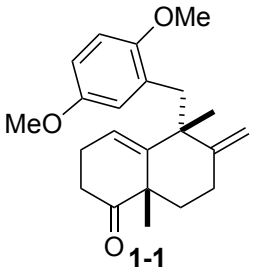
Problem Session (1)

2023.01.28 Manaka Matsumoto

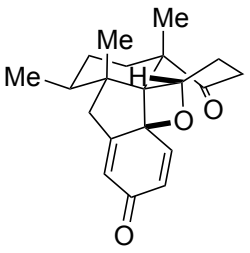
Please provide the reaction mechanisms.

1

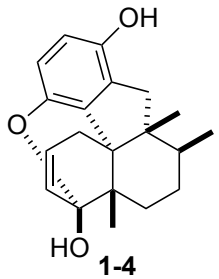


1-1

1. H_2 balloon, $(Ph_3P)_3RhCl$ (0.25 eq), benzene, 40ºC, 96%, d.r.=1.9:1
2. PIFA (3.0 eq), H_2SO_4 (9.0 eq), MeCN/H_2O=3/1, 0 ºCto rt, 82%
3. *hv* (365 nm), MeCN, rt, 17% for **1-2**, 54% for **1-3**

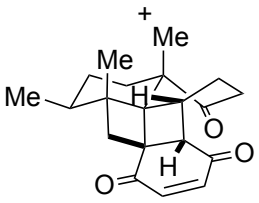


1-2



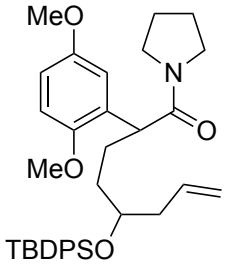
1-4
(from **1-3**)

4. $Bu_4N^+AcO^-$ (5.2 eq), MeCN, rt, 63%

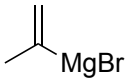


1-3

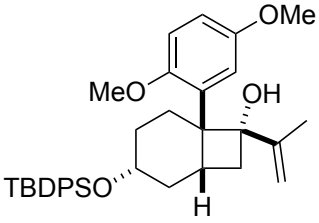
2



2-1

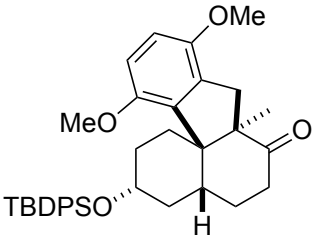
1. DBMP (1.14 eq), Tf_2O (1.05 eq), $(CH_2Cl)_2$, 80ºC, 73%
2.  (1.50 eq), THF, rt

51% for **2-2**, 47% for **2-3**



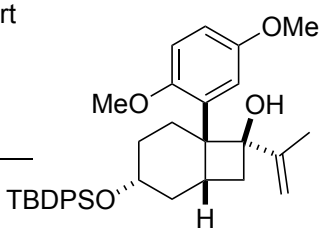
2-2

3. $Pd(OAc)_2$ (0.10 eq), Ag_2CO_3 (2.2 eq), DMSO/toluene=1/19, 110ºC, 46%
4. TMSOTf (2.5 eq), Et_3N (10 eq), CH_2Cl_2, 0ºC
5. CH_2I_2 (5.0 eq), Et_2Zn (6.0 eq), CH_2Cl_2, 0ºC to rt
6. $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol%), KH_2PO_4 (2.0 eq), Bu_4NPF_6 (0.2 eq), H_2O (20 eq), TolSH (2.0 eq), blue LEDS, DMF, rt, 81%, 3 steps

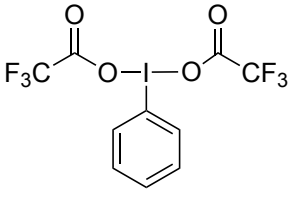


2-4
(from **2-3**)

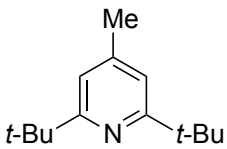
+



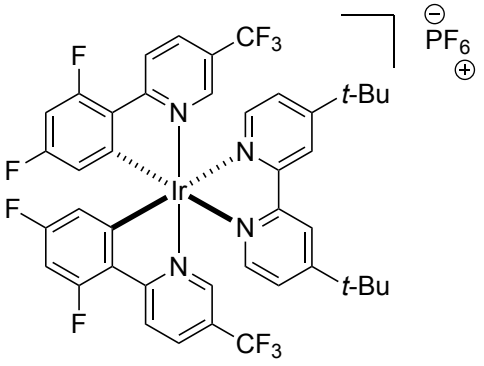
2-3



PIFA



DBMP



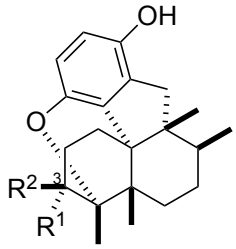
$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$

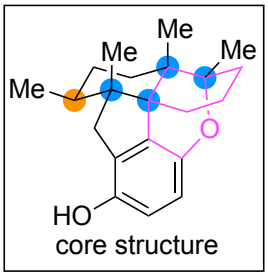
Problem Session (1) Answer

2023.01.28 Manaka Matsumoto

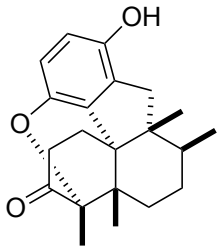
Topic: Construction of the tetracyclic core structure of Dysiherbols

Introduction:

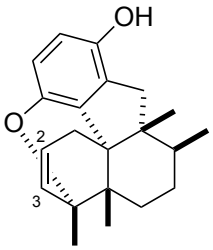




Dysiherbol A: R^1=R^2=H
Dysiherbol B: R^1=OH, R^2=H



Dysiherbol C



Dysiherbol D

Isolation:
from the *Dysidea* sp. marine sponge (Dysiherbol A-C, 2016)[1)]
from the *Dysidea avara* marine sponge (Dysiherbol D, 2022)[2)]

Structual features:
6/6/5/6/6 pentacyclic skeleton
oxabicyclo [3,3,1] ring system
5-6 contiguous stereogenic centers
four quaternary centers

Total syntheses:
Lu's group (Dysiherbol A, 2021)[3)]
Schmalz's group (Dysiherbol A, 2021)[4)]
Tang's group (Dysiherbol A,C,D, 2022)[5)]

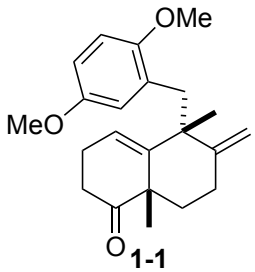
Biological activities:
Dysiherbol A:
cytotoxic activity against the cacner cell line NCI H-929
inhibitory activity toward NF-κB[1)]

Reference:

1) Jiao, W.-H.; Shi, G.-H.; Xu, T.-T.; Chen, G.-D.; Gu, B.-B.; Wang, Z.; Peng, S.; Wang, S.-P.; Li, J.; Han, B.-N.; Zhang, W.; Lin, H.-W *J. Nat. Prod.* **2016**, *79*, 406.
2) Liu, H.-Y.; Zhou, M.; Shang, R.-Y.; Hong, L.-L.; Wang, G.-H.; Tian, W.-J.; Jiao, W.-H.; Chen, H.-F.; Lin, H.-W. *Chin. J. Nat. Med.* **2022**, *20*, 148.
3) a) Chong, C.; Zhang, Q.; Ke, J.; Zhang, H.; Yang, X.; Wang, B.; Ding, W.; Lu, Z. *Angew. Chem. Int. Ed.* **2021**, *60*, 13807.
b) Chong, C.; Lu, Z. *Synlett.* **2021**, *32*, 1777.
4) Baars, J.; Grimm, I.; Blunk, D.; Neudörfl, J.-M.; Schmalz, H.-G. *Angew. Chem. Int. Ed.* **2021**, *60*, 14915.
5) Hu, S.; Tang, Y. *J. Am. Chem. Soc.* **2022**, *144*, 19521.

