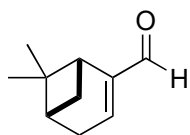


Please provide the reaction mechanisms.

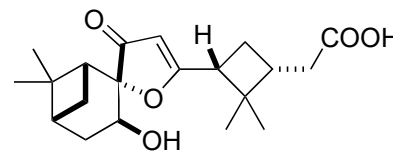
1

1. TiCl_4 (10 eq), Zn/Cu (40 eq)*, dimethoxyethane, 65 °C, 53%
2. O_2 (1 atm), methylene blue (2 mol%), CH_2Cl_2 , -40 °C, $h\nu^{**}$; DBU (5 eq), -40 to -20 °C, 56%
3. Dess-Martin periodinane (1.3 eq), CH_2Cl_2 , rt, 95%
4. O_2 (1 atm), $\text{Mn}(\text{dpm})_3$ (20 mol%)
t-BuOOH (1.5 eq), PhSiH_3 (2.5 eq, added over 12 h)
i-PrOH/ CH_2Cl_2 (6.5/1), -10 °C; PPh_3 (2.1 eq), 52%
5. FeCl_2 (80 mol%), H_2O (13 eq), MeCN, rt, 42%



1-1
(-)-myrtenal

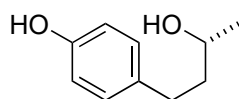
* TiCl_4 and Zn/Cu were pre-mixed under heat reflux temperature for 5 hours.
** 500 W halogene lamp



1-2

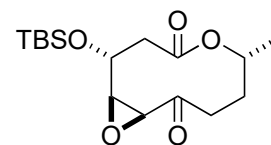
2

1. Oxone (8 eq), NaHCO_3 (24.8 eq), $\text{H}_2\text{O}/\text{MeCN}$ (10/1, 0.05 M), rt, 65%
2. *p*-TsOH (12 mol%), CHCl_3 , -20 °C; triton B (24 mol%), rt, 49%
3. NaBH_4 (0.75 eq), EtOH, rt, 96%
4. TBSOTf (1.5 eq), 2,6-lutidine (2.0 eq), CH_2Cl_2 , rt, 95%
5. PCC (15.6 eq), NaOAc (22.8 eq), CH_2Cl_2 , rt, 68%

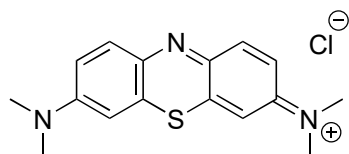


2-1

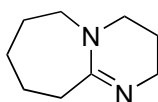
Oxone: $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$



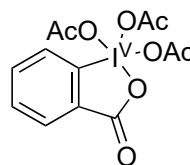
2-2



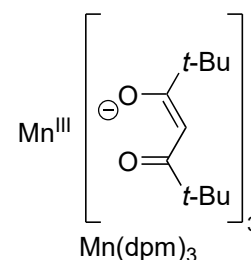
methylene blue



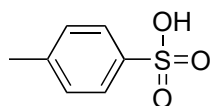
DBU



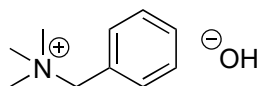
Dess-Martin periodinane



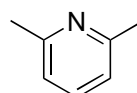
$\text{Mn}(\text{dpm})_3$



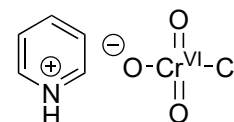
p-TsOH



triton B



2,6-lutidine



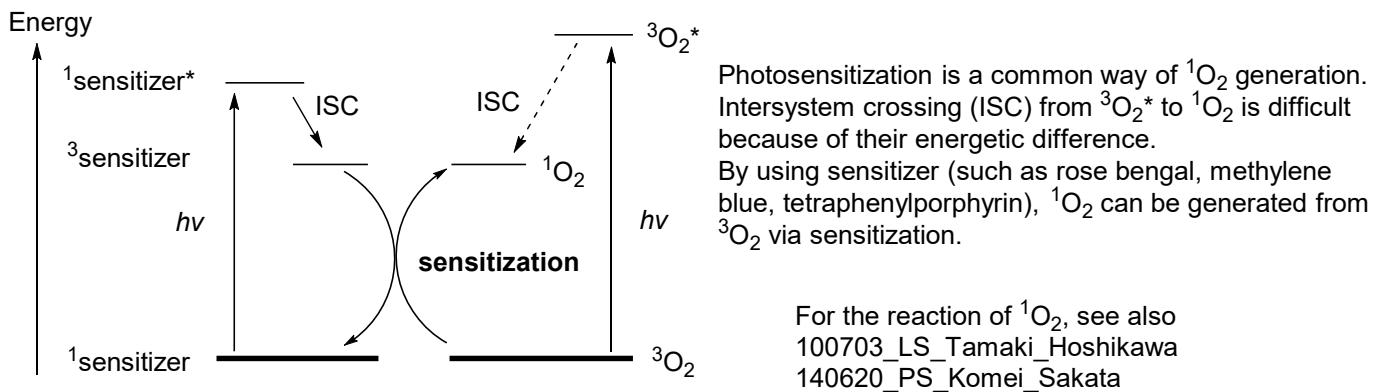
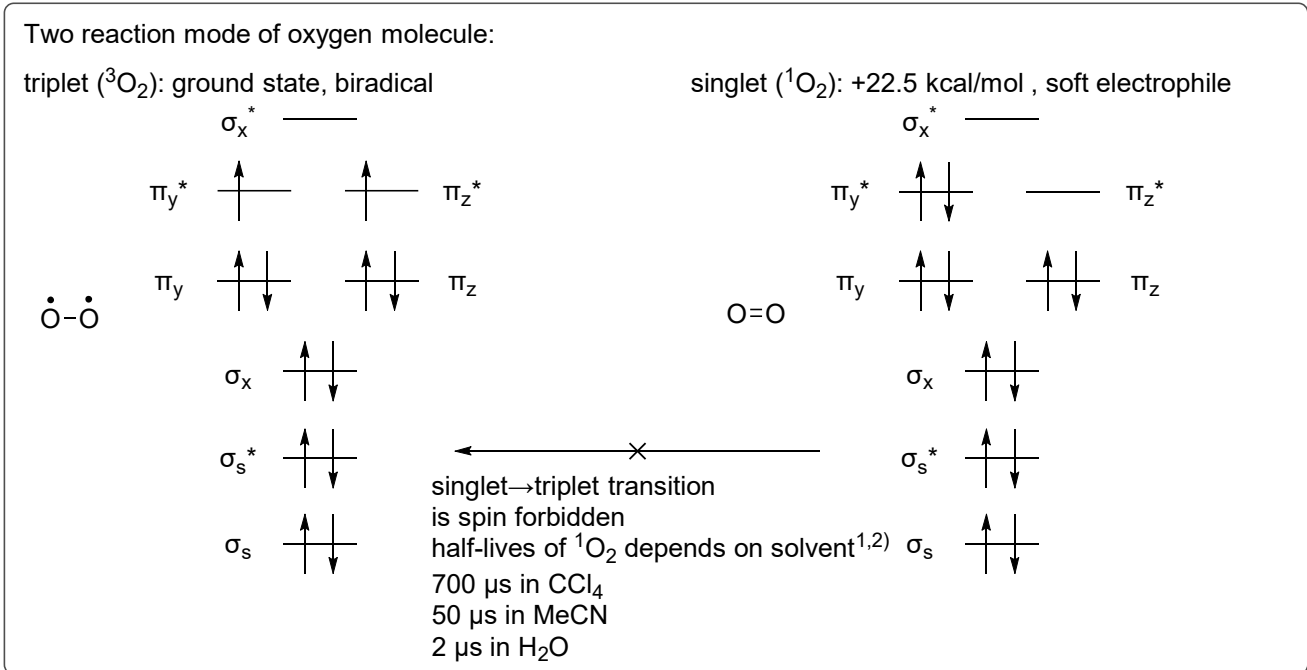
PCC

