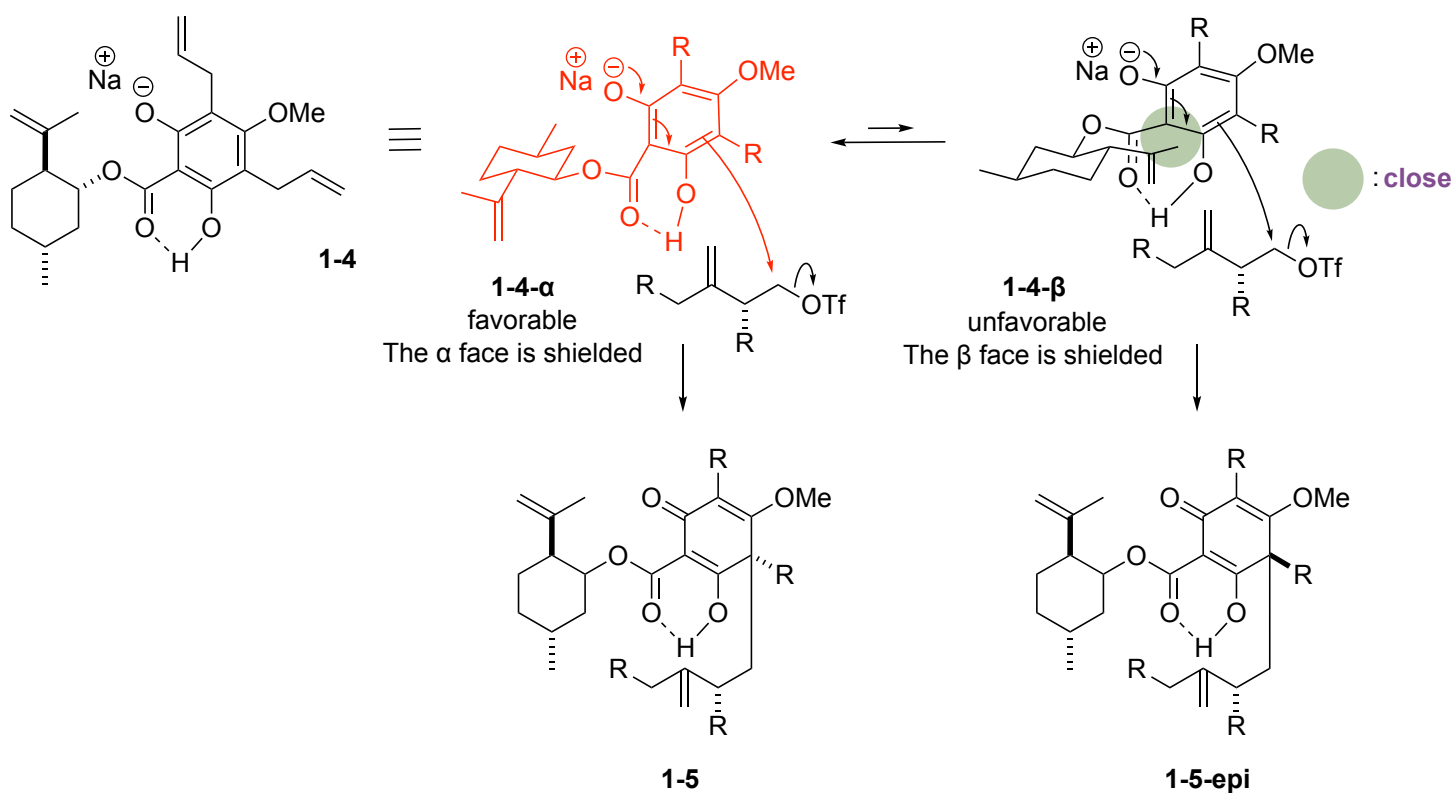
- Olefin **A** is too close to the electrophilic center, requiring much strain to align parallel to the aromatic ring.
- Olefin **C** is positioned at such a distance that the conformations with an optimal alignment for the donor-accepter interactions are entropically unfavorable.



The steric repulsion
destabilizes **1-0'-β**, thereby
inhibiting an attack from the
β face.