Problem 1: Total synthesis of Dysiherbol A, C, D by Tang's group

1



1-1

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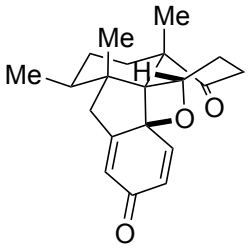
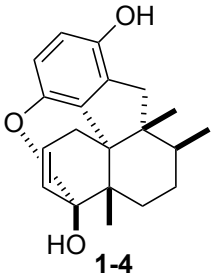
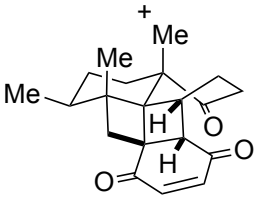


1-2



1-4
(from **1-3**)

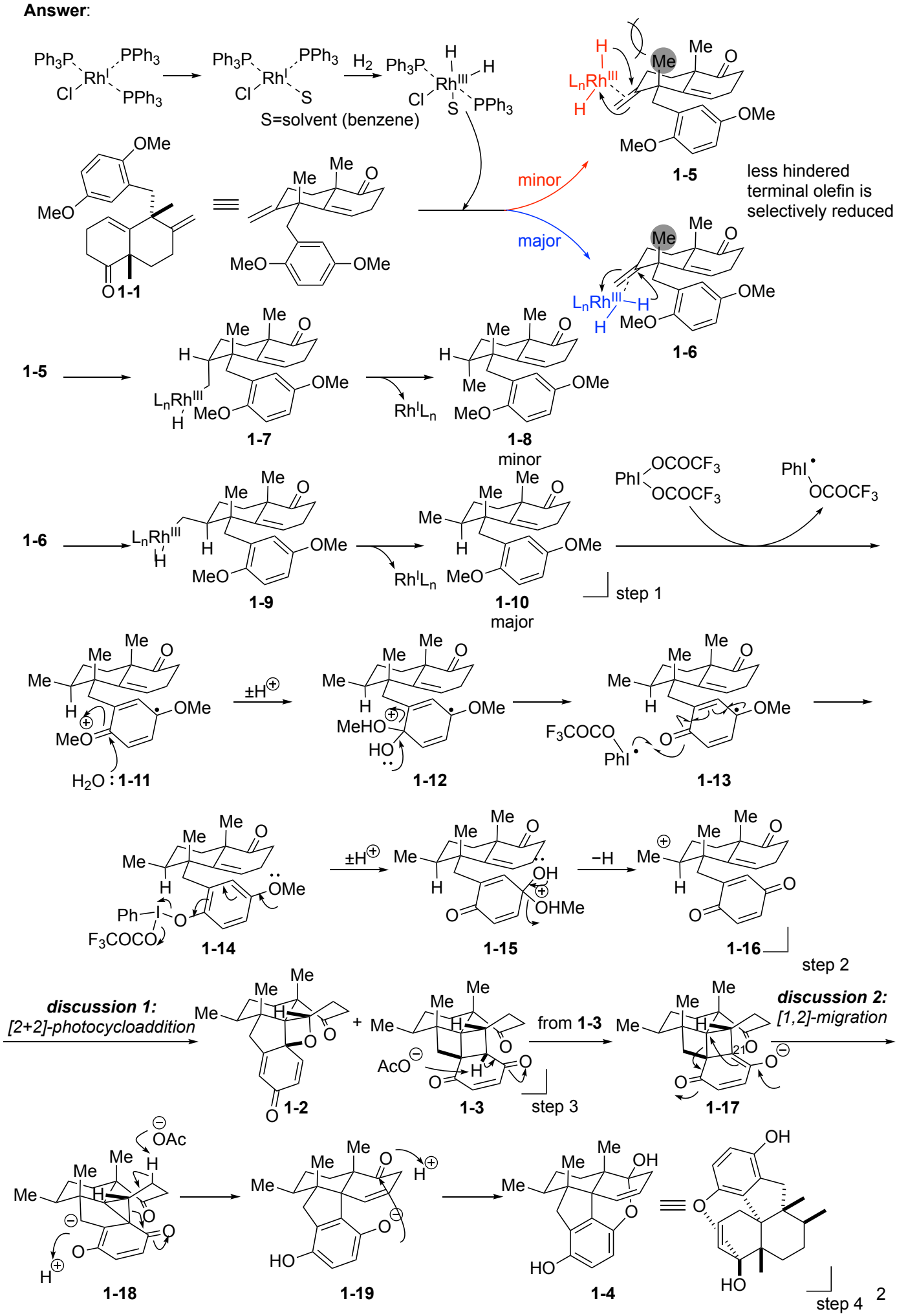
4. $Bu_4N^+AcO^-$ (5.2 eq), MeCN, rt, 63%



1-3

Hu, S.; Tang, Y. *J. Am. Chem. Soc.* **2022**, *144*, 19521

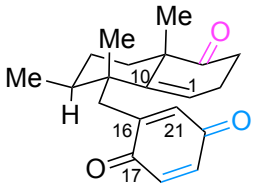
Answer:


S=solvent (benzene)
minor
major
less hindered terminal olefin is selectively reduced
1-1
1-5
1-6
1-7
1-8
1-9
1-10
major
step 1
1-11
1-12
1-13
1-14
1-15
1-16
step 2
discussion 1:
[2+2]-photocycloaddition
1-2
1-3
from 1-3
step 3
discussion 2:
[1,2]-migration
1-17
1-18
1-19
1-4
step 4

2

Discussion 1: [2+2] photocycloaddition

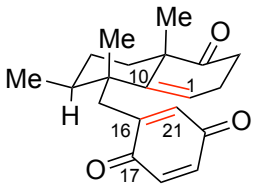
1-1. Regio- and stereo- selectivity



1-16

The C=O bond shown in pink is too far to interact with any double bonds of the quinone moiety.
Two double bonds shown in blue are too far to interact with the C1=C10 of sesquiterpene moiety.
Therefore, there are two pairs of double bonds that possibly engage in [2+2]-photocycloaddition. One is C1=C10 and C16=C21 (A), and the other is C1=C10 and C17=O (B).