Problem Session (5) Answer

2024.4.20 Kyohei Takaoka

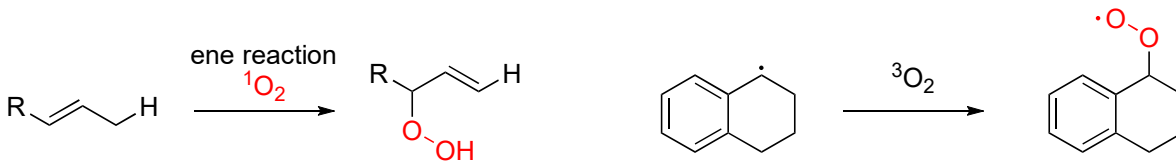
Topic: The reaction with O₂ in total synthesis

Introduction:

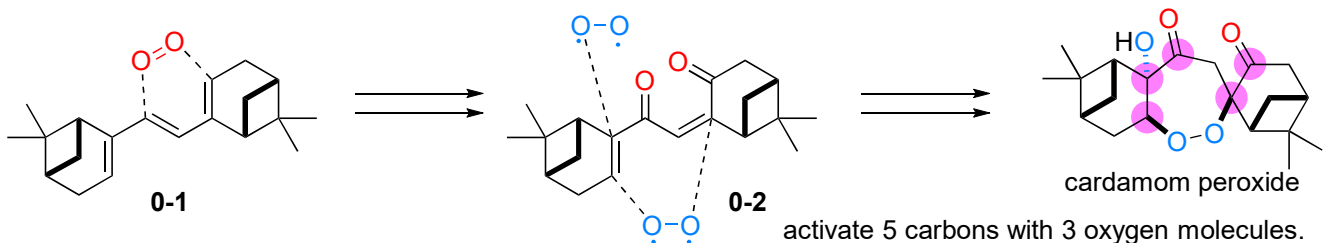


Unique feature of oxygen molecule:

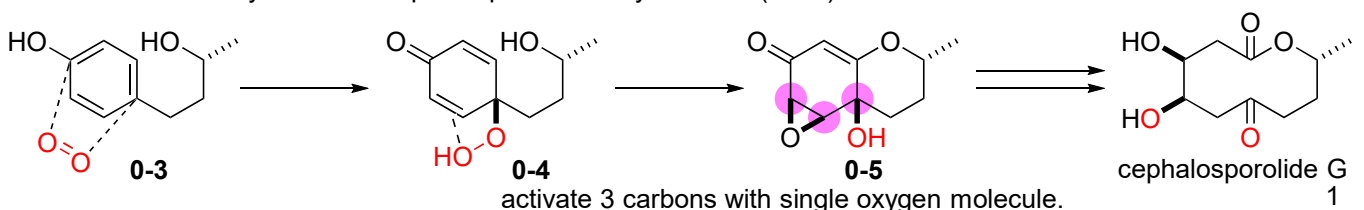
Usually, product contains O-O bond, which can be used as an oxidant. → O₂ can activate more than 1 position.



Problem 1: Total synthesis of cardamom peroxide by Maimone (2014)

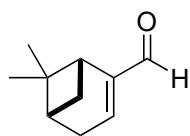


Problem 2: Total synthesis of cephalosporolide G by Carreño (2009)

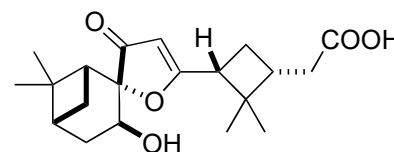


1

1. TiCl_4 (10 eq), Zn/Cu (40 eq), dimethoxyethane, 65°C , 53%
2. O_2 (1 atm), methylene blue (2 mol%), CH_2Cl_2 , -40°C , $h\nu^{**}$; DBU (5 eq), -40 to -20°C , 56%
3. Dess-Martin periodinane (1.3 eq), CH_2Cl_2 , rt, 95%
4. O_2 (1 atm), $\text{Mn}(\text{dpm})_3$ (20 mol%)
 $t\text{-BuOOH}$ (1.5 eq), PhSiH_3 (2.5 eq, added over 12 h)
 $i\text{-PrOH}/\text{CH}_2\text{Cl}_2$ (6.5/1), -10°C ; PPh_3 (2.1 eq), 52%
5. FeCl_2 (80 mol%), H_2O (13 eq), MeCN, rt, 42%