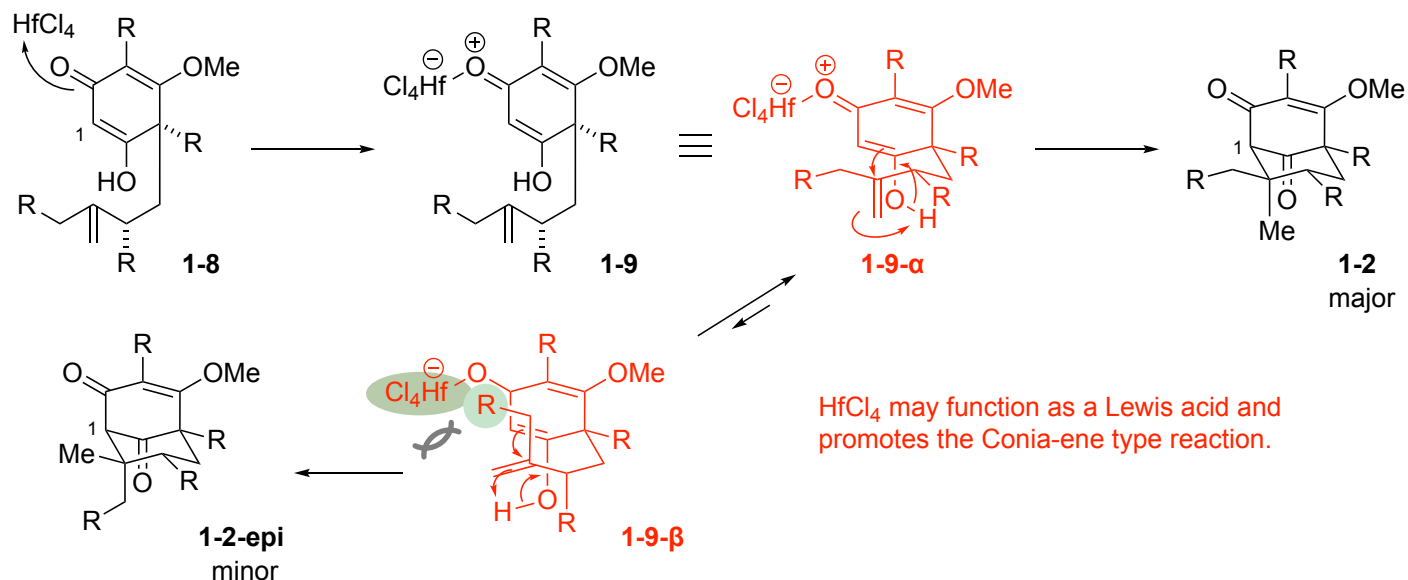
These effects might be possible,
but may not be dominant ones.

1-2-2. The role of chiral auxiliary



1-3. **discussion 2: HfCl₄-mediated cyclization**

1-3-1. Reaction mechanism



1-3-2. HfCl₄ as a Lewis acid

Table 2

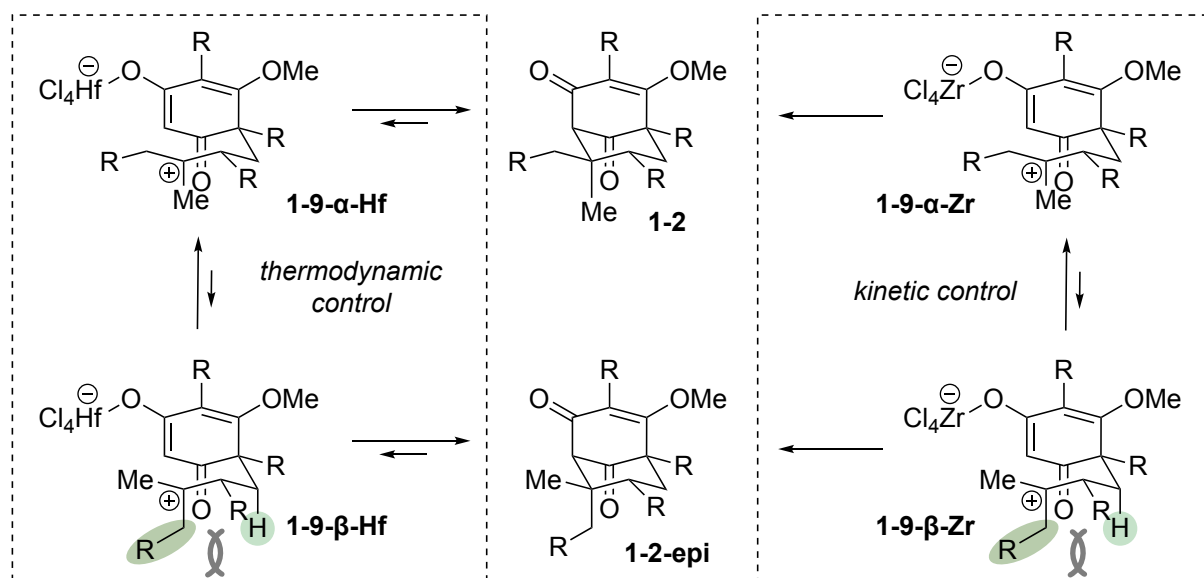
entry	Lewis acid	temperature	yield	dr at C1
1	AlCl ₃	rt to 80 °C	<u>no reaction</u>	-
2	Sc(OTf) ₃	80 °C	<u>14%</u>	2.6 : 1
3	ZrCl ₄	rt	47%	<u>1.4 : 1</u>
4	Hf(OTf) ₄	rt to 80 °C	<u>no reaction</u>	-
5	HfCl ₄	rt	43%	2.6 : 1

Hafnium is more oxophilic than most metals, which is one of the reasons for its high Lewis acidity.

No reaction proceeded with Hf(OTf)₄ (entry 4). This can be attributed to its strong electronegativity, which inhibits electron flow from oxygen.