A. Alkene-alkene [2+2]-photocycloaddition

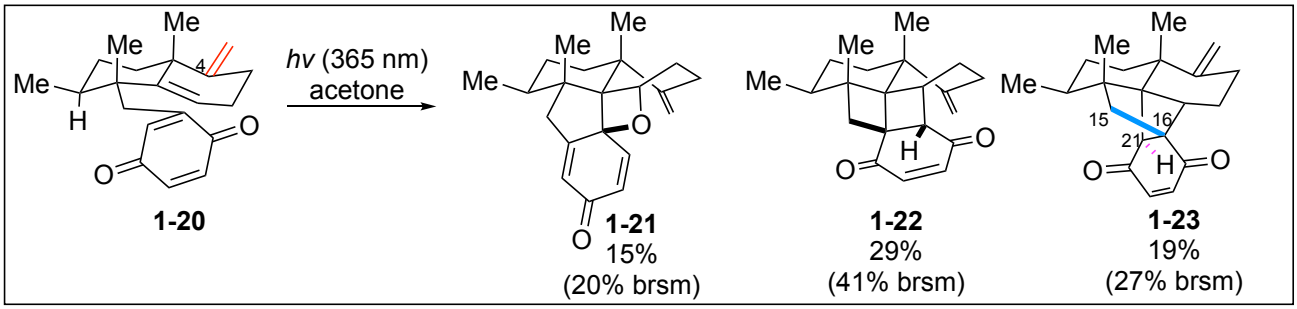


1-16

There are two possible regioisomers.

1: parallel cycloadduct (C1-C21 and C10-C16 bonds are generated)
2: crossed cycloadduct (C1-C16 and C10-C21 bonds are generated)

A-0. Concerted or stepwise



1-20

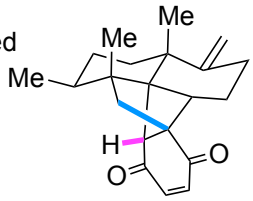
1-21 15% (20% brsm)

1-22 29% (41% brsm)

1-23 19% (27% brsm)

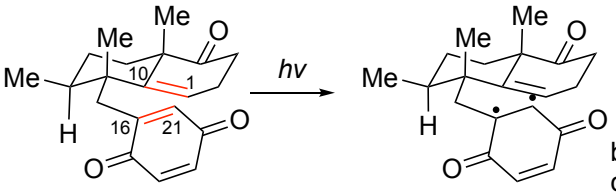
In case of similar substrate **1-20** (**1-20** has olefin group at C4 instead of carbonyl group), the compound **1-23** was obtained.
The trans relationship between C21-H and C15-C16 suggests that the reaction proceeded though a stepwise pathway. If the raction proceeded in a concerted way, **1-24**, whose C21-H and C15-C16 are in cis relationship, would be generated.

In analogy, the reaction from **1-16** should be stepwise.



1-24

A-1. Which bond will be formed first ?

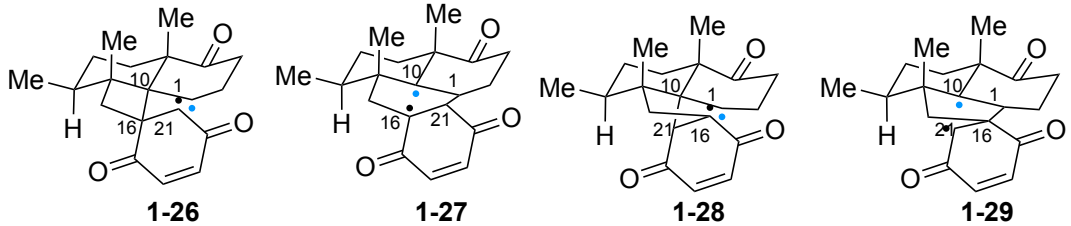


1-16

1-25

biradical stabilized by carbonyl groups

C10-C16 C1-C21 C10-C21 C1-C16



1-26 **1-27** **1-28** **1-29**

*stereochemistry will be discussed later

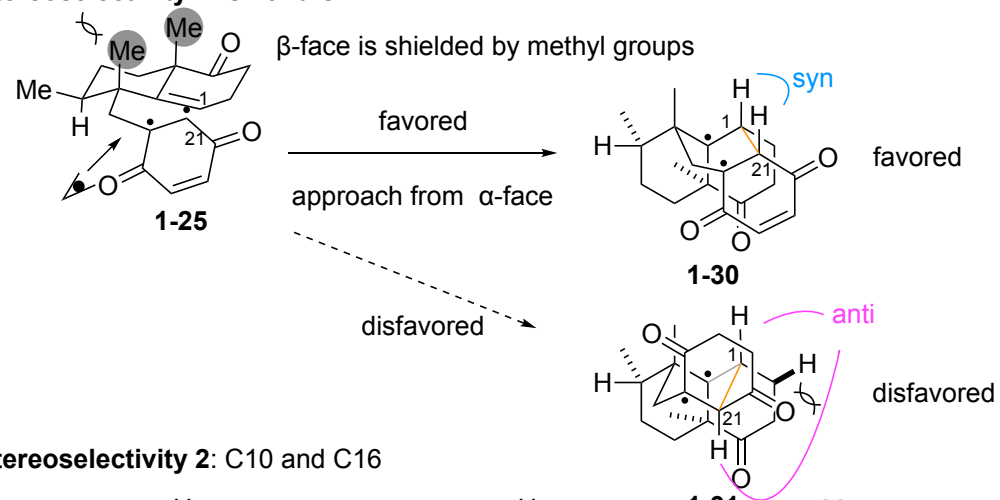
There are three factors to determine which bond will be formed first.
1. Steric hinderance between binding two carbons
2. The mode of cyclization
3.. The stability of generated biradical

bond	1 (steric hinderance)	2 (cyclization mode)	3 (stability)
C10-C16	large (tertiary and tertiary)	favored (4-exo-trig)	low (secondary and secondary)
C1-C21	small (seconadry and secondary)	favored (6-endo-trig)	high (tertiary and tertiary)
C10-C21	medium (tertiary and secondary)	favored (5-exo-trig)	medium (secondary and tertiary)
C1-C16	medium (seconadry and tertiary)	disfavored (5-endo-trig)	medium (tertiary and secondary)

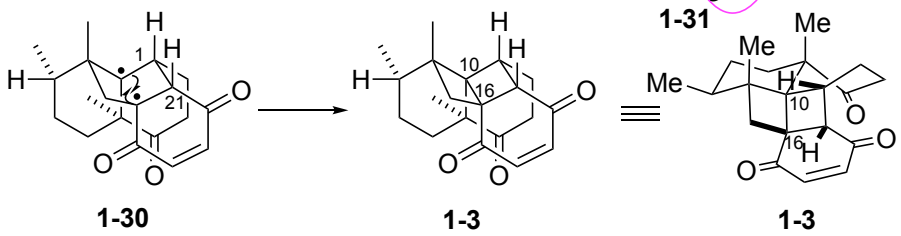
Considering the three factors, C1-C21 will be formed the fastest. (Formation of C10-C21 is second fastest, but C1-C21 will be formed much faster.)
Therefore, **1-27** will be selectively generated in the first step of the cycloaddition.