1-1
(-)-myrtenal



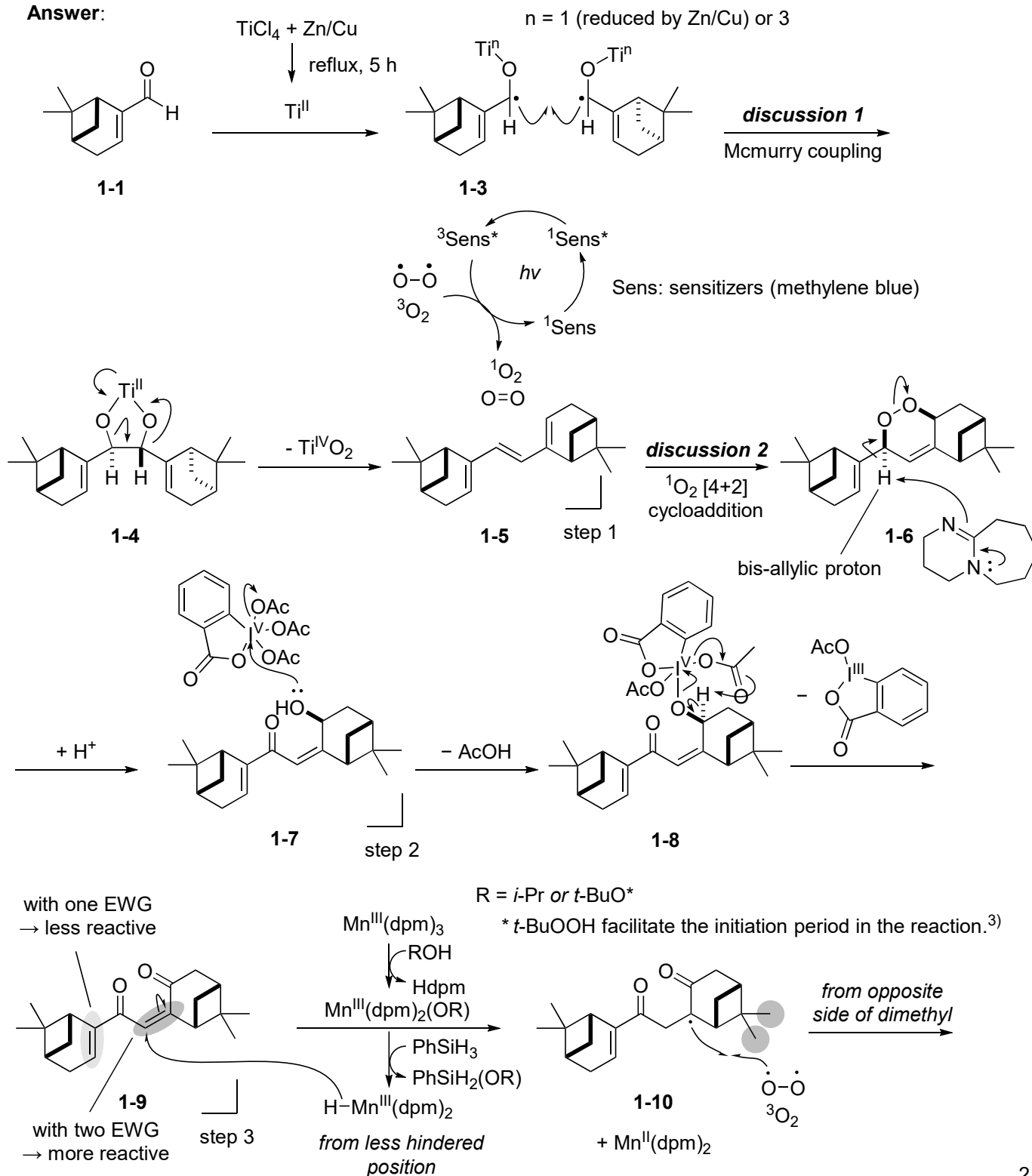
1-2

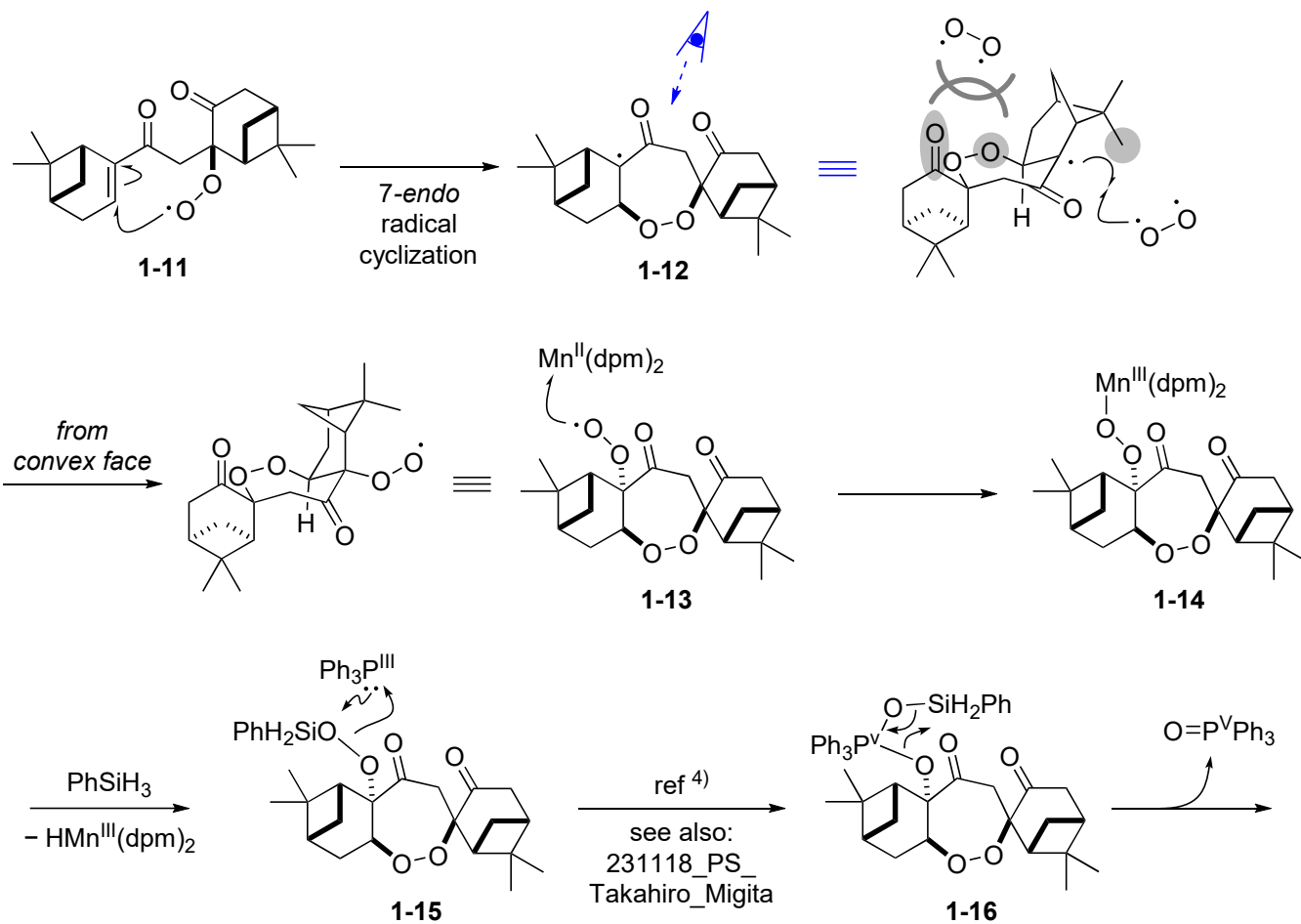
* TiCl_4 and Zn/Cu were pre-mixed under heat reflux temperature for 5 hours.

