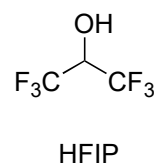
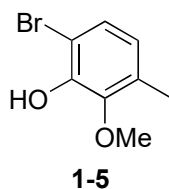
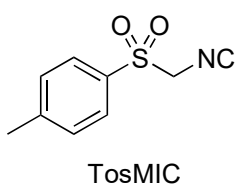
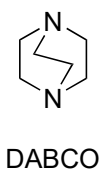
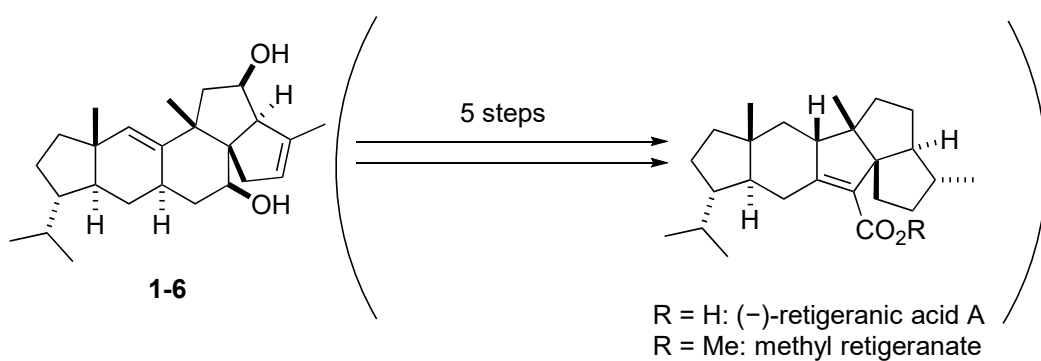
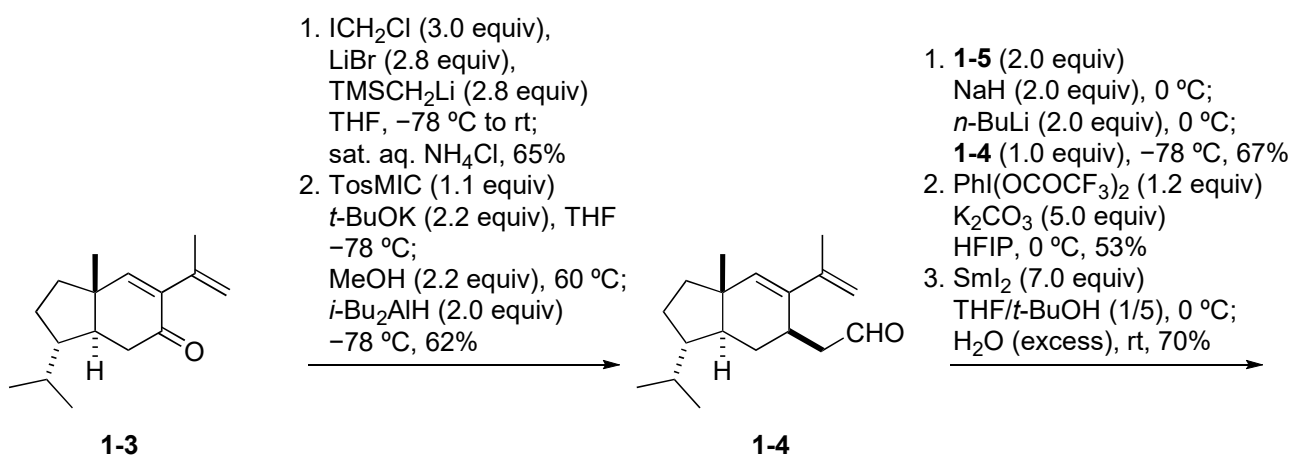
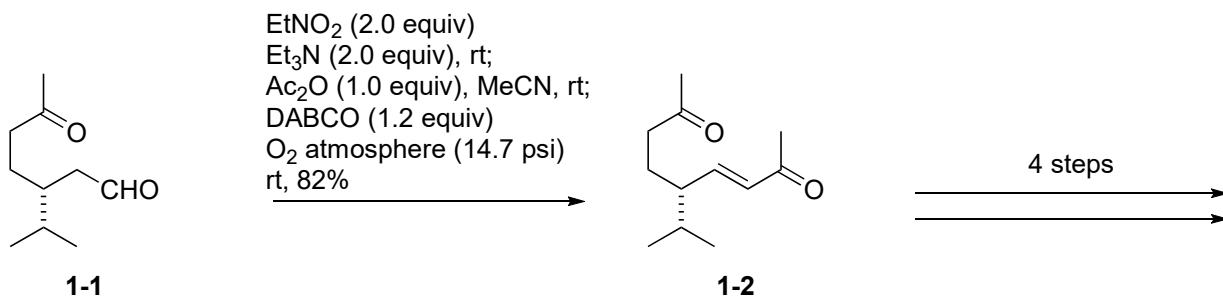


Problem Session (4)

2023.6.10 Junichi Taguchi

Please explain each reaction mechanism.



Problem Session -Answer- (4)