A-2. Stereoselectivity of C1-C21 formation and following reaction pathway

Stereoselectivity 1: C1 and C21

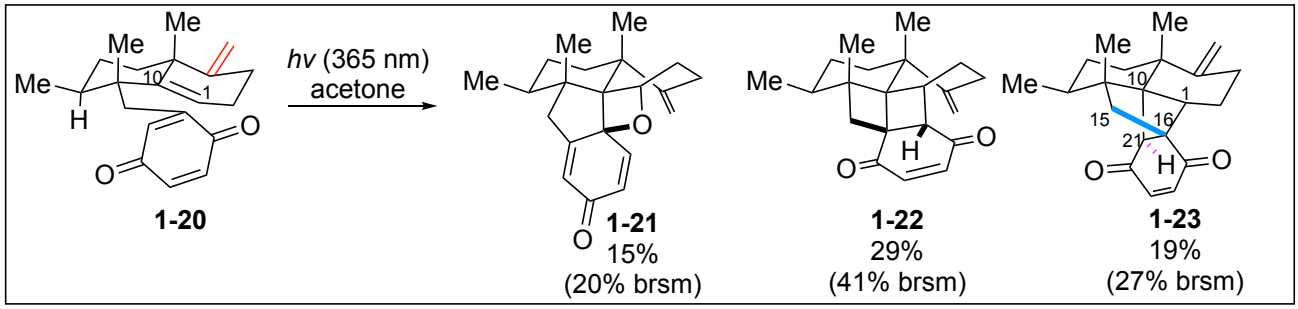


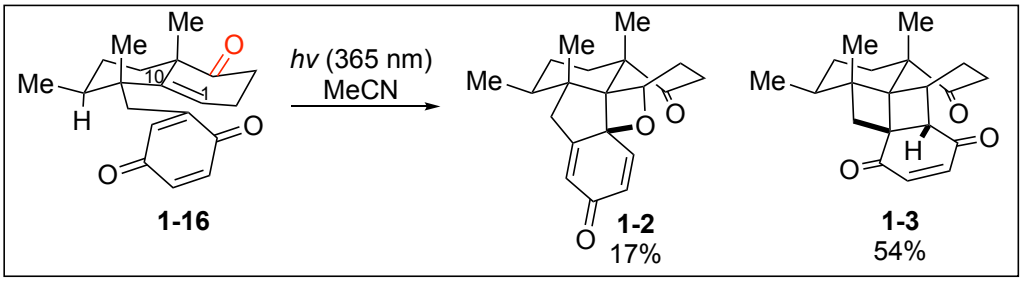
Stereoselectivity 2: C10 and C16



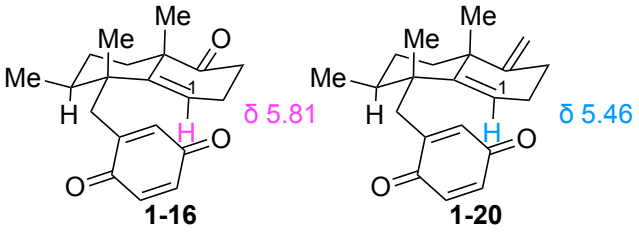
As soon as **1-30** is generated, two radicals will recombinate from this conformer, excluding generation of any other stereoisomers.

A-3. The differences between reaction from **1-20** and from **1-16**





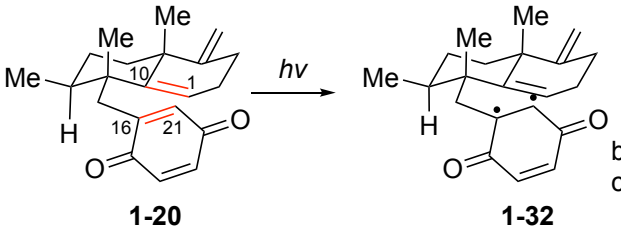
Unlike the reaction from **1-16**, the reaction from **1-20** gave two regioisomers of alkene-alkene [2+2] cycloaddition.
1-22 corresponds to **1-3** but **1-23**, which has C10-C16 and C1-C21, is only generated in the reaction from **1-20**.
The only difference between twos reaction is C4 structure of the starting material. (olefin vs ketone)



1-16 **1-20**

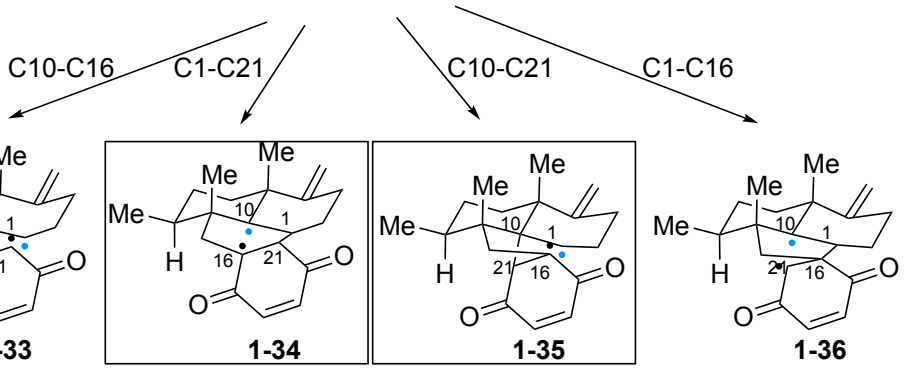
Judging from the chemical shift, the hydrogen atom of C1-H is electron richer in **1-16**.

In analogy, a radical on C1 would be more stabilized by electron fonation in **1-20** than in **1-16**.



1-20 **1-32**

biradical stabilized by carbonyl groups

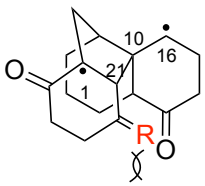


1-33 **1-34** **1-35** **1-36**

bond	1 (steric hinderance)	2 (cyclization mode)	3 (stability)
C10-C16	large (tertiary and tertiary)	favored (4-exo-trig)	low (secondary* and secondary)
C1-C21	small (seconadry and secondary)	favored (6-endo-trig)	high (tertiary and tertiary)
C10-C21	medium (tertiary and secondary)	favored (5-exo-trig)	medium (secondary* and tertiary)
C1-C16	medium (seconadry and tertiary)	disfavored (5-endo-trig)	medium (tertiary and secondary)

* stabilized by electron donation

With the same discussion as in the case of **1-16**, C1-C21 formation is the fastest and C10-C21 formation is the second fastest.
Because the radical on C1 is stabilized in **1-35**, formation of C10-C21 is accereted and **1-23** was obtained as a result.