** 500 W halogene lamp

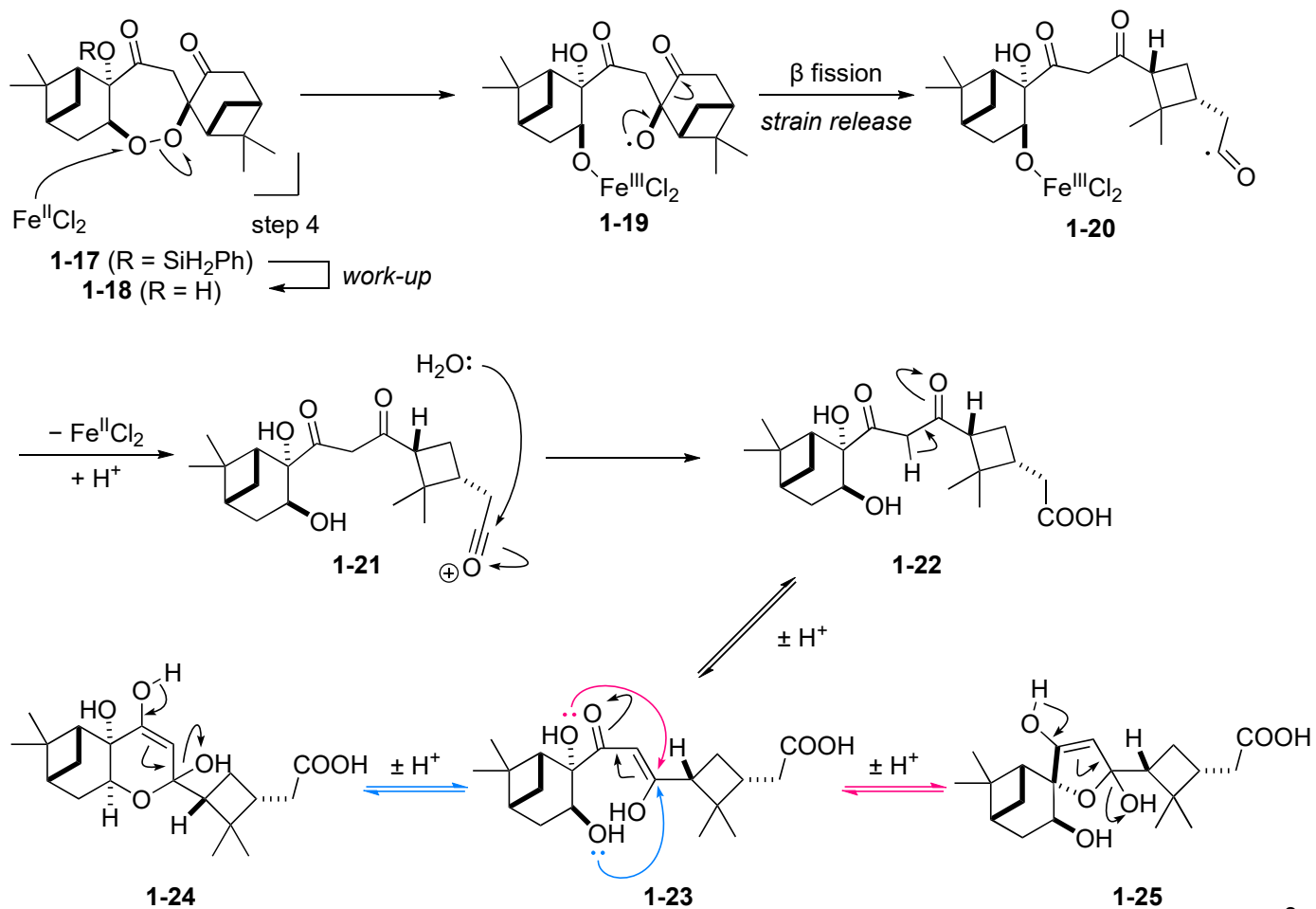
Hu, X.; Maimone, T. J. *J. Am. Chem. Soc.* **2014**, *136*, 5287.

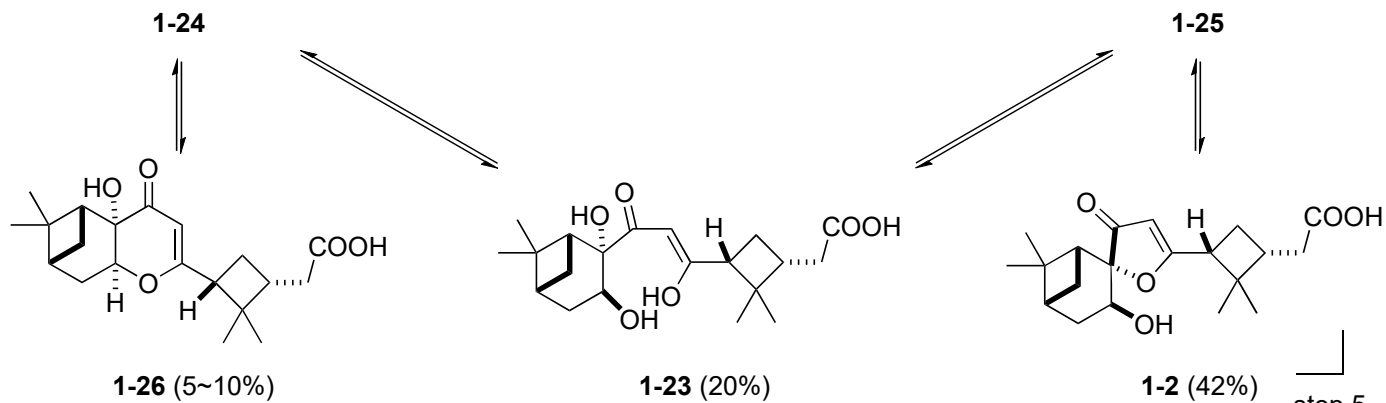
Answer:





* Slow addition of PhSiH_3 suppressed premature reduction of peroxy radical **1-13**.