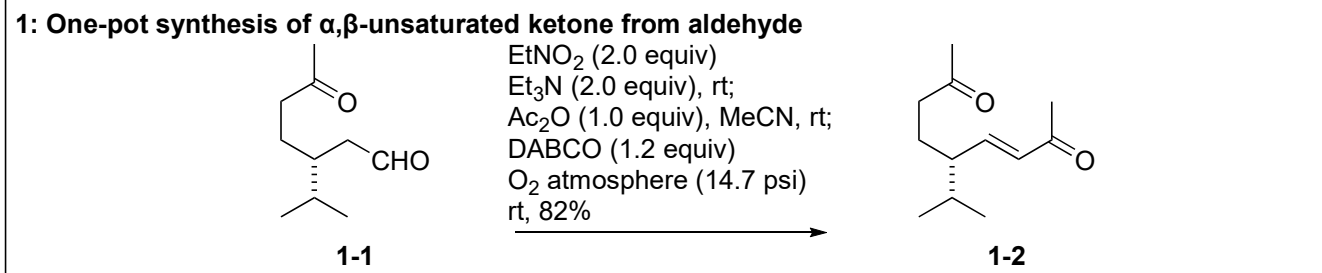
2023.6.10 Junichi Taguchi

topic: Total synthesis of (-)-retigeranic acid A by Ding group

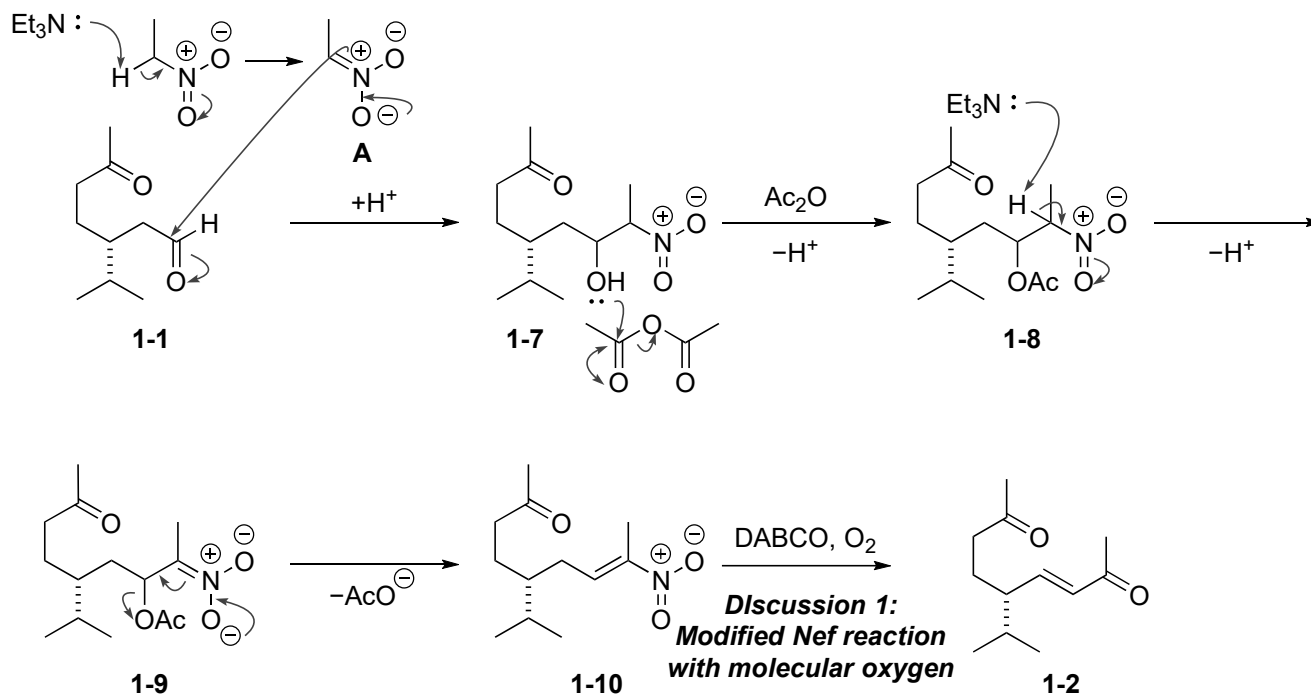
main paper: Sun, D.; Chen, R.; Tang, D.; Xia, Q.; Zhao, Y.; Liu, C.-H.; Ding, H. *J. Am. Chem. Soc.* **2023**, *in press*.

DOI: 10.1021/jacs.3c03178

See also 150307_PS_Daiki_Kamakura (Total synthesis of retigeranic acid A by other groups)



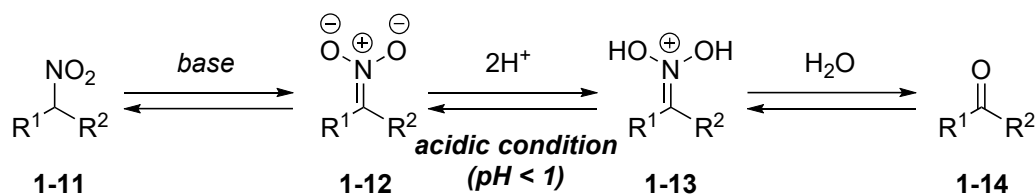
Reaction mechanism:



Discussion 1: Modified Nef reaction with molecular oxygen

1. Classical Nef reaction

The original procedure for the nitro to carbonyl transformation, as described by Nef, was essentially the hydrolysis in strongly acidic conditions (**typically pH ≤ 1**) of nitronate salt **1-12** produced by basic treatment of a nitroalkane **1-11**.^{ref.1}



The harsh conditions have encouraged the development of alternative methods that can be performed under oxidative, reductive, or nearly neutral conditions.

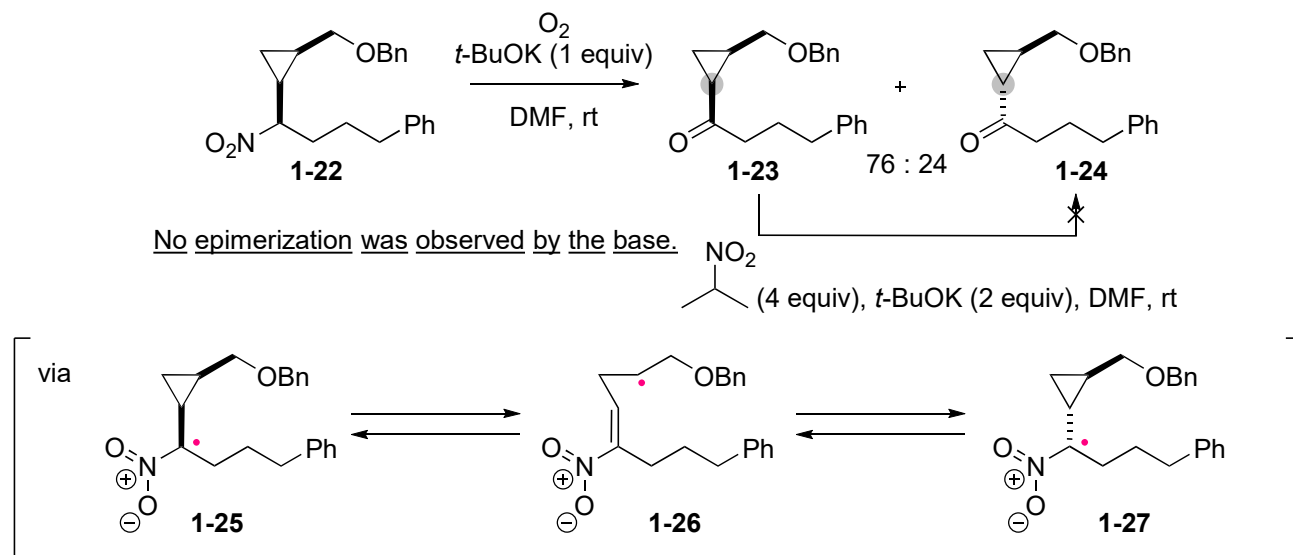
The modified condition used in the problem was one of the 'mild' Nef reaction developed by the Hayashi group.^{ref.2}

2. Mechanistic insights^{ref.2}

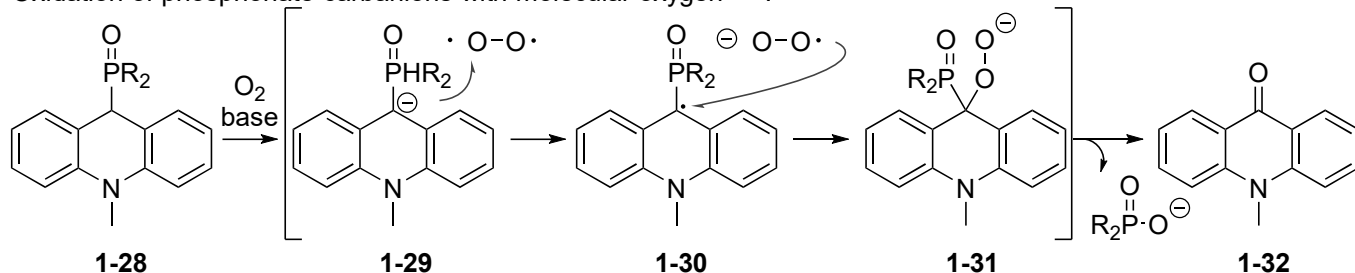
2-1. The origin of the keto-oxygen

entry	conditions	comments
1	<p>DABCO, air MeCN, rt, 20 h</p>	control experiment
2	<p>DABCO, air MeCN, rt, 20 h</p>	The keto-oxygen was not derived from NO ₂ group
3	<p>DABCO, air MeCN/H₂¹⁸O rt, 20 h</p>	The keto-oxygen was not derived from H ₂ O.
4	<p>DABCO ¹⁸O₂ (1 atm) MeCN, rt, 20 h</p>	The keto-oxygen was derived from O ₂ . 90% incorporation of ¹⁸ O.
5	<p>DABCO Ar atmosphere degassed MeCN rt, 20 h</p>	Ketone 1-16 was not generated without O ₂ . DABCO would assist the isomerization.