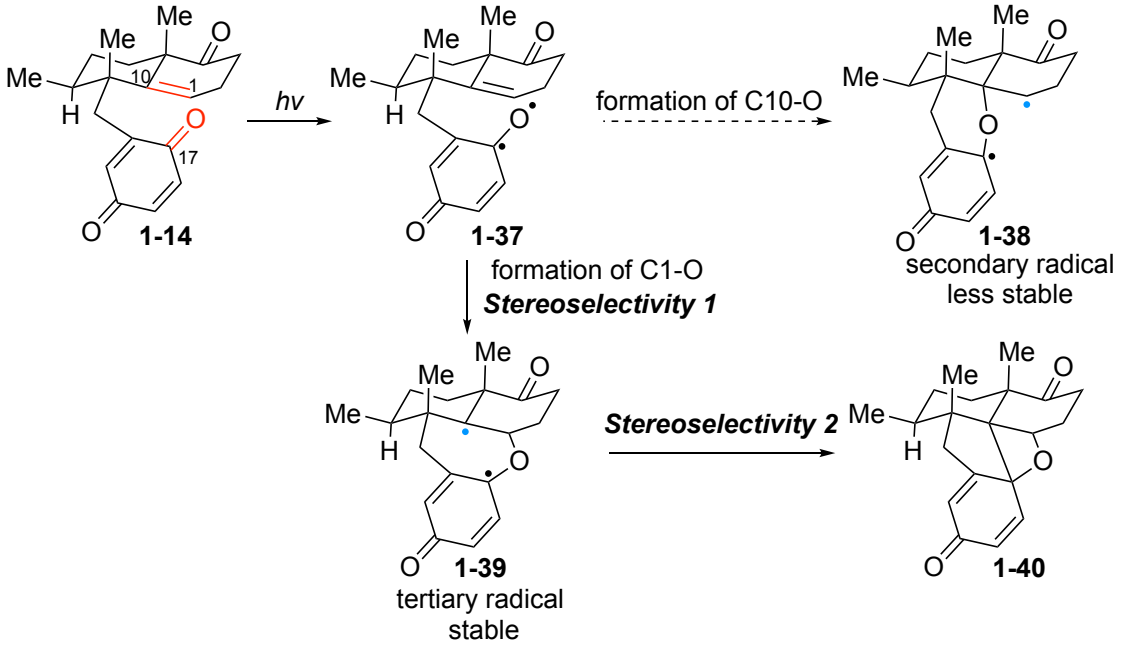


1-28 or **1-35**

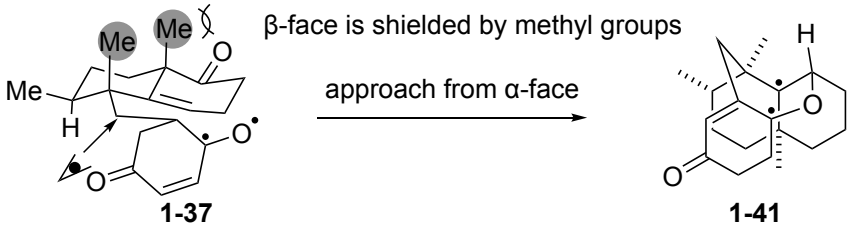
R=O (**1-28**)
R=CH_2 (**1-35**)

Additionally, in the intermediate after the formation of C10-C21, R and a carbonyl group are near.
Steric repulsion of two groups would be larger when both are arbonyl groups (**1-28**), preventing the formation of C10-C21.
This would be another factor to differentiate the reactions from **1-16** and **1-20**.

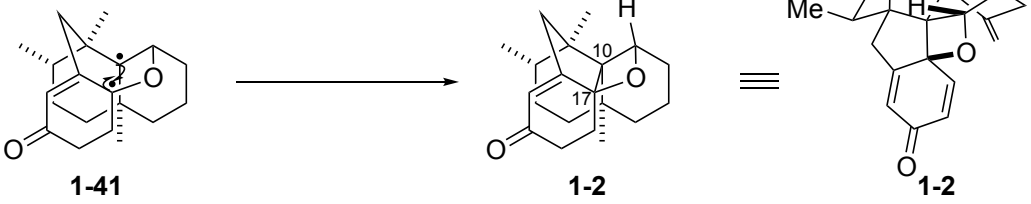
B. Ketone-alkene [2+2]-photocycloaddition



Stereoselectivity 1:C1



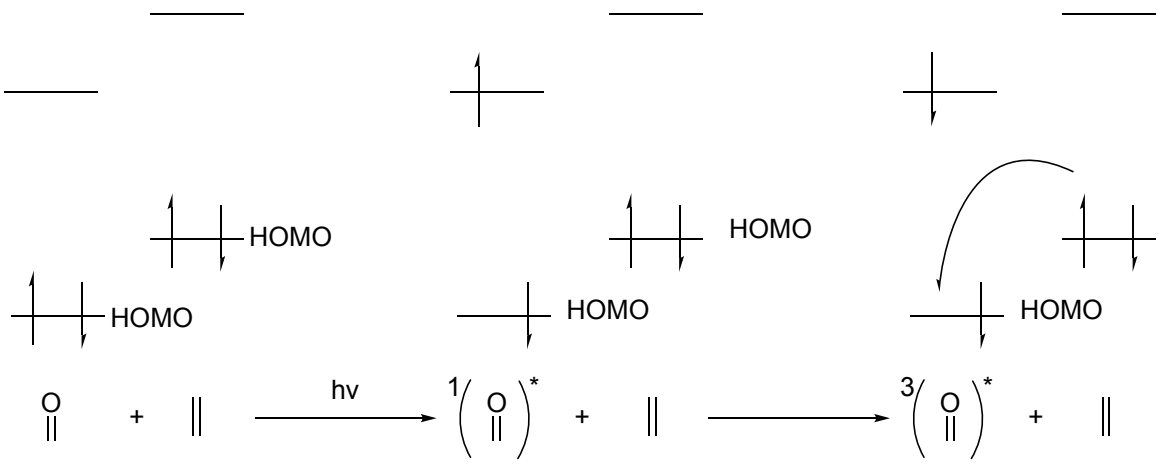
Stereoselectivity 2:C10 and C17

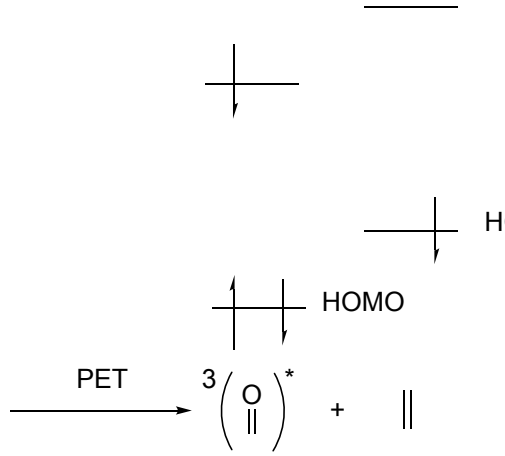


Once **1-41** is generated, two radicals will recombinate from this conformer, excluding generation of any other stereoisomers.

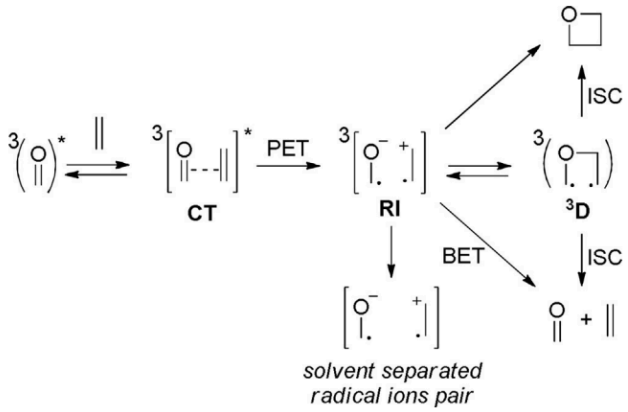
1-2. The ratio of **1-2** and **1-3**

1-2-1. Detailed mechanism of Carbonyl-alkene [2+2] cycloaddition[6)7)]





Carbonyl-alkene [2+2] cycloaddition involves photoinduced enectron-transfer process (PET) from HOMO of grond-state alkene to the semi-occupied n_p orbital of excited carbonyl. This process unlikely takes place in alkene-alkene [2+2] cycloaddition beause energy gap between HOMO of two alkenes are relatively small and stabilizing effect of PET is lower.



After PET, a radical-ion pair (**RI**) is formed. **RI** will move on to the cycloaddition, or be separated by solvent, or revert to the ground state through back electron transfer (BET).