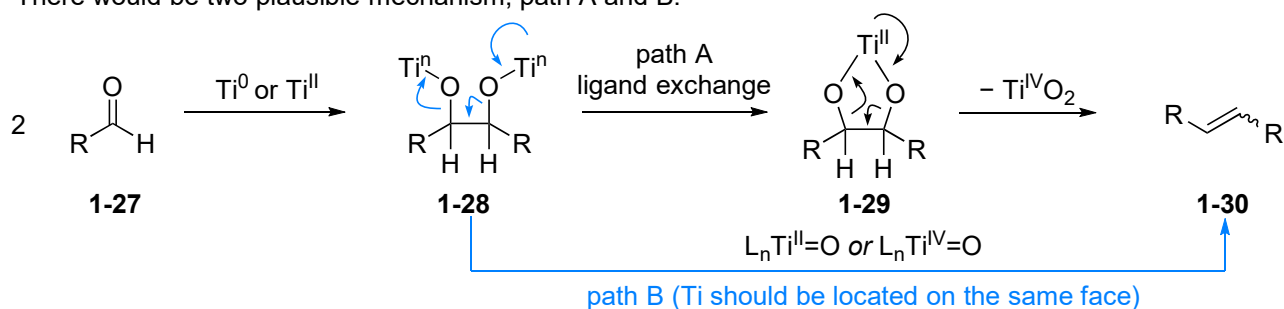




* 1-23 converts to 1-26 and 1-2 upon standing in solution (CDCl₃).

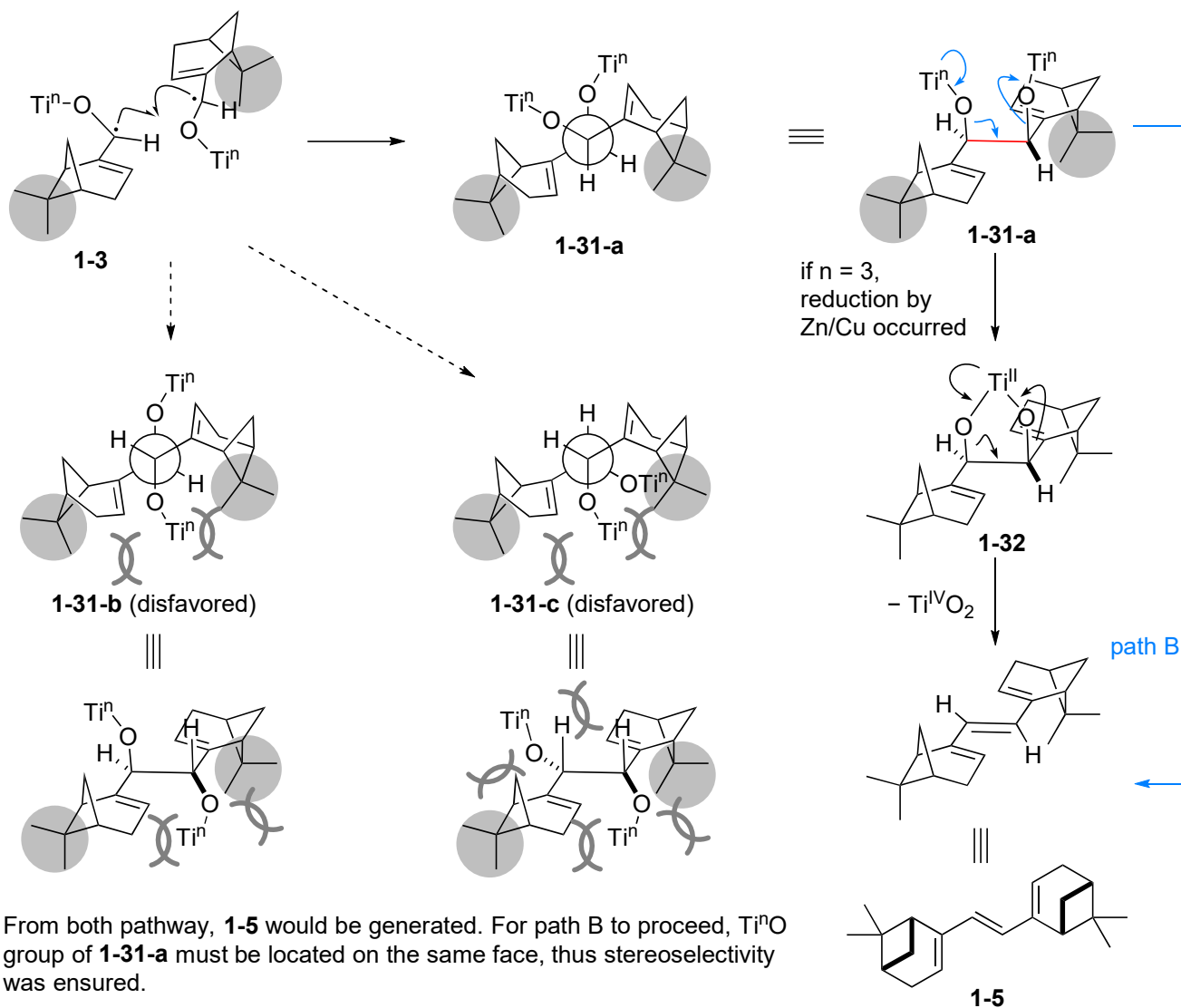
Discussion 1: McMurry coupling

There would be two plausible mechanism, path A and B.



The first dimerization proceeds from less hindered face.