2. The involvement of radical species



Oxidation of phosphonate carbanions with molecular oxygen^{ref.3}:



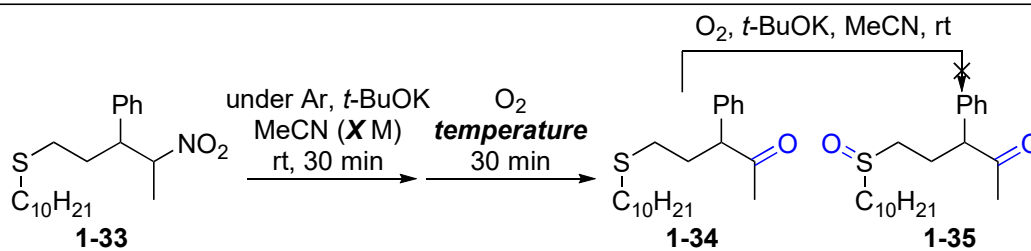
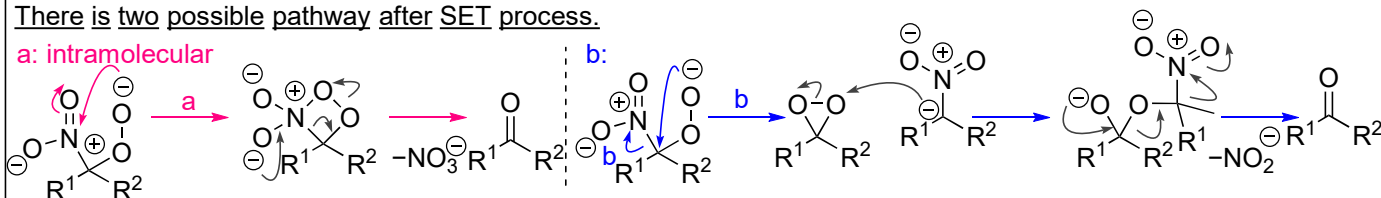
In this reaction, a single-electron transfer (SET) process occurred.

A similar reaction mechanism can be considered in this problem.

3. Intramolecular vs. Intermolecular

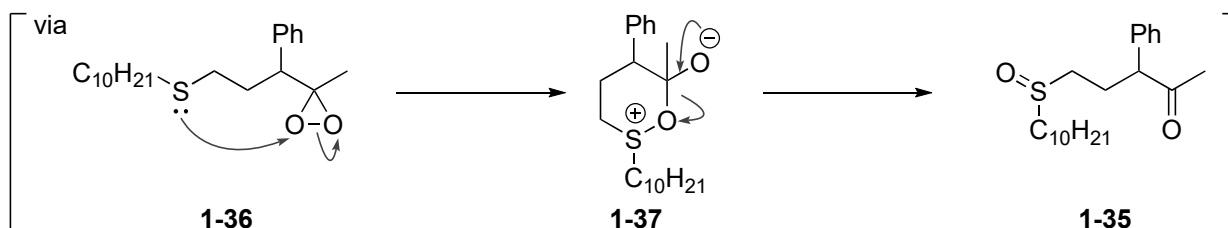
There is two possible pathway after SET process.

a: intramolecular



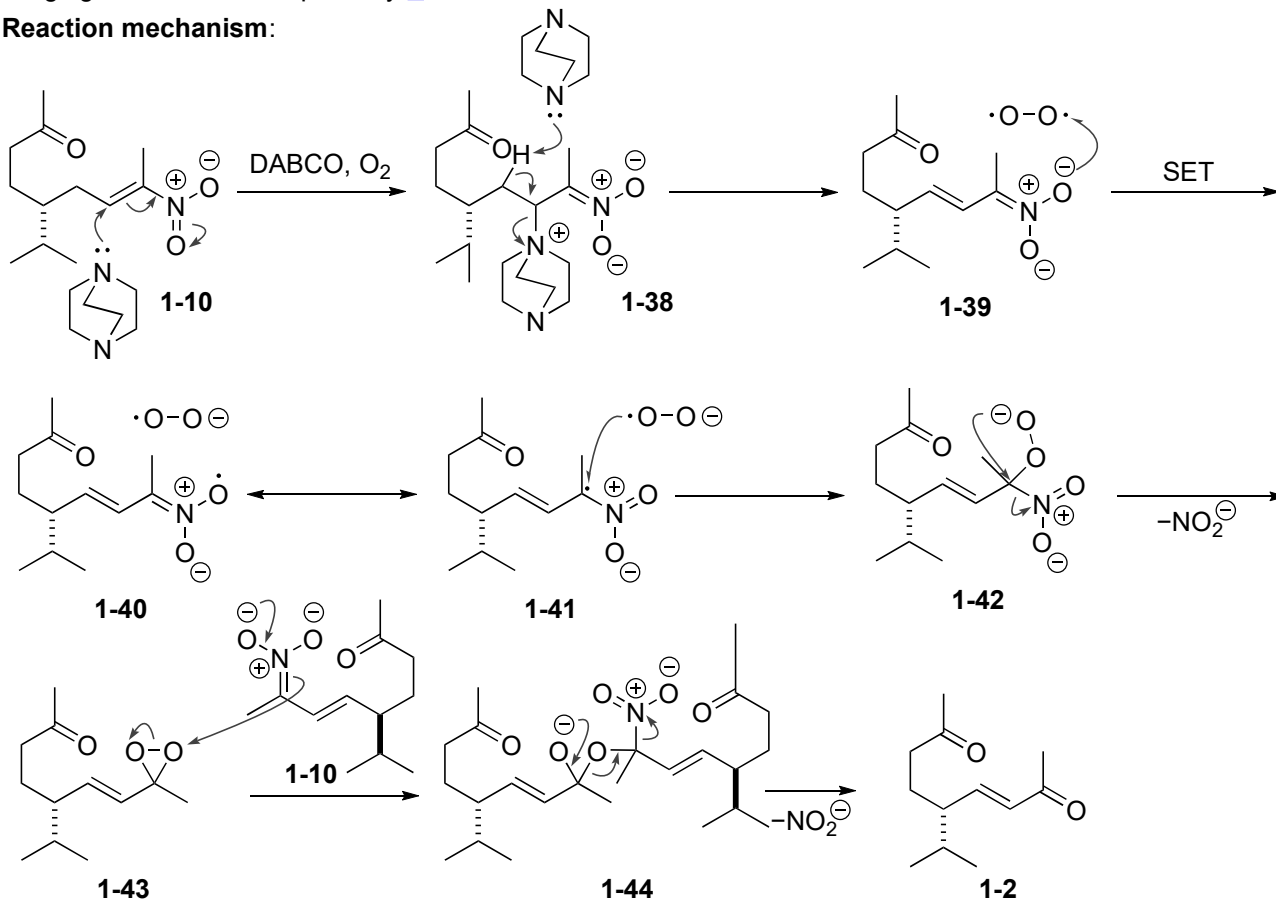
entry	concentration [M]	temperature [°C]	isolated yield [%]	
1	0.25	23	82	<5
2	0.005	23	71	8
3	0.005	-40	65	16

The sulfoxide **1-35** was formed during the oxidative conversion of the nitro group into the ketone and the yield of **1-35** increased at lower concentrations and lower temperatures. In addition, sulfide **1-34** was not oxidized by molecular oxygen. These results indicate that the sulfide was oxidized in an intramolecular manner, which would support the involvement of a 1,1-dioxirane species **1-36** during the course of the reaction.



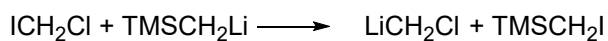
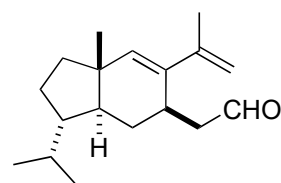
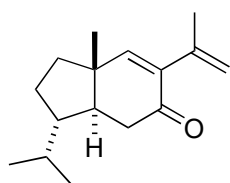
Judging from the results, pathway **b** is more favorable.