It is known that for triplet mediated PET, solvent effect plays an important role in determinating the rate of BET.[7)]
The more polar the solvent is, the faster BET proceeds.

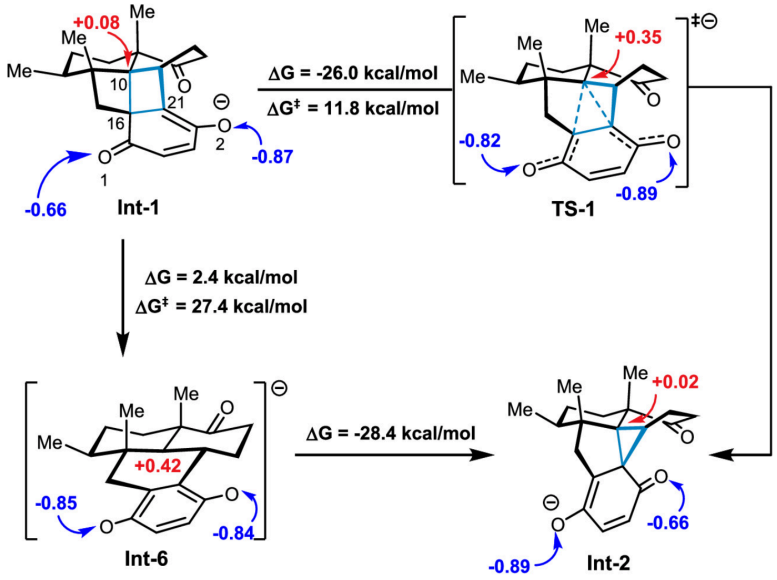
2-2-2. Optimization of solvent

solvent	**1-2**:**1-3** (ratio, 5 min)
benzene (0.01 M)	1:1.8
acetone (0.01 M)	1:2.3
MeCN (0.01 M)	1:2.5
MeCN (0.001 M)	1:3.0

The reaction gave better selectivity with more polar solvent and lower concentration.
It can be explained that polarity of solvent promoted BET process and quinone-alkene [2+2] cycloaddition was reduced. When the concentration is low, the solvent effect seems to increase.

Discussion 2: Reaction mechanism of [1,2]-migration

2-1. Concerted or stepwise

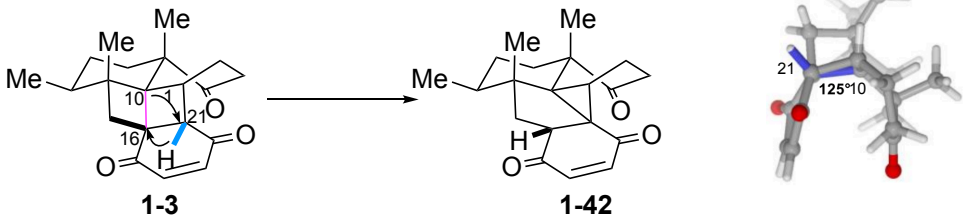


DFT calculation shows that concerted manner is thermodynamically and kinetically favored.

calculated at the M06-2X/6-311+G**, SMD (MeCN) level

2-2. Other possible pathways

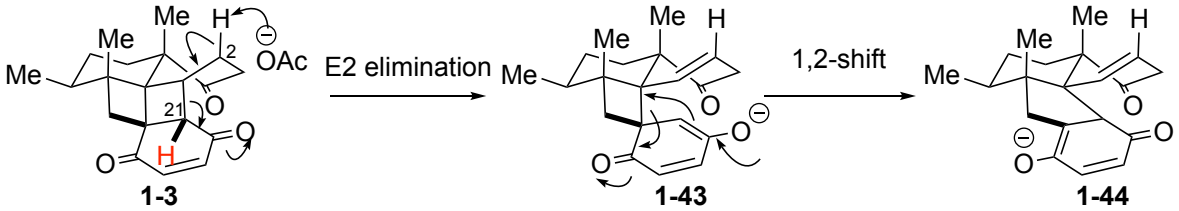
2-2-1. Dyotropic rearrangement



1-3 **1-42**

The optimized conformation of **1-3** suggests that dihedral angle between C10-C16 and C21-H is 125º and not suitable for dyotropic rearrangement, which requires anti-coplanar alignment of two migrating bond in the transition state.

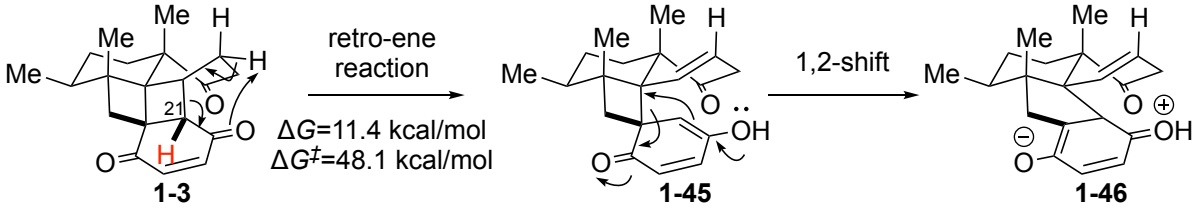
2-2-2. Base-promoted elimination/ 1,2-migration pathway



1-3 **1-43** **1-44**

This pathway is not plausible because basity of AcO^- is not so strong as to cause E2 elimination. Also, C21-H, which locates the α position of carbonyl group and bears more acidity, would be deprotonated faster than C2-H.

2-2-3. Retro-ene/ 1,2-migration pathway

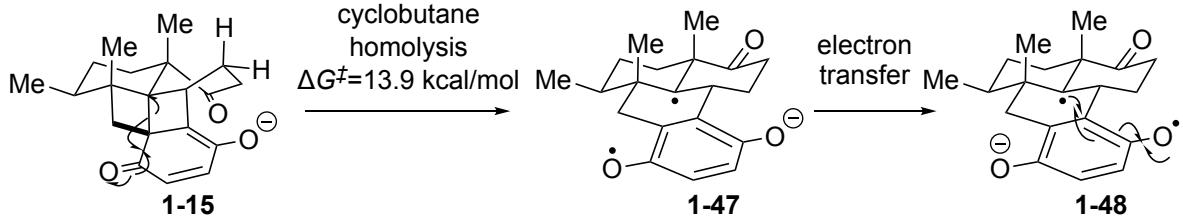


1-3 **1-45** **1-46**

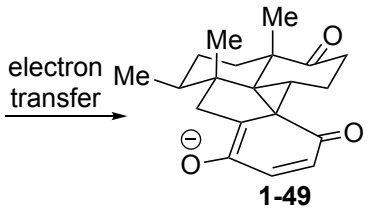
calculated at the M06-2X/6-311G(d,p), SMD(MeCN) level

Extremely high energetic barrier makes this reaction unlikely to take place.