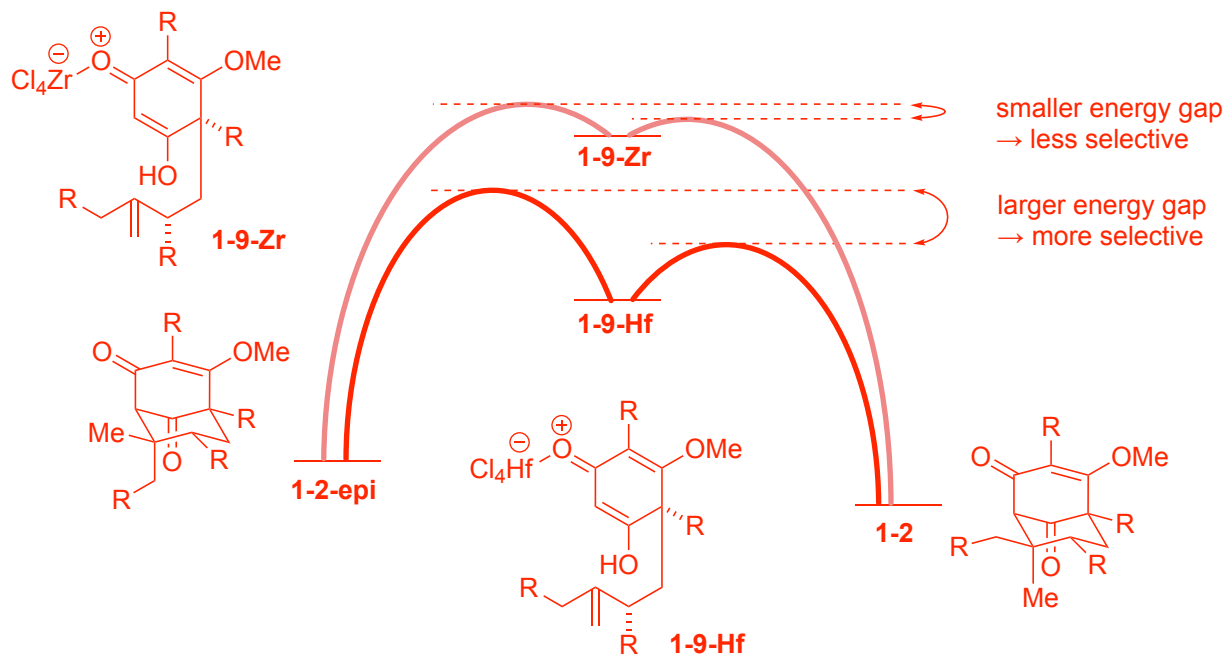
*1 eq of Lewis acid was used in each reaction.

**Solvent: dichloroethane



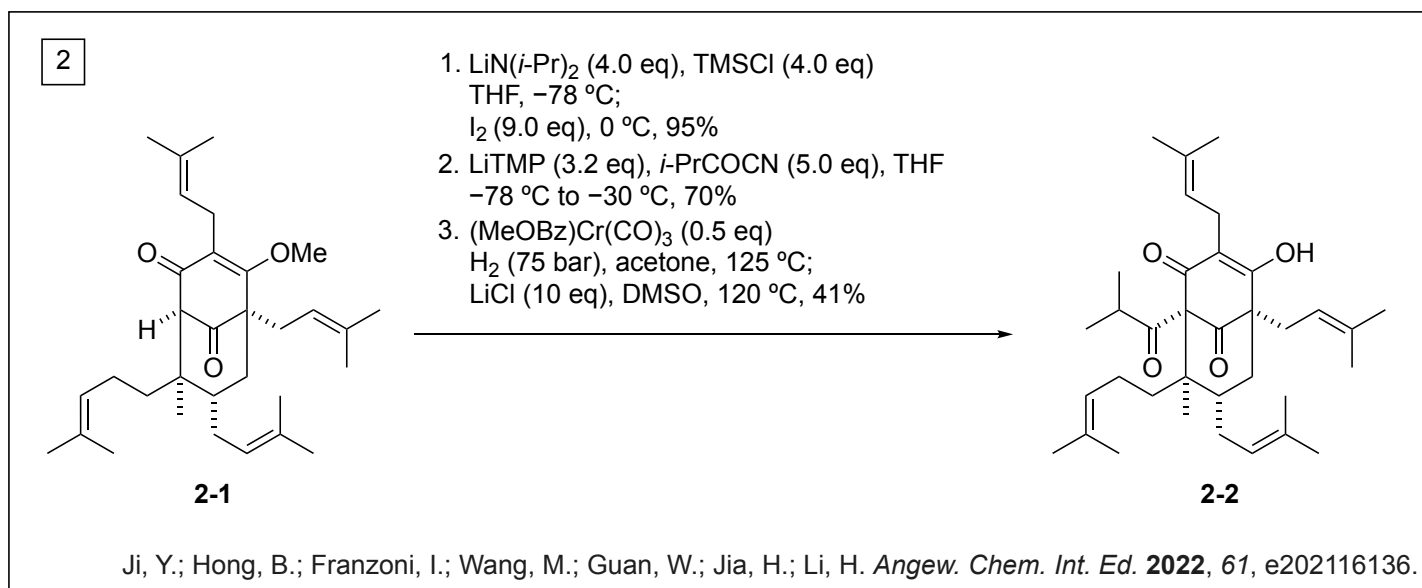
The alkylation step might be reversible with hafnium due to its high oxophilicity and could afford the products **1-2** and **1-2-epi** in the ratio thermodynamically determined.

The kinetic product with zirconium is **1-2** too, but the diastereomer excess can be different.