Reaction mechanism:

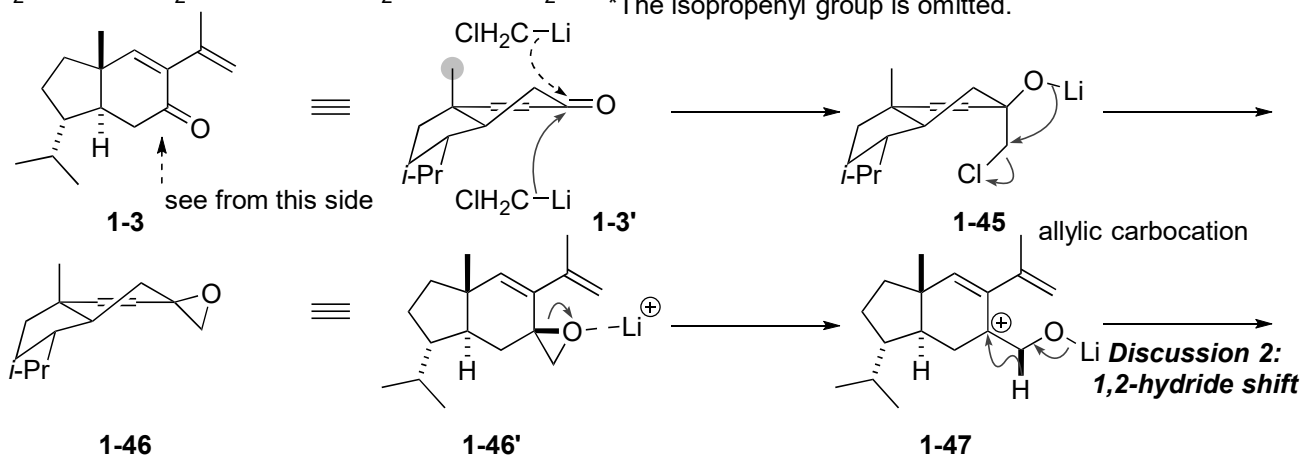


2: Preparation of aldehyde

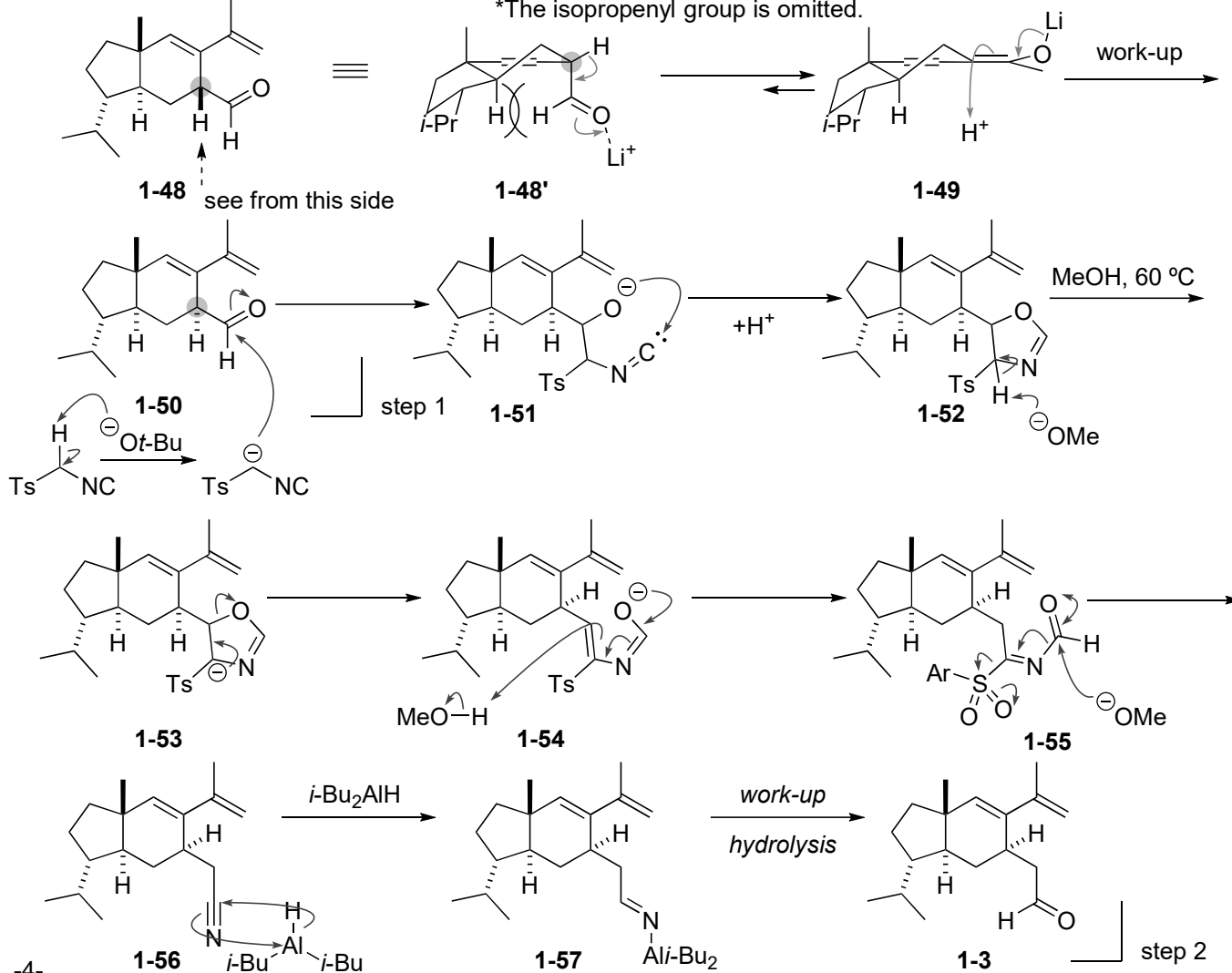
1. ICH₂Cl (3.0 equiv),
LiBr (2.8 equiv),
TMSCH₂Li (2.8 equiv)
THF, -78 °C to rt;
sat. aq. NH₄Cl, 65%
2. TosMIC (1.1 equiv)
t-BuOK (2.2 equiv), THF
-78 °C;
MeOH (2.2 equiv), 60 °C;
i-Bu₂AlH (2.0 equiv)
-78 °C, 62%



*The isopropenyl group is omitted.

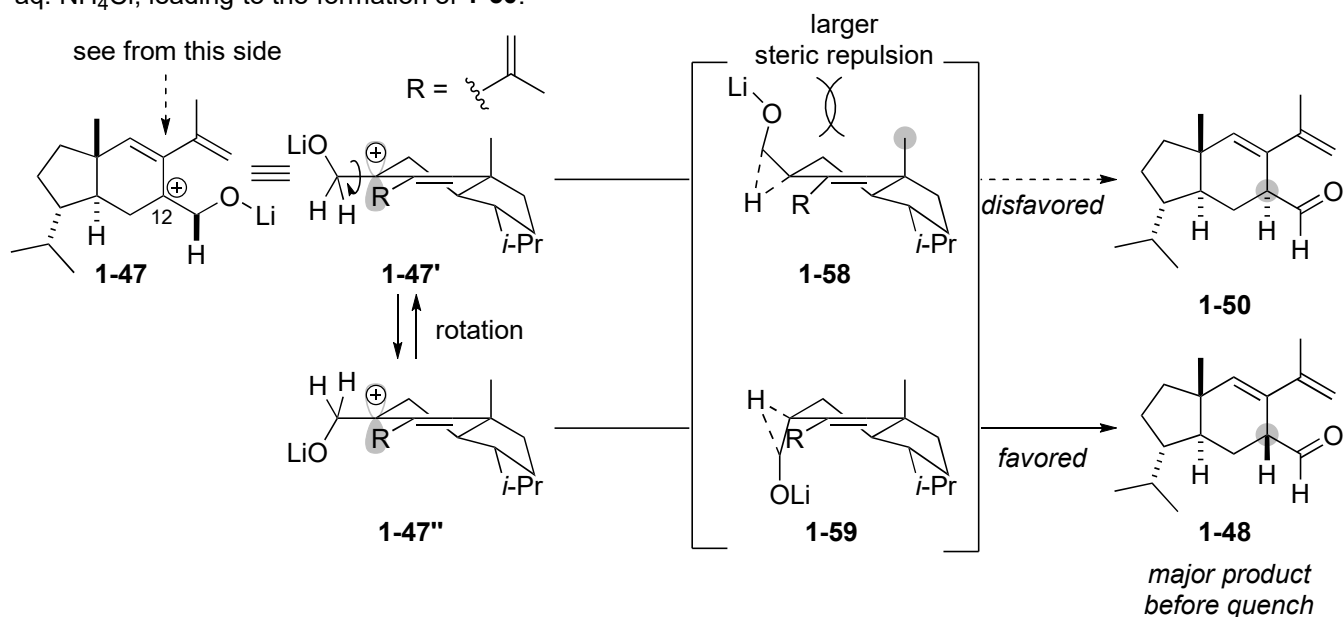


*The isopropenyl group is omitted.