2-2-4. Radical pathway



1-15 **1-47** **1-48**

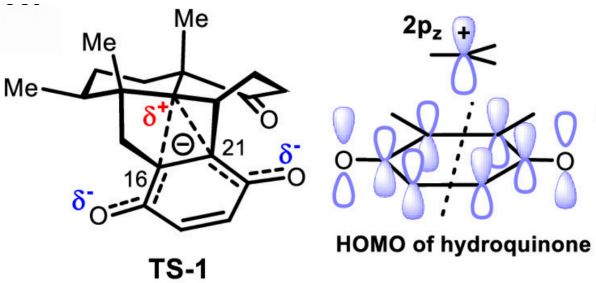


1-49

Energy barrier is still higher than concerted rearrangement pathway ($\Delta G^{\ddagger}$=11.8 kcal/mol).

calculated at the UM06-2X/6-311+G(d,p), SMD(MeCN) level

2-3. Interpretation of low energy barrier of concerted rearrangement



TS-1

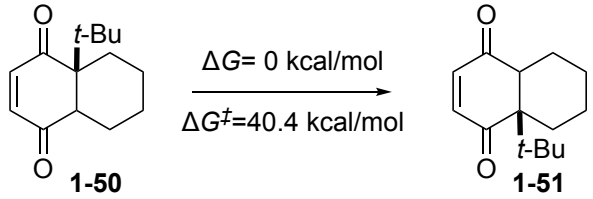
Concerted rearrangement is symmetry forbidden. Positive charge on C10 in the transition state suggests that $2p_z$ of C10 and HOMO of hydroquinone interact during the reaction. However, the interaction is impossible because HOMO of hydroquinone has one node between C16 and C21, making it difficult for $2p_z$ of C10 to access.

Despite the symmetry-forbidden characteristic, energy barrier of this reaction is low, compared to other pathways.

According to the authors, there are two main factors to lower the energy barrier.

2-3-1. Strain-releasing factor

Virtual [1,2]-anionic rearrangement without strain-releasing



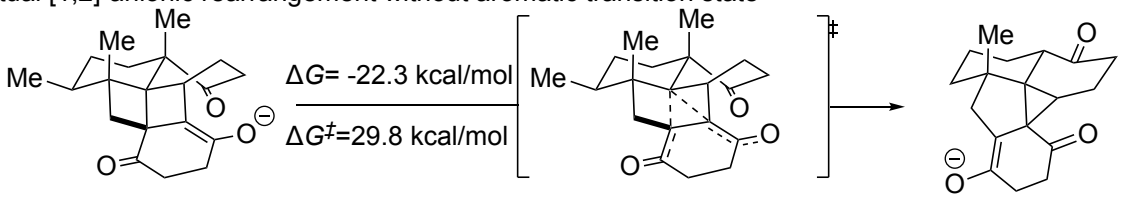
1-50 **1-51**

calculated at the M06-2X/6-311+G**, SMD(MeCN) level

Without strain-releacing factor, the rearrangement process would be kinetically disfavored.

2-3-2. Aromatic transition state

Virtual [1,2]-anionic rearrangement without aromatic transition state

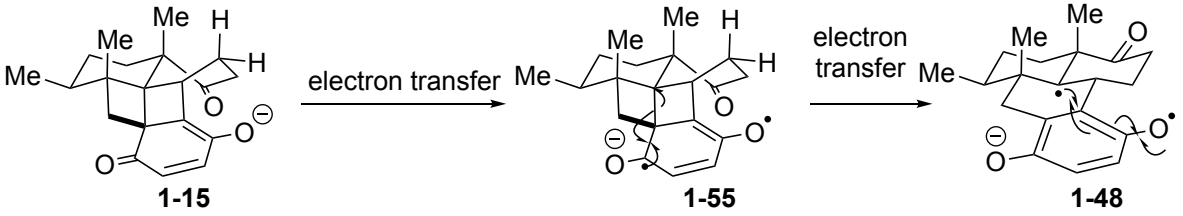


1-52 **1-53** **1-54**

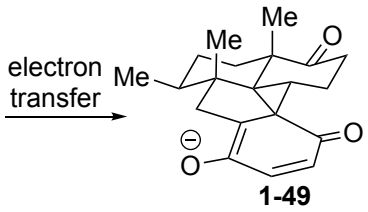
calculated at the M06-2X/6-311G**, SMD(MeCN) level

If the transition state were not stabilized with aromaticity, the rearrangement would be kinetically unfavored.

2-4. The mechanism proposed by Prof. Inoue



1-15 **1-55** **1-48**



1-49

This pathway is not discussed in the paper and seems to be plausible.

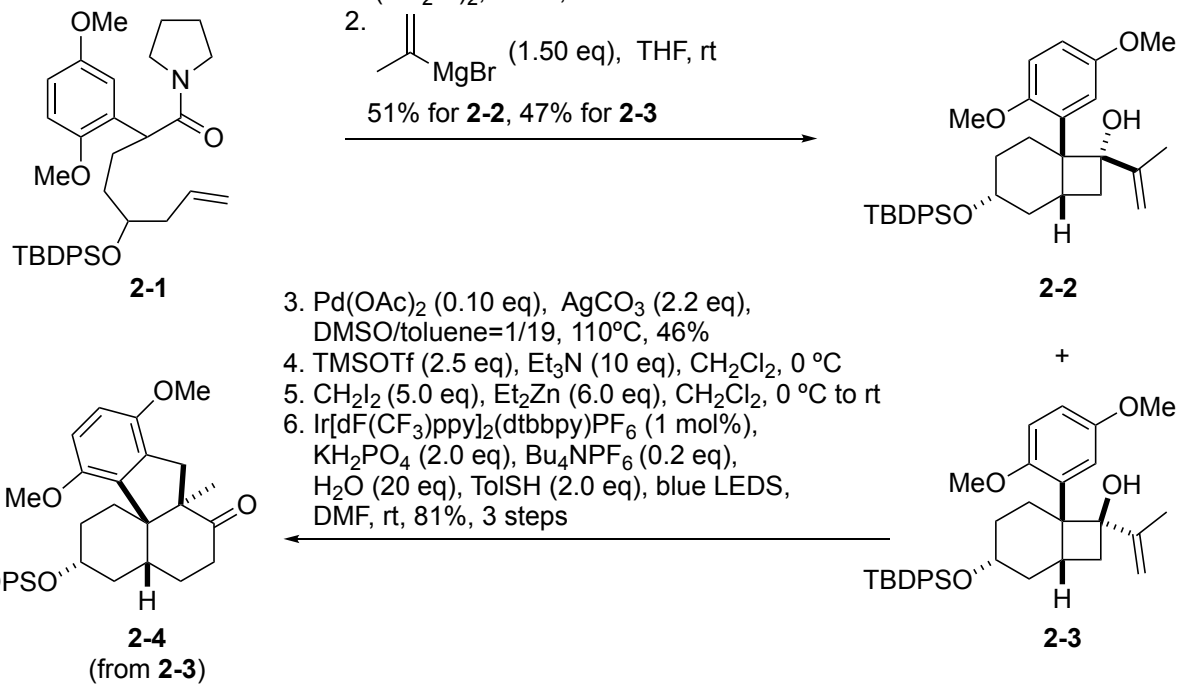
Reference:

6) Fréneau, M.; Hoffmann, N. *J. Photochem. Photobiol. C* **2017**, *33*, 83.