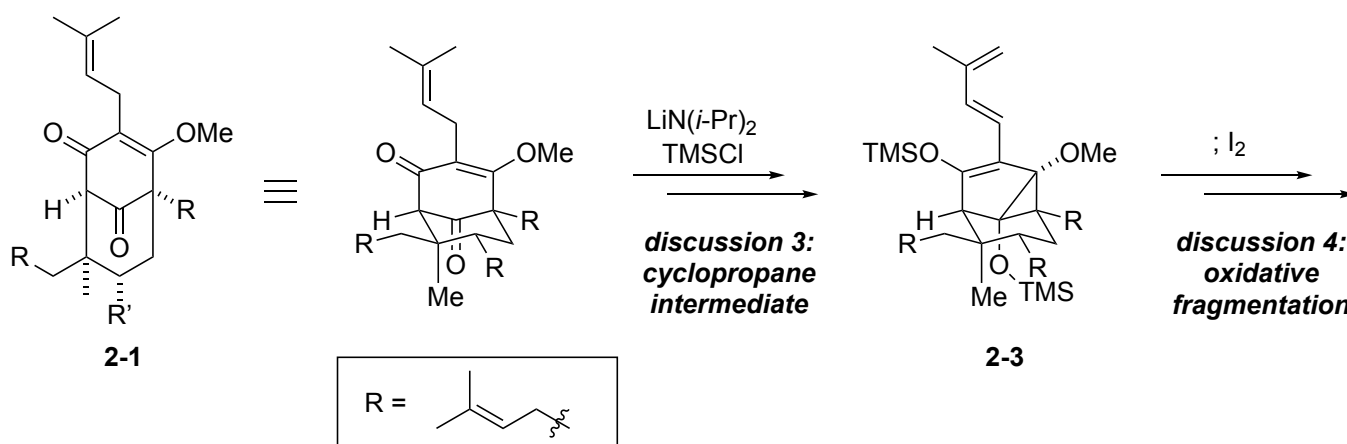


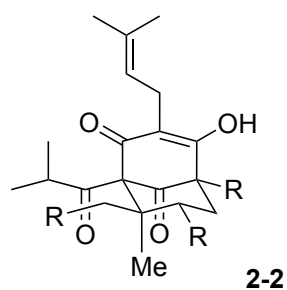
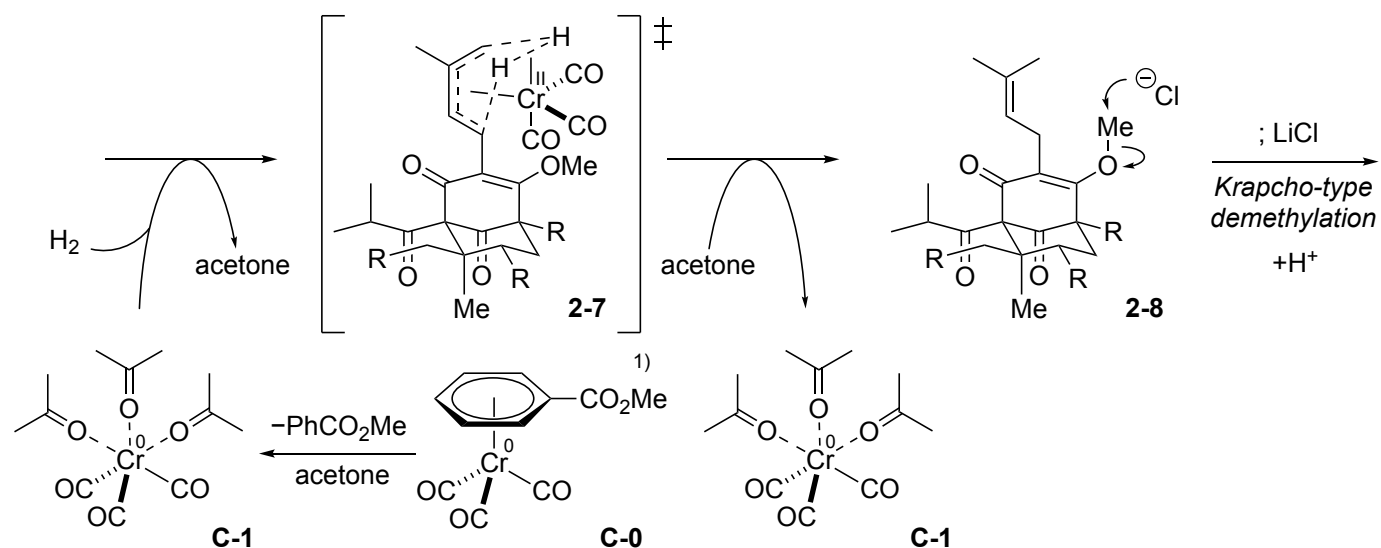
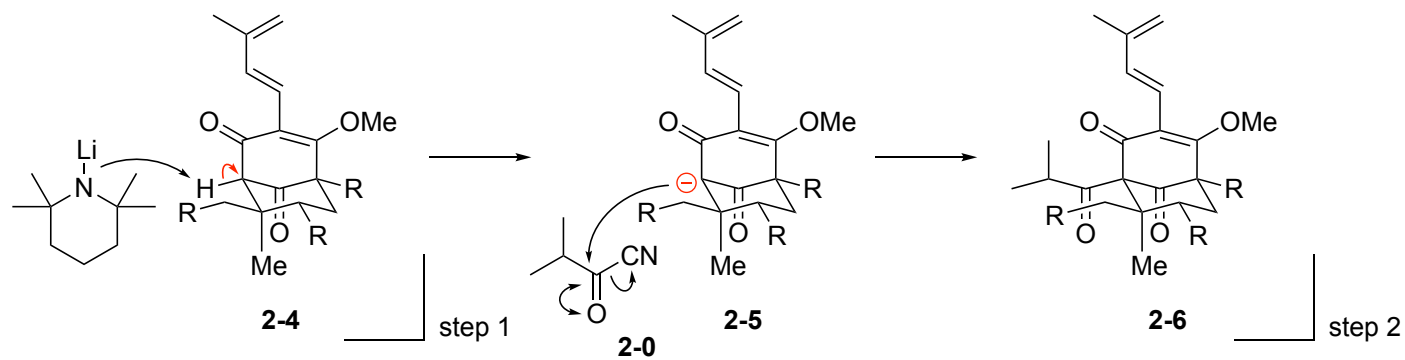
Moreover, the instability of **1-9-Zr** in comparison to **1-9-Hf**, arising from the relatively weaker Zr-O bond, likely reduces the stereoselectivity of the reaction by narrowing the energy gap between the two transition state leading to **1-2** and **1-2-epi** (early transition state).