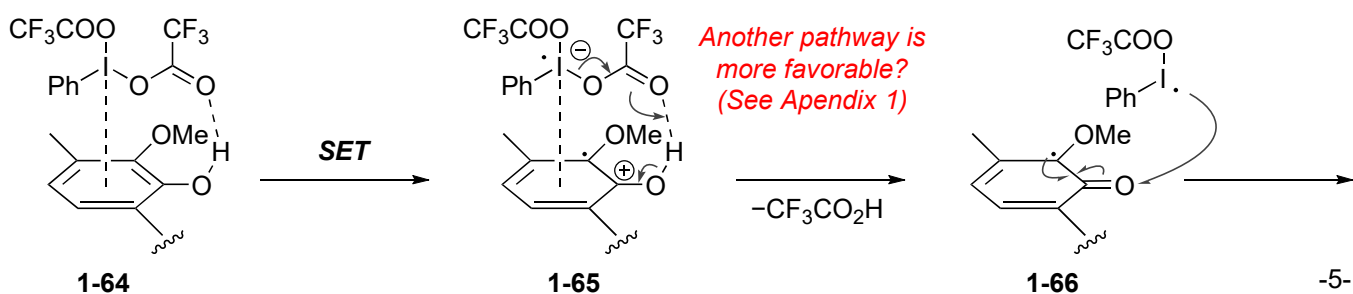
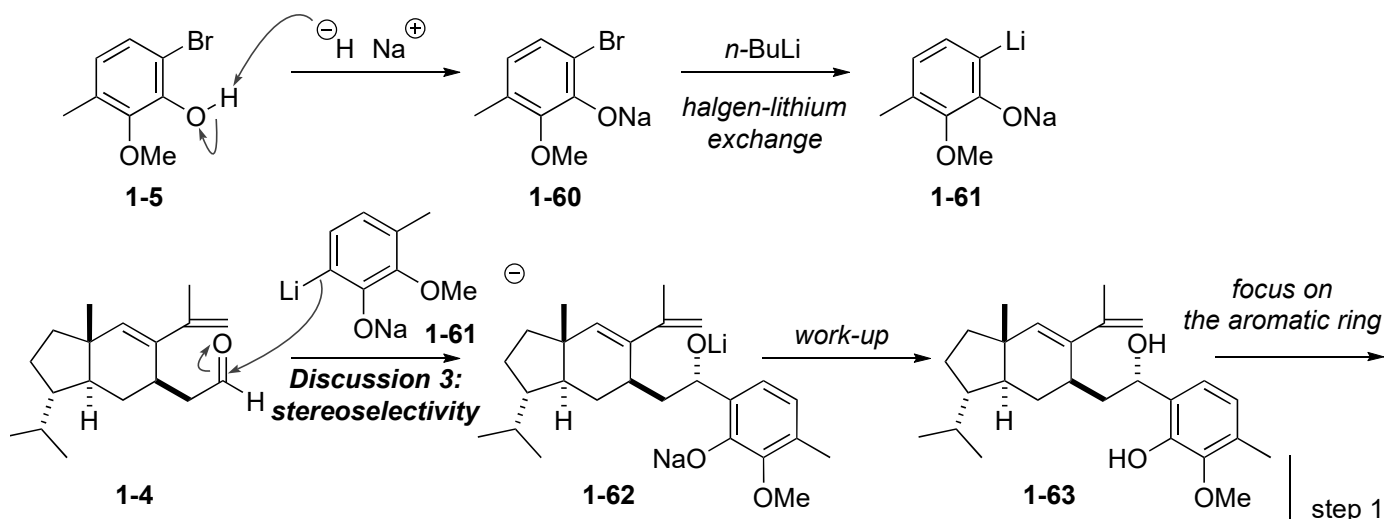
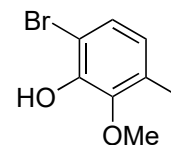
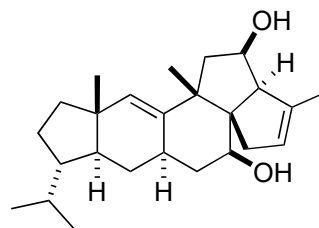
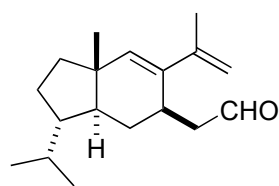
Discussion 2: 1,2-hydride shift

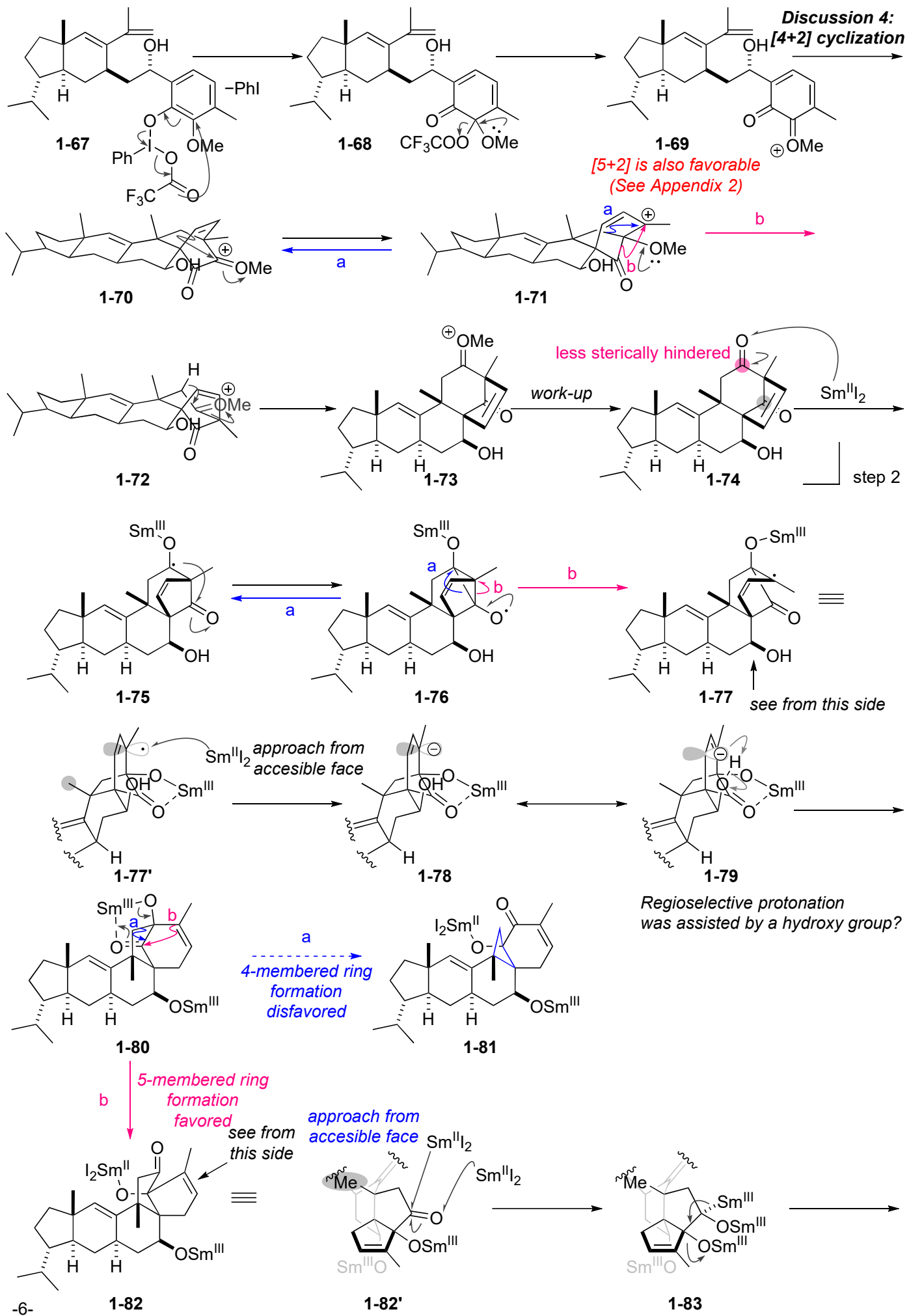
The author said that a spontaneous epimerization at C12 position was observed upon quenching the reaction with aq. NH_4Cl , leading to the formation of **1-50**.