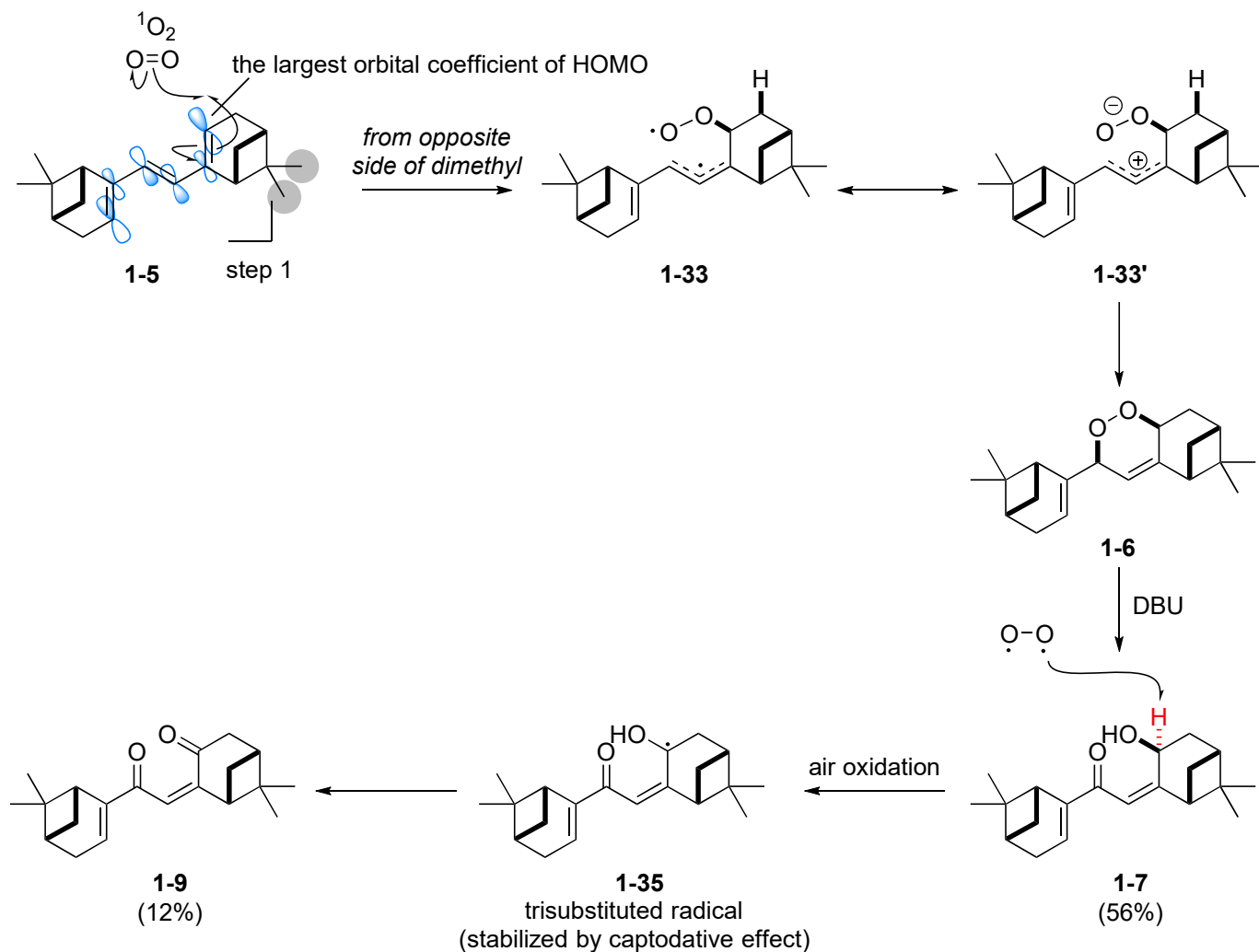
OTiⁿ avoid large dimethyl-cyclobutane ring, and generates 1-31-a.



From both pathway, 1-5 would be generated. For path B to proceed, TiⁿO group of 1-31-a must be located on the same face, thus stereoselectivity was ensured.

Discussion 2: $^1\text{O}_2$ [4+2] cycloaddition

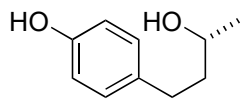
[4+2] cycloaddition of $^1\text{O}_2$ is proposed to proceed with diradical pathway^{8,9} (except for benzene with $^1\text{O}_2$).



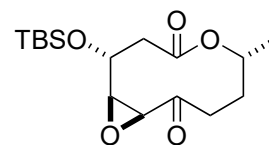
Author mentioned that **1-9** was also obtained in 12% yield in step 2. Radical **1-35** is stabilized by captodative effect, thus BDE of highlighted C-H would be lowered. It might be the cause of auto oxidation.

2

1. Oxone (8 eq), NaHCO₃ (24.8 eq), H₂O/MeCN (10/1, 0.05 M), rt, 65%
2. *p*-TsOH (12 mol%), CHCl₃, -20 °C;
triton B (24 mol%), rt, 49%
3. NaBH₄ (0.75 eq), EtOH, rt, 96%
4. TBSOTf (1.5 eq), 2,6-lutidine (2.0 eq), CH₂Cl₂, rt, 95%
5. PCC (15.6 eq), NaOAc (22.8 eq), CH₂Cl₂, rt, 68%