This effect appears more plausible in the context of this reaction, which involves the formation of strong C-C bonds and does not seem to be reversible.

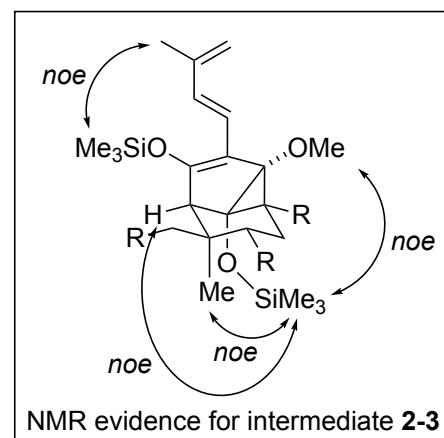


2-1. Reaction mechanism



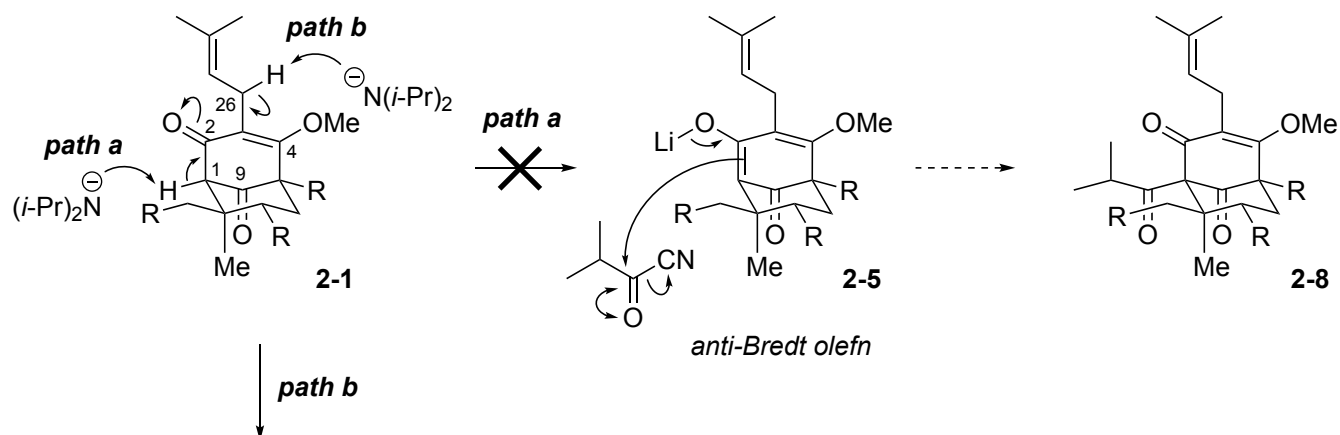


step 3

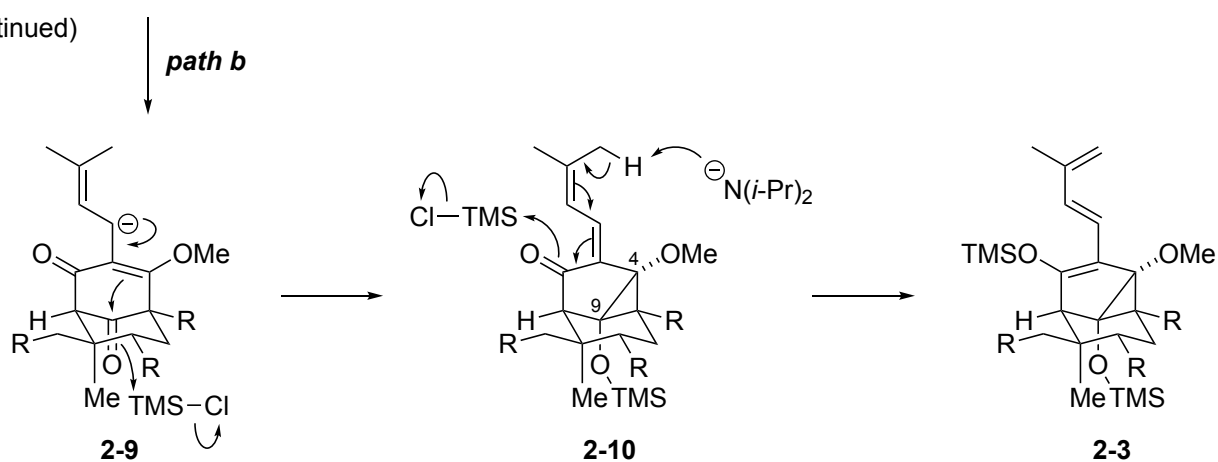


2-2. discussion 3: cyclopropane intermediate

2-2-1. Reaction mechanism - author's proposal



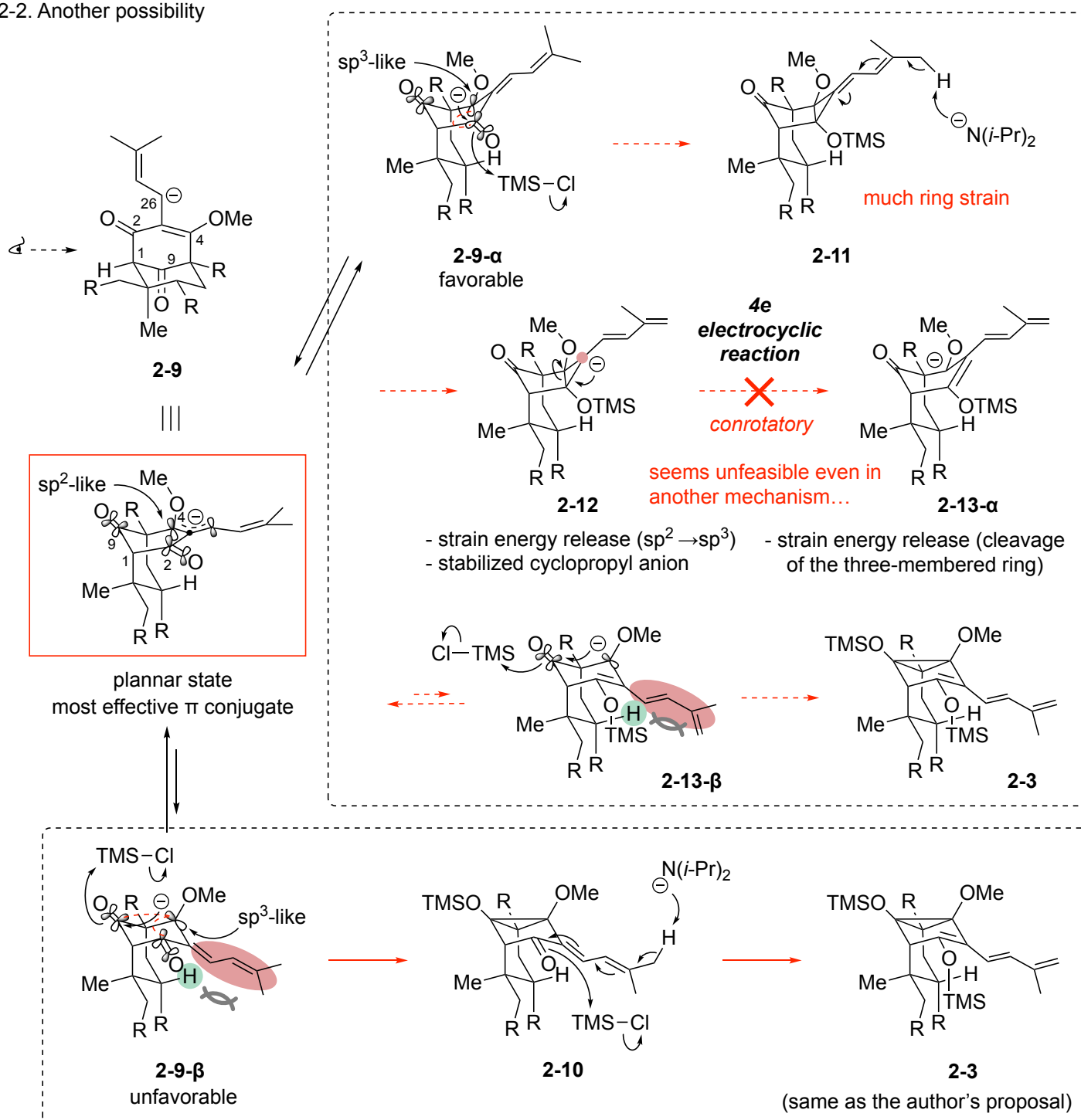
(continued)



The author initially aimed for direct alkylation via the enolate generated by deprotonation at the activated methylene, C1 (**path a**). However, this approach failed due to the low acidity of the proton, located on the bridgehead, with a σ bond poorly overlapping with adjacent π orbital.

Instead, the C26 proton was removed first to generate a bond between C4-C9 (**path b**).

2-2-2. Another possibility



2-3 can be generated via intermediate **2-11**, which has the C2-C4 bond. However, the formation of this bond requires sp^2 carbon in the cyclopropane ring, and thus hard to achieve.