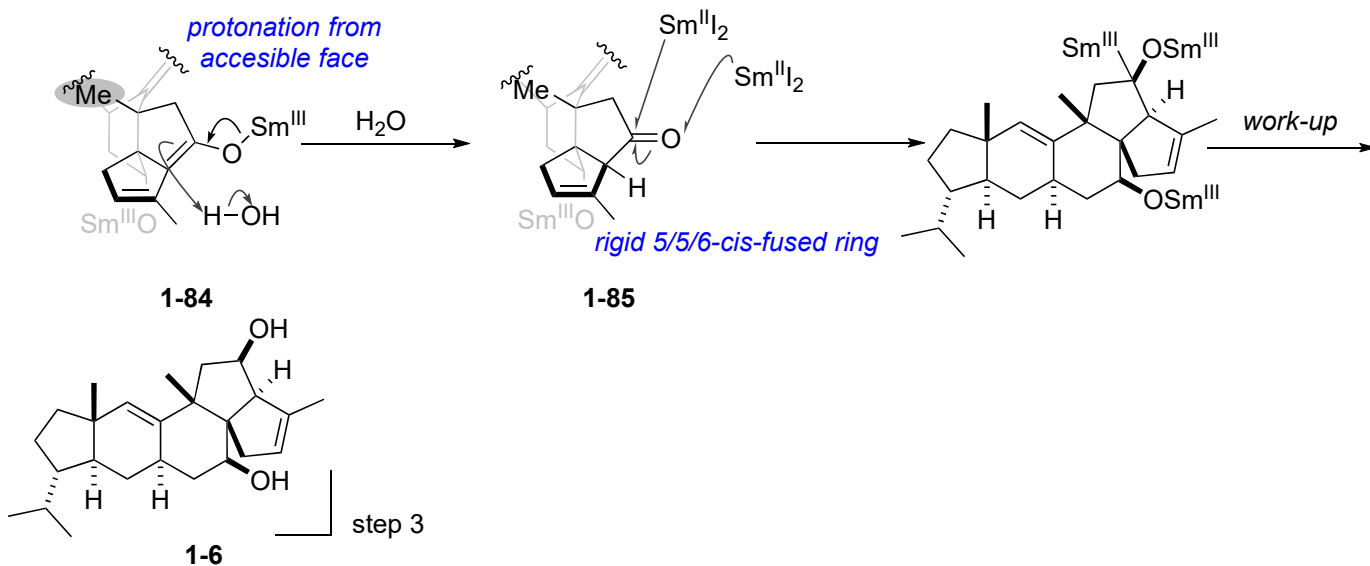


3: Reductive skeletal rearrangement cascade

- 1-5** (2.0 equiv)
 NaH (2.0 equiv), 0°C ;
 $n\text{-BuLi}$ (2.0 equiv), 0°C ;
1-4 (1.0 equiv), -78°C , 67%
- $\text{PhI}(\text{OCOCF}_3)_2$ (1.2 equiv)
 K_2CO_3 (5.0 equiv)
 HFIP , 0°C , 53%
- SmI_2 (7.0 equiv)
 $\text{THF}/t\text{-BuOH}$ (1/5), 0°C ;
 H_2O (excess), 70%



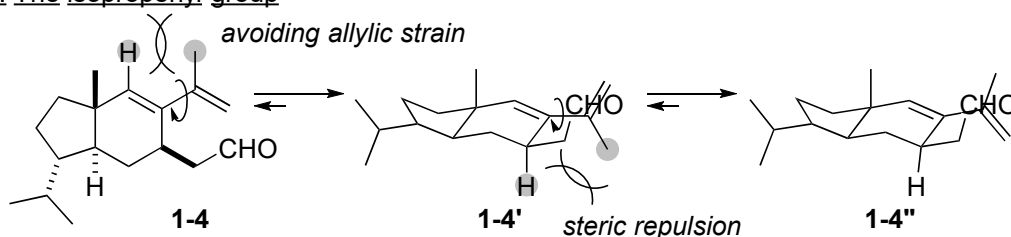




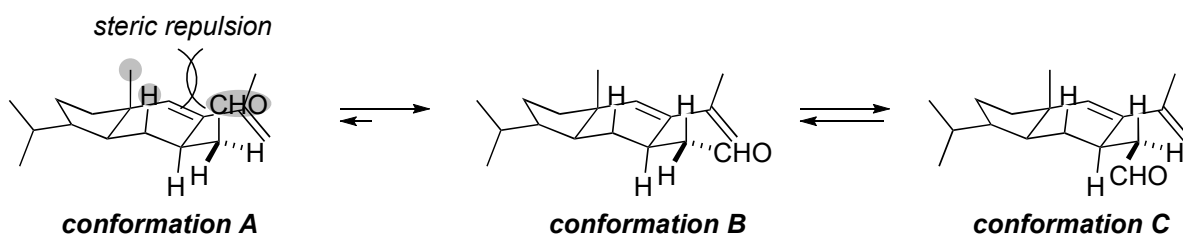
Discussion 3: Stereoselectivity

To consider the stereoselectivity of the addition reaction, it is important to analyze the most stable conformation of the aldehyde involved in the reaction. The stability of the conformation can influence the preferred orientation of the incoming nucleophile during the addition process.