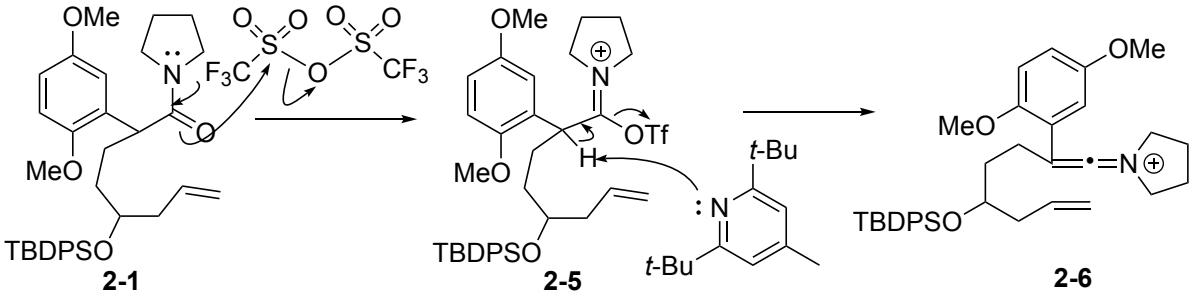
7) Zanini, G. P.; Montejano, H. A.; Previtali, C. M. *J. Photochem. Photobiol., A* **2000**, *132*, 161.

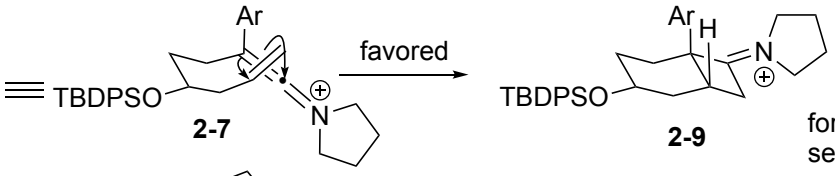
Problem 2: Construction of tetracyclic core structure of Dysiherbols by Liu's group

2

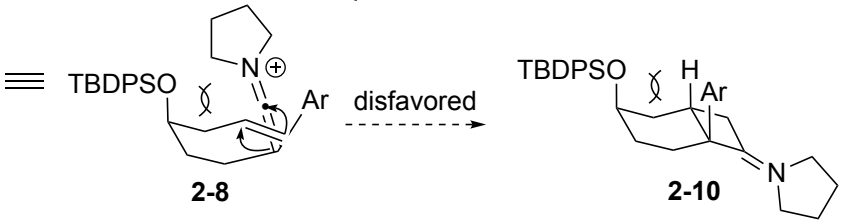


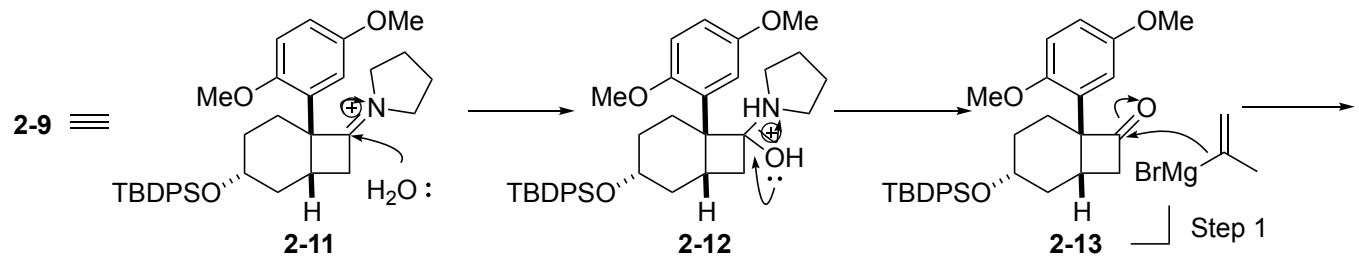
Liu, R.; Xia, M.; Ling, C.; Fu, S.; Liu, B. *Org. Lett*. **2022**, *24*, 1642

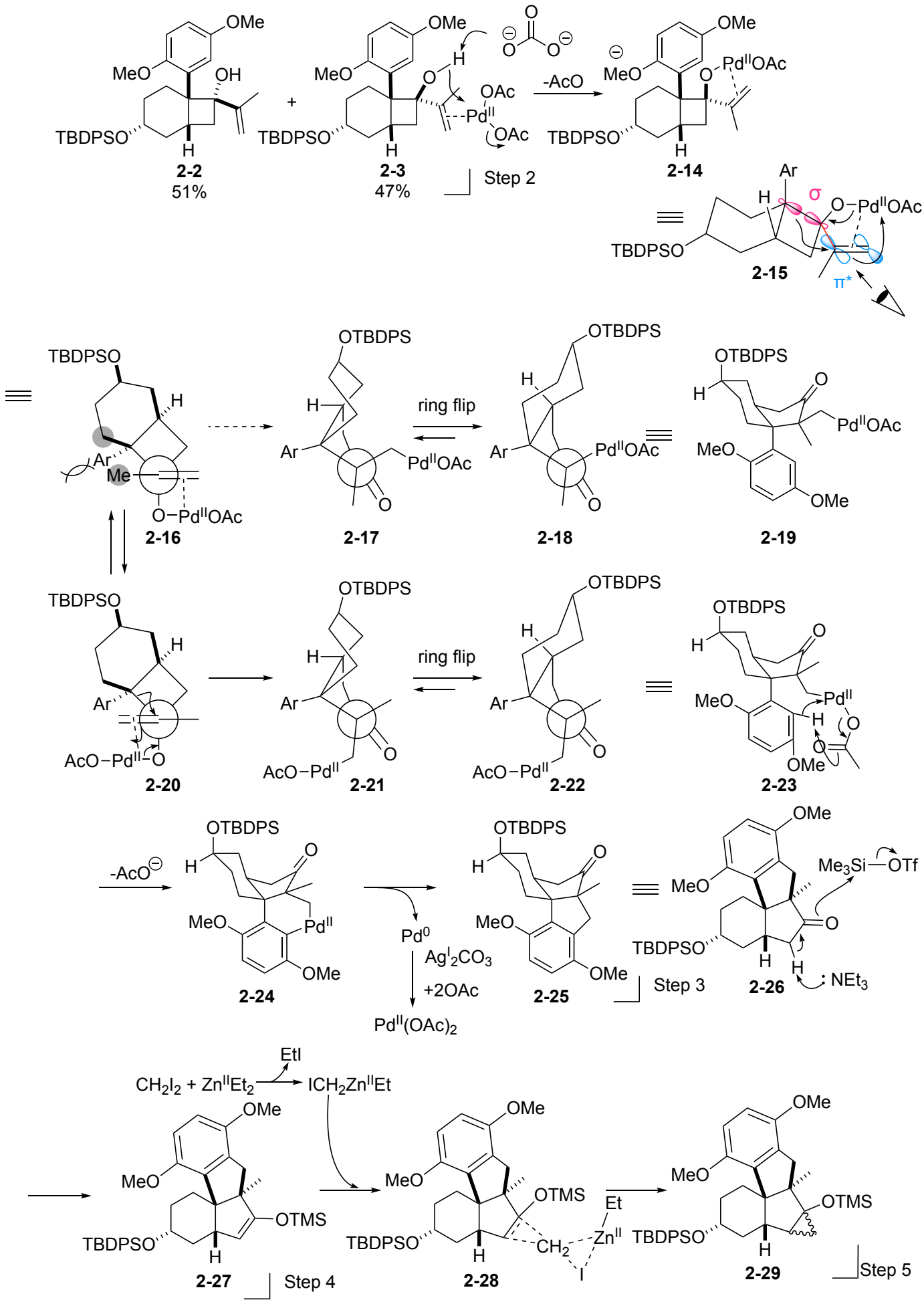