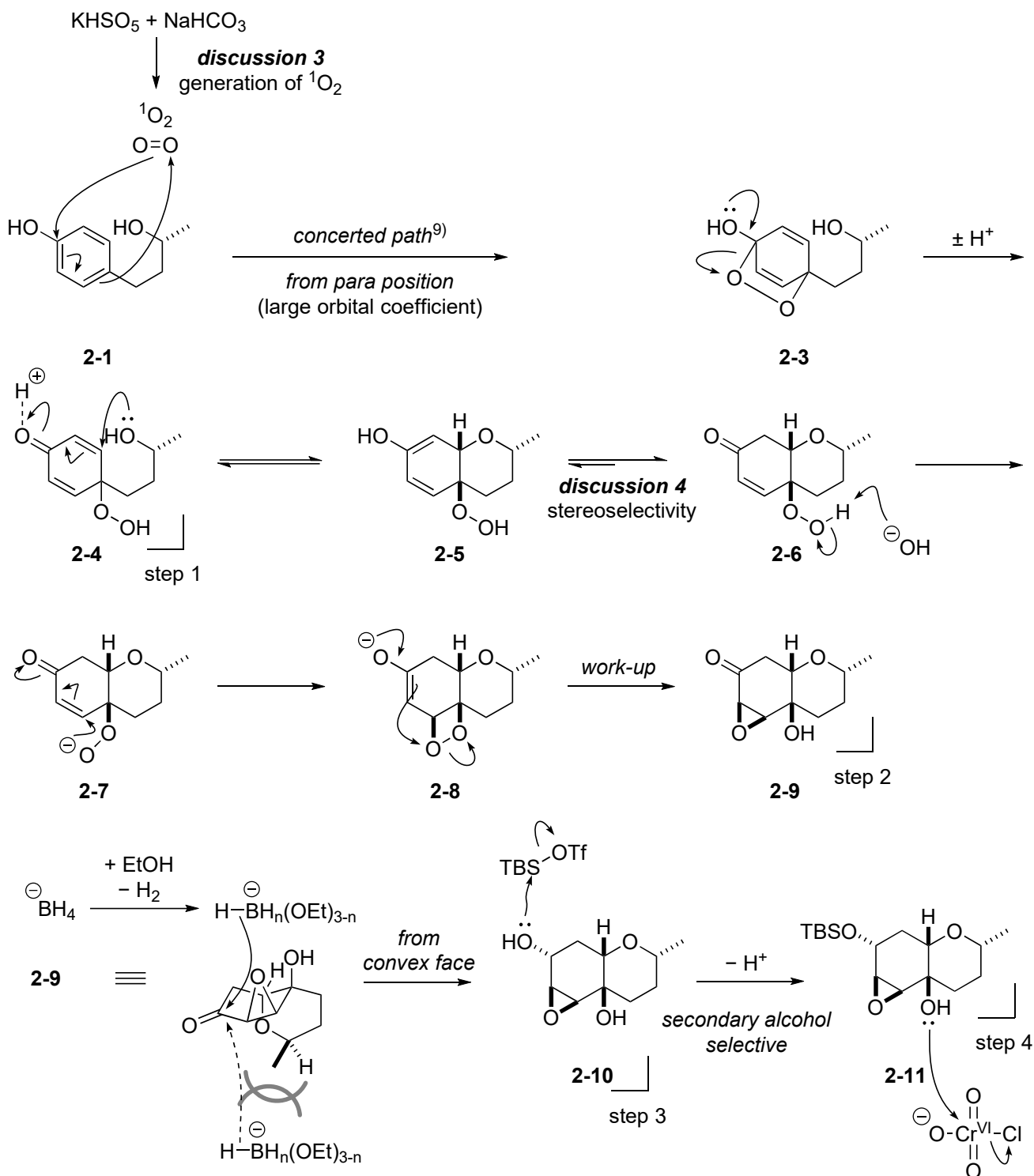
2-1

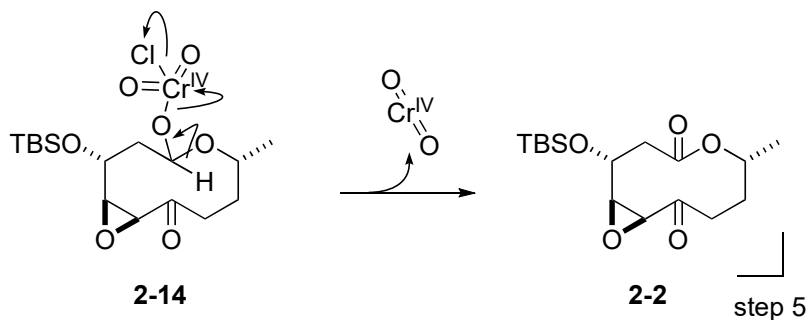
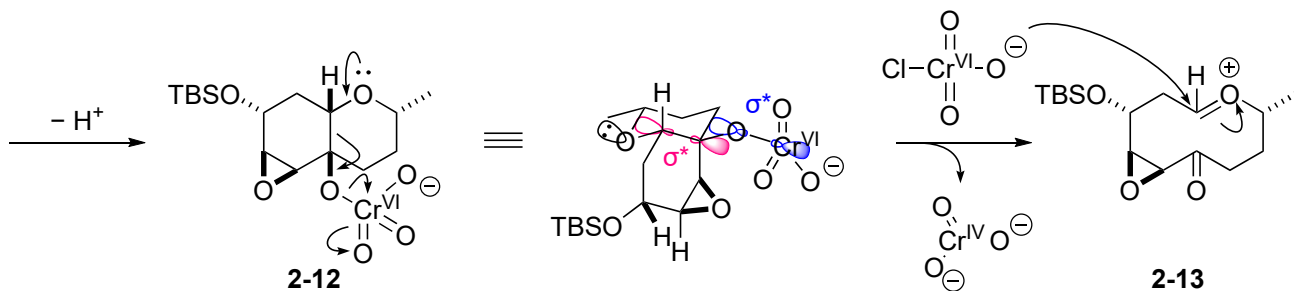
Oxone: 2KHSO₅·KHSO₄·K₂SO₄

2-2

Barradas, S.; Urbano, A.; Carreño, M. C. *Chem. Eur. J.* **2009**, *15*, 9286.

Answer:



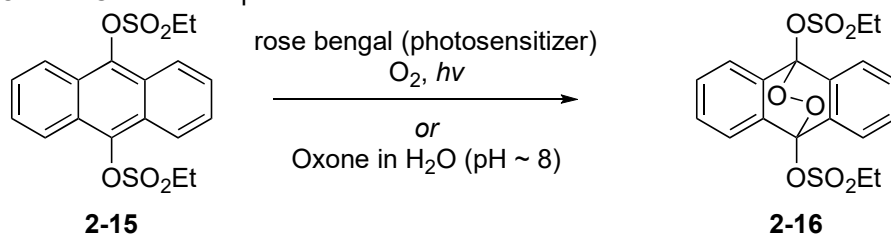


Discussion 3: Generation of singlet oxygen from peroxide

1. Detection of 1O_2

O_2 can be generated by decomposition of hydrogen peroxide or organic peroxides, and it is described that the generated oxygen molecule is 1O_2 , not ground state 3O_2 .⁵⁾

In case of Oxone: Chemical trap⁶⁾



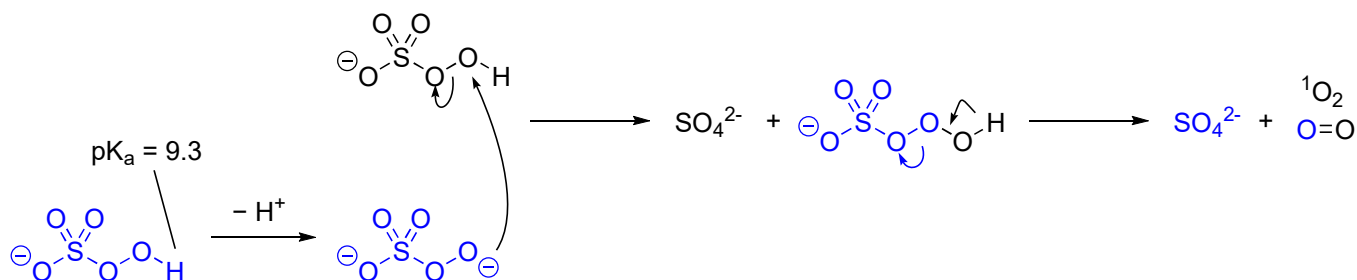
detected in both conditions

2-15 was used as a trap for 1O_2 , and Oxone under basic conditions gave endoperoxide **2-16**.

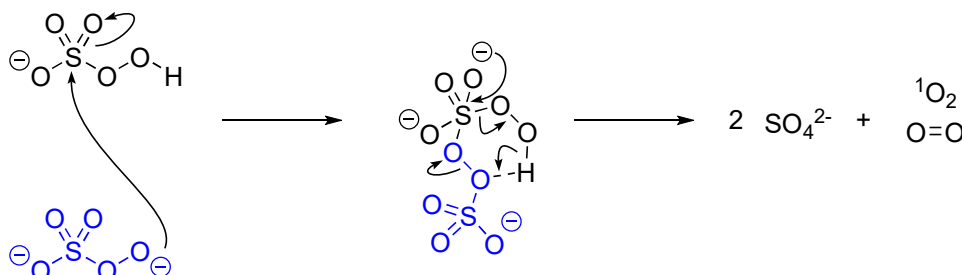
2. Plausible mechanism of decomposition of HSO_5^-

Path A or path B seems plausible in the reaction.