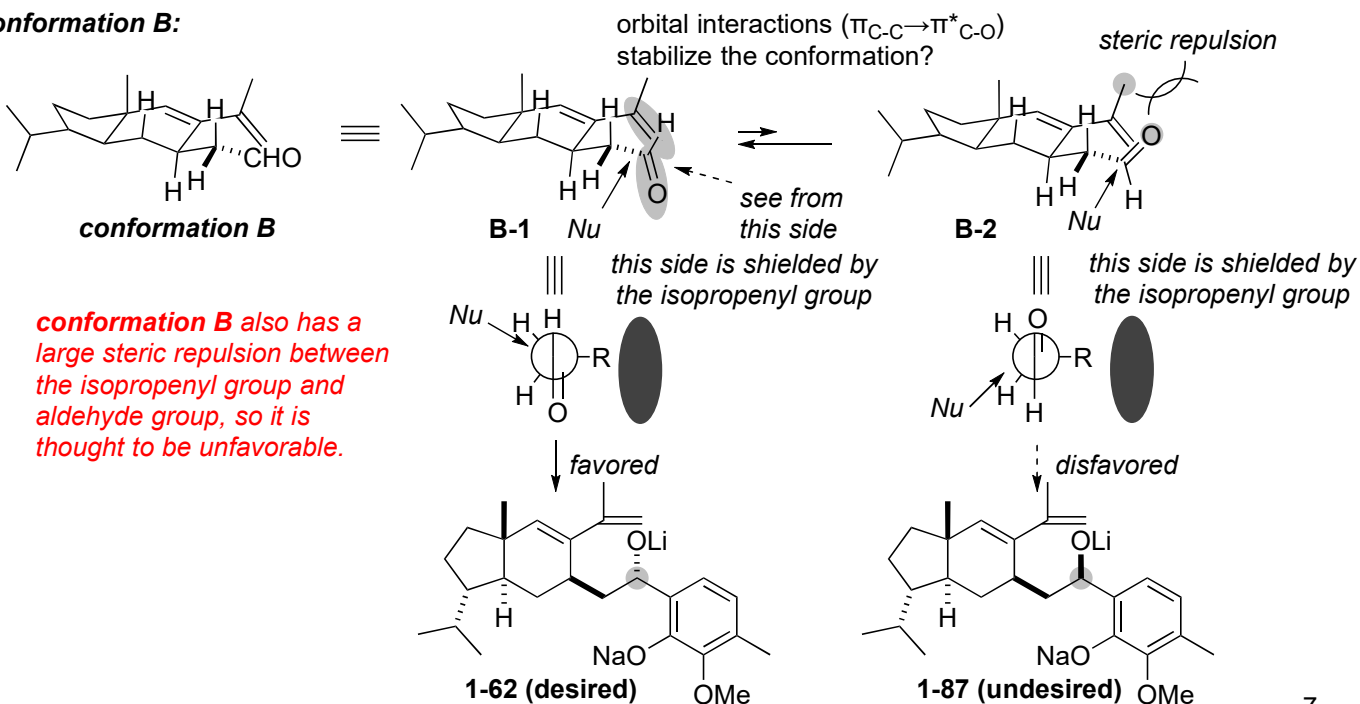
1. The isopropenyl group



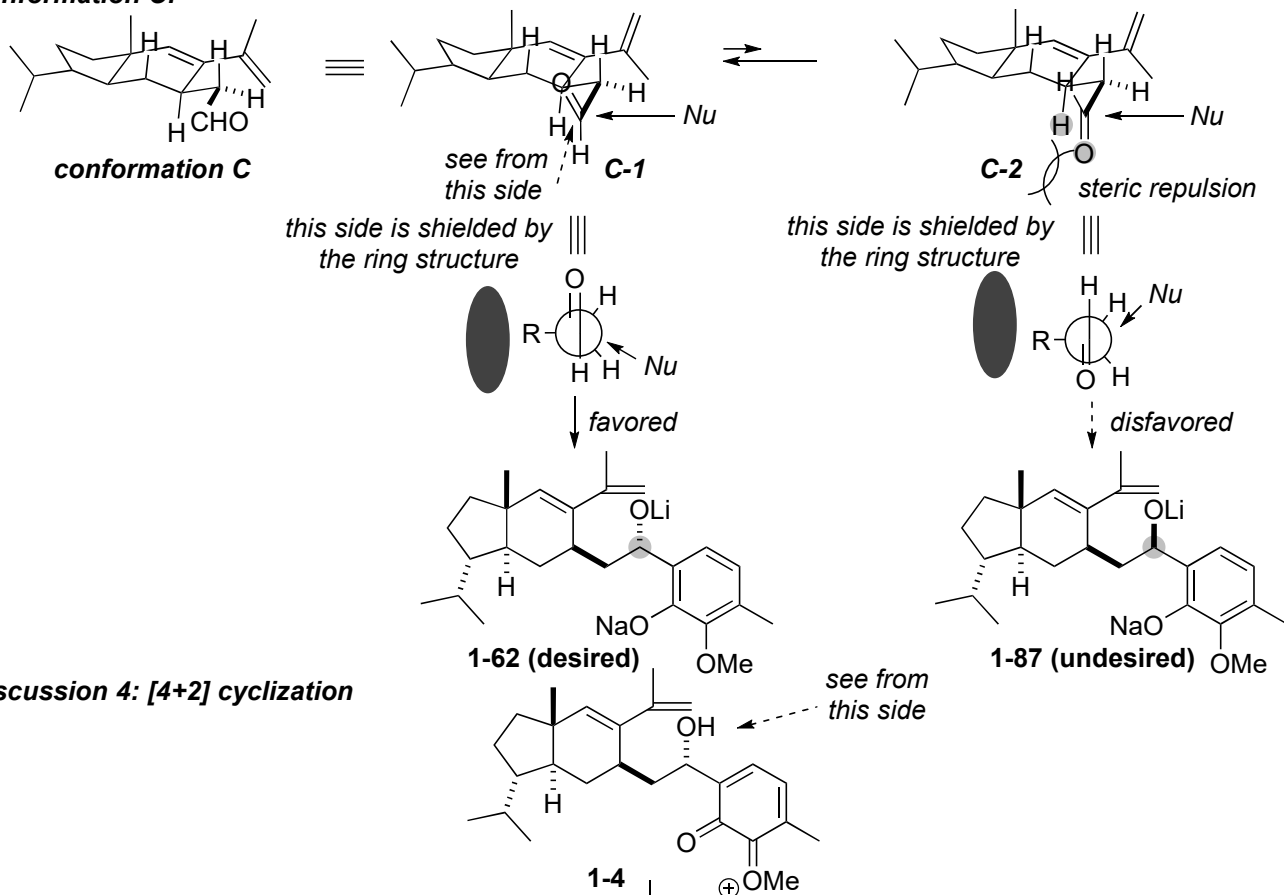
2. The aldehyde group **conformation A** is unfavorable due to the steric repulsion highlighted in the above.



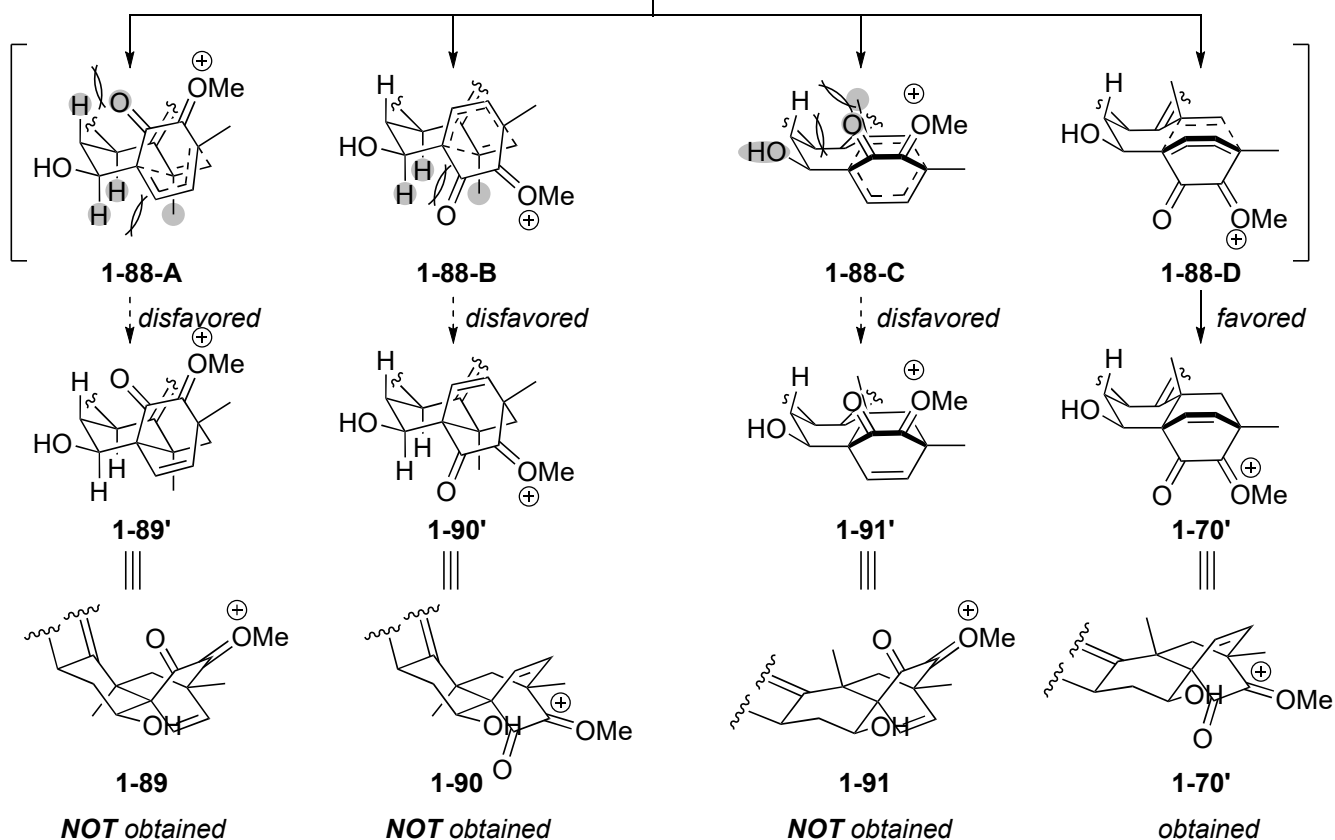
conformation B:



conformation C:



Discussion 4: [4+2] cyclization

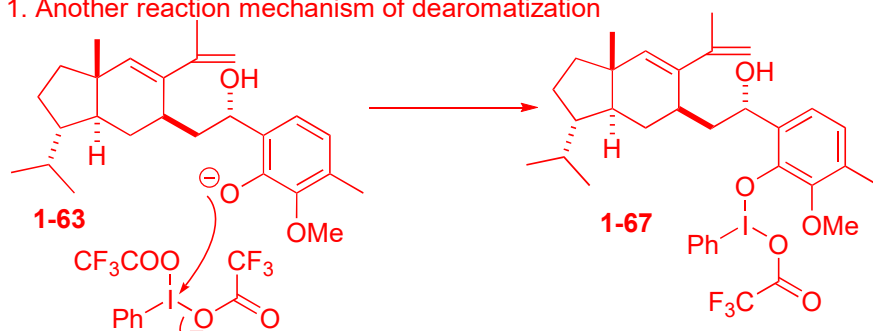


References:

- Review, see; Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.
- Umemiya, S.; Nishino, K.; Aato, I.; Hayashi, Y. *Chem. Eur. J.* **2014**, *20*, 15753.
- Motoyoshiya, J.; Ikeda, T.; Tsuboi, S.; Kusaura, T.; Takeuchi, Y.; Hayashi, S.; Yoshioka, S.; Takaguchi, Y.; Aoyama, H. *J. Org. Chem.* **2003**, *68*, 5950.

Appendix:

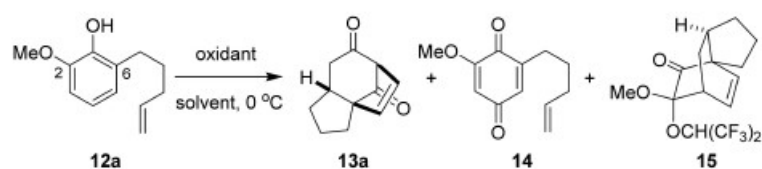
1. Another reaction mechanism of dearomatization



2. [4+2] vs [5+2] (ref. He, C.; Hu, J.; Wu, Y.; Ding, H. *J. Am. Chem. Soc.* **2017**, *139*, 6098.)

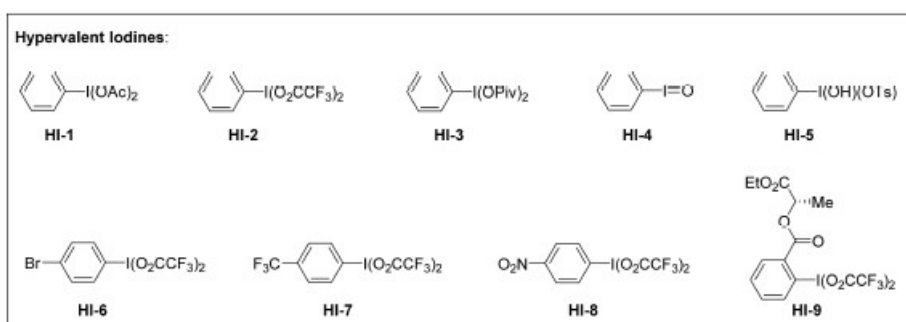
As no computational chemistry analysis of the reaction mechanism has been conducted by Ding group, and clear data on the reaction mechanism is unavailable, it was not possible to determine whether the reaction proceeds through a [4+2] or [5+2] pathway.

However, based on the initial investigation conducted by Ding group (shown below), the results suggest that the type of cycloaddition reaction is influenced by the oxidizing agent used. In other words, if the oxidizing agent readily reacts with the aromatic ring and generates a cationic intermediate through the elimination, then the reaction is more likely to proceed via the [4+2] pathway.

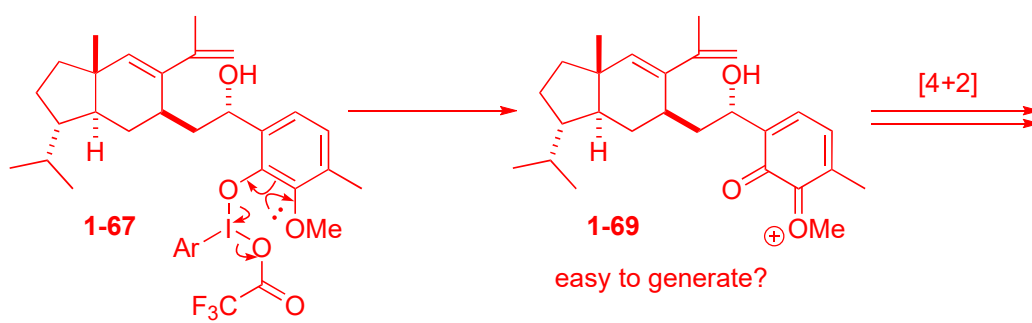


Entry	Oxidant	Solvent	Yield (%) ^b		
			13a	14	15
1	Pb(OAc) ₄ ^c	CHCl ₃	7	15	-
2	HI-1	CHCl ₃	16	30	-
3	HI-1	toluene	25	37	-
4	HI-1	TFE	42	23	-
5	HI-1	HFIP	63	<5	18
6	HI-2	HFIP	78	<5	<5
7	HI-3	HFIP	29	<5	20
8	HI-4	HFIP	30	<5	26
9	HI-5	HFIP	44	<5	15
10	HI-6	HFIP	47	<5	25
11	HI-7	HFIP	34	<5	38
12	HI-8	HFIP	20	<5	52
13	HI-9	HFIP	69	<5	<5
14	IBX	HFIP	16	54	<5

^aUnless stated otherwise, the reactions were performed with **12a** (0.2 mmol) and oxidant (1.1 equiv) in solvent (4 mL) at 0 °C for 20 min. ^bIsolated yields. ^cRun at -40 °C for 10 min.



If an oxidants can act as a "good" leaving group... (such as **HI-6** and **HI-7**)



In this problem, [5+2] cycloaddition would occur from **1-68**. CF_3CO_2 would eliminate during the cycloaddition like "a leaving group of $\text{S}_{\text{N}}2$ reaction"