2-3. discussion 4: oxidative fragmentation

2-3-0. Screening of oxidants

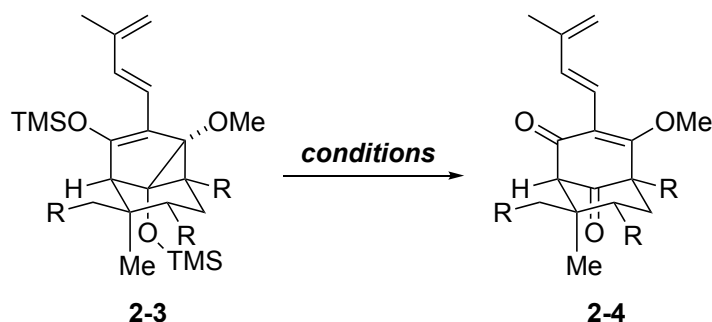
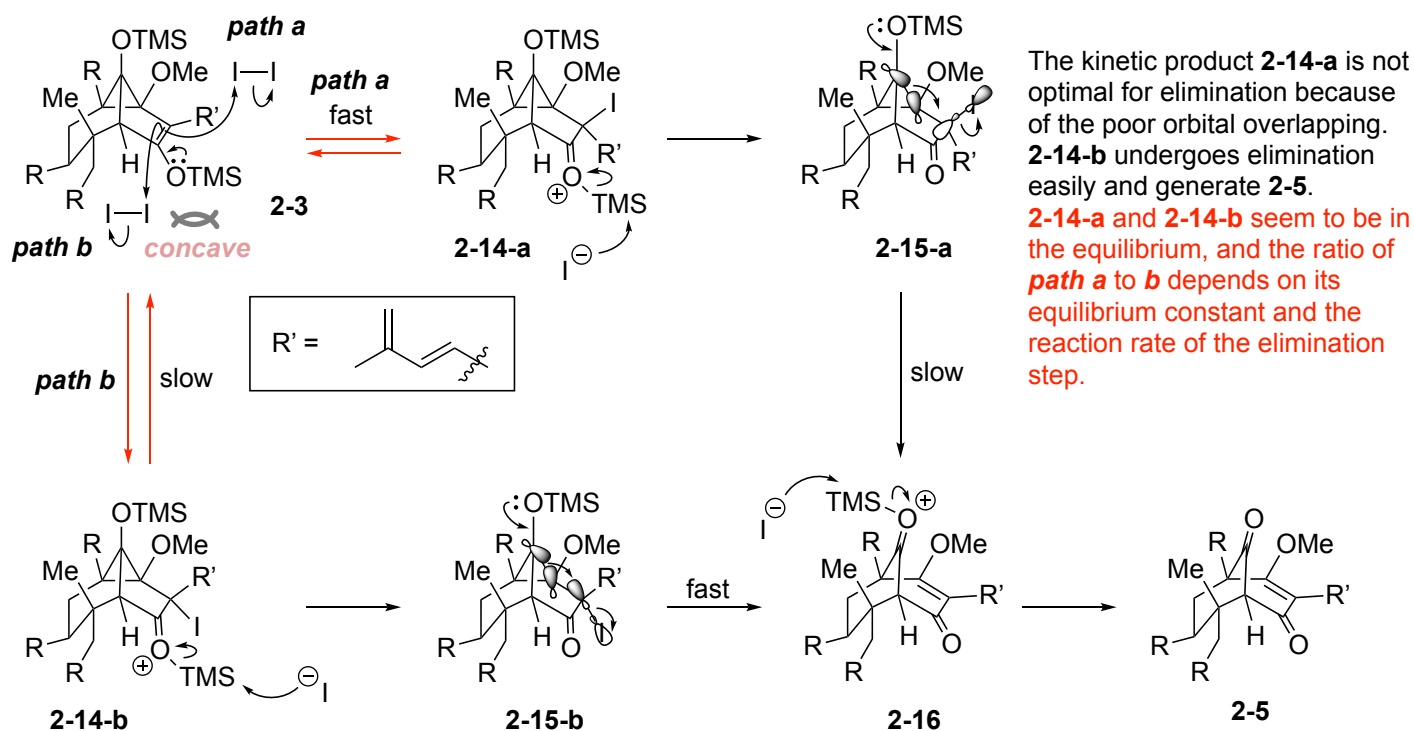


Table 3

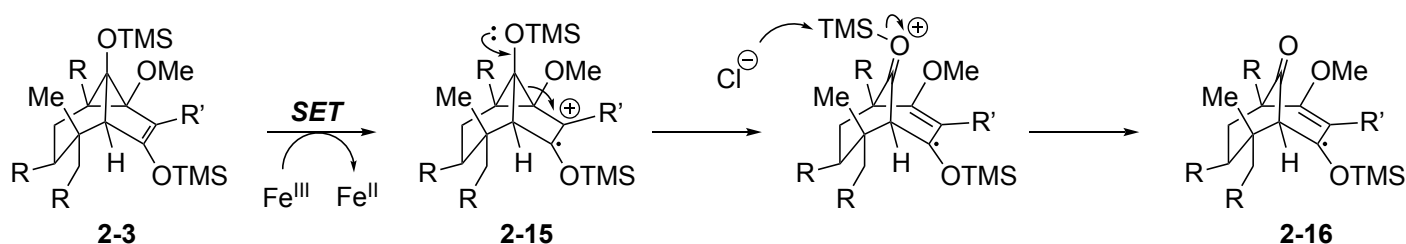
entry	conditions	yield
1	FeCl_3 (9.0 eq), THF, 0 °C	41%
2	$\text{PhI}(\text{OAc})_2$ (2.0 eq), THF, 0 °C	21%
3	I_2 (9.0 eq), THF, 0 °C	73%