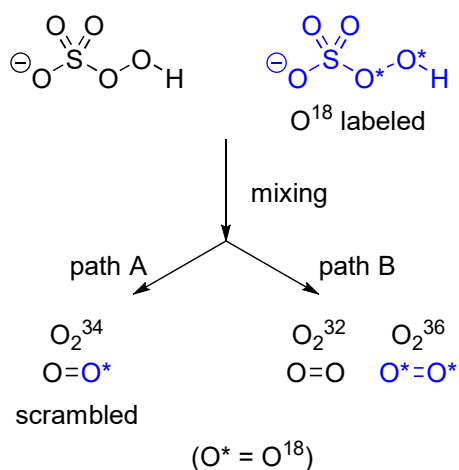
Path A: nucleophilic attack on O atom



Path B: nucleophilic attack on S atom



2.2. O¹⁸ labeling experiment⁶⁾



result: peroxy acid	path A (attack on O)	path B (attack on S or C)
AcOOH	17%	83%
	90%	10%
	74%	26%
	76%	24%

O¹⁸ labeling experiment was conducted. In the experiment, authors mixed O¹⁸ labeled peroxy acid and normal peroxy acid, then measured the molecule weight of O₂. If path A proceeds, scrambled O₂³⁴ would be observed. From the ratio of generating O₂³⁶, we can judge which pathway is more favorable. Authors measured 4 peroxy acids described above. The result showed that path A was more favorable in case of Oxone.

For other peroxy acids, the tendency of the reaction pathway depends on leaving ability of RO⁻ and bulkiness of carbonyl group.

Note: Experimental results show that the rate of Oxone loss follows a second-order reaction of Oxone concentration and the decomposition speed can be expressed as $v = k [\text{OSO}_4\text{H}][\text{OSO}_4^{2-}]$.

The rate constant in aqueous solution at pH=pK_a ([OSO₄H⁻]=[OSO₄²⁻]) was measured:

$$k \approx 4.7 \cdot 10^{-2} \text{ [L/mol/s]} \text{ at } 25 \text{ } ^\circ\text{C}^{6)}$$

In this problem, the initial concentration of Oxone was about 0.45 M, so assuming that the solution was at pH = pK_a = 9.2, the half-life $t_{1/2}$ of Oxone is

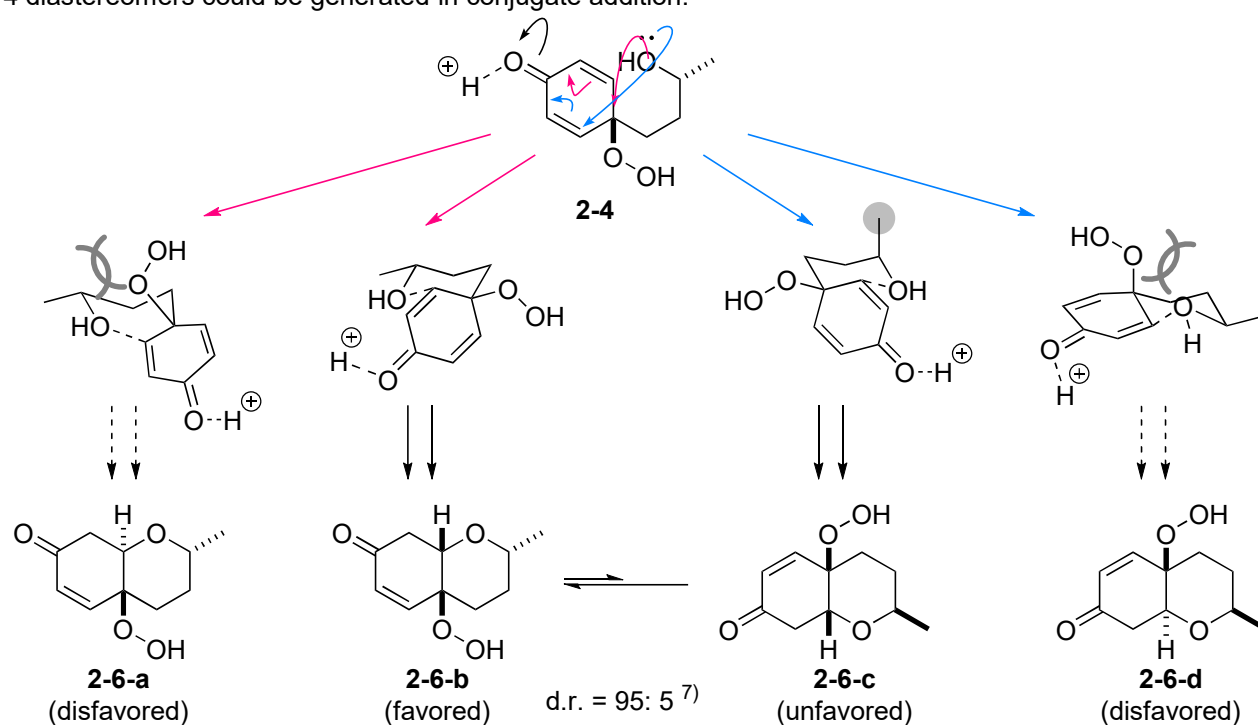
$$t_{1/2} = 1/k[\text{OSO}_4^{2-}] = 1/(47 \cdot 10^{-2} \cdot 0.45/2) = 94 \text{ [s]}.$$

The actual half-life should be longer than this time because the actual pH is not likely to be 9.2, but the rate of singlet oxygen generation is considered fast enough.

Therefore, this reaction should be reacted from singlet oxygen rather than from Oxone.

Discussion 4: Stereoselective conjugate addition

4 diastereomers could be generated in conjugate addition.



Construction of *trans*-6/6 ring seems hard in this substrate due to steric repulsion between OOH and side chain. In comparison with 2-6-b and 2-6-c, 2-6-b is more stable because methyl group locates on equatorial position. The reaction is reversible, thus more stable 2-6-b was obtained as a major product.

Reference:

- 1) Ogilby, P. R.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 3423.
- 2) Hurst, J. R.; McDonald, J. D.; Schustre, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 2065.
- 3) Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595.
- 4) Harris, J. R.; Haynes, M. T.; Thomas, A. M.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 5083.
- 5) Adam, W.; Kazakov, D. V.; Kazakov, V. P. *Chem. Rev.* **2005**, 3371.
- 6) Koubek, E.; Welsch, J. E. *J. Org. Chem.* **1968**, *33*, 445.
- 7) Barradas, S.; Carreño, M. C.; López, M. G.; Latorre, A.; Urbano, A. *Org. Lett.* **2007**, *9*, 5019.
- 8) Organic Chemistry: Theory, Reactivity and Mechanisms in Modern Synthesis
- 9) Leach, A. G.; Houk, K. N. *Chem. Commun.* **2002**, 1243.