2-3-1. Reaction mechanism

2-3-1-1. Reaction mechanism when I_2 is used as oxidant

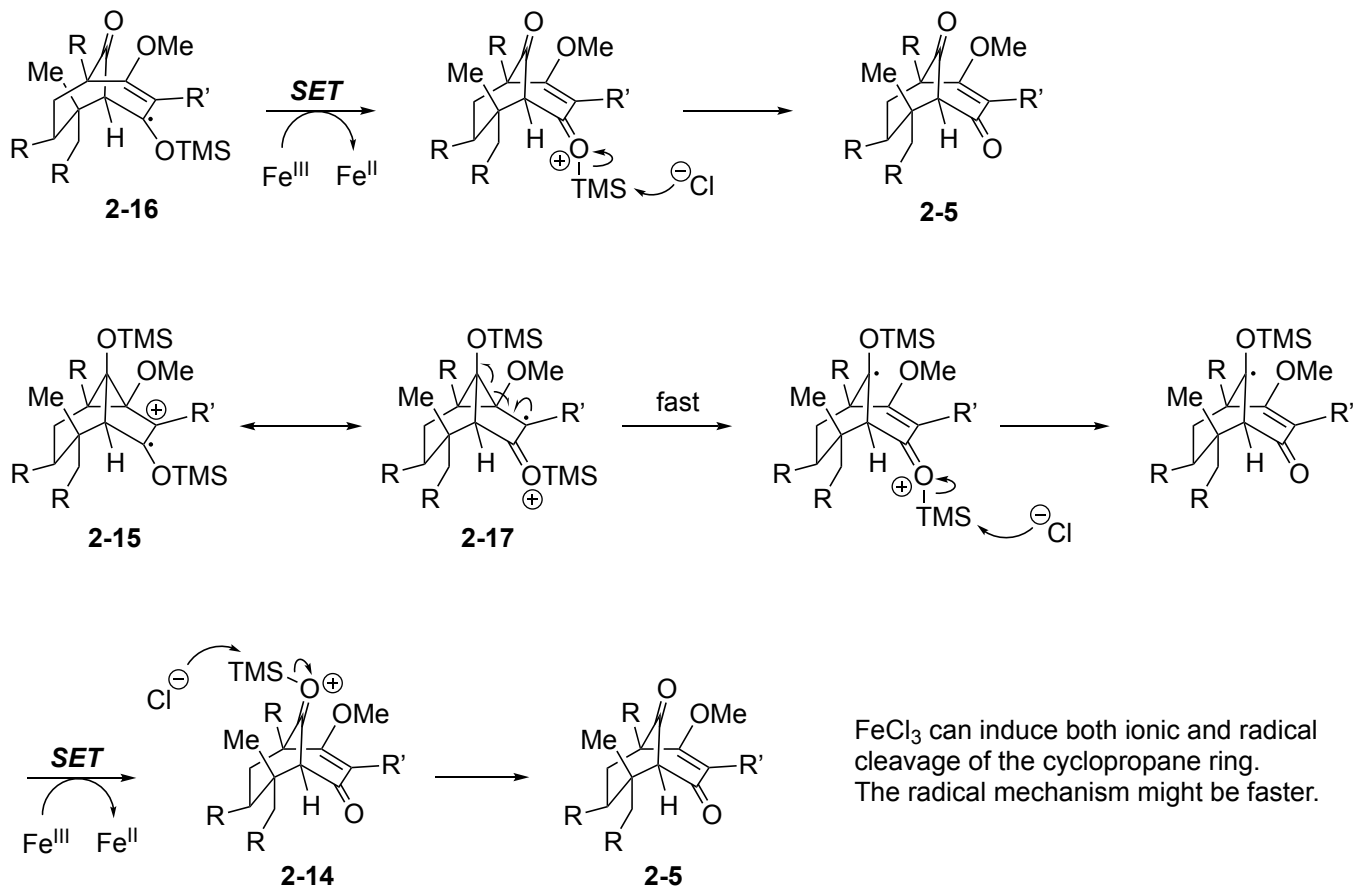


2-3-1-2. Reaction mechanism when FeCl_3 is used as oxidant

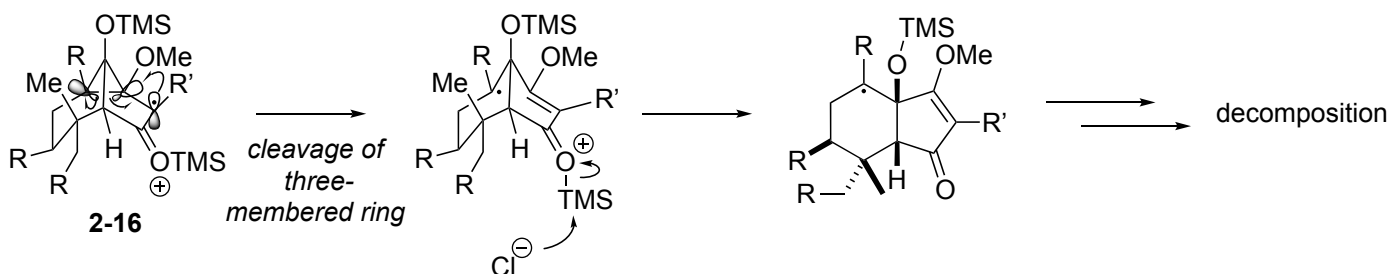


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(continued)



2-3-2. Possible side pathway led by a single electron oxidant



References:

- 1) (a) Frankel, E. N.; Selke, E.; Glass, C. A. *J. Am. Chem. Soc.* **1968**, *90*, 2446.
(b) Vasil'ev, A. A.; Serebryakov, E. P. *Russ. Chem. Bull.* **2002**, *51*, 1341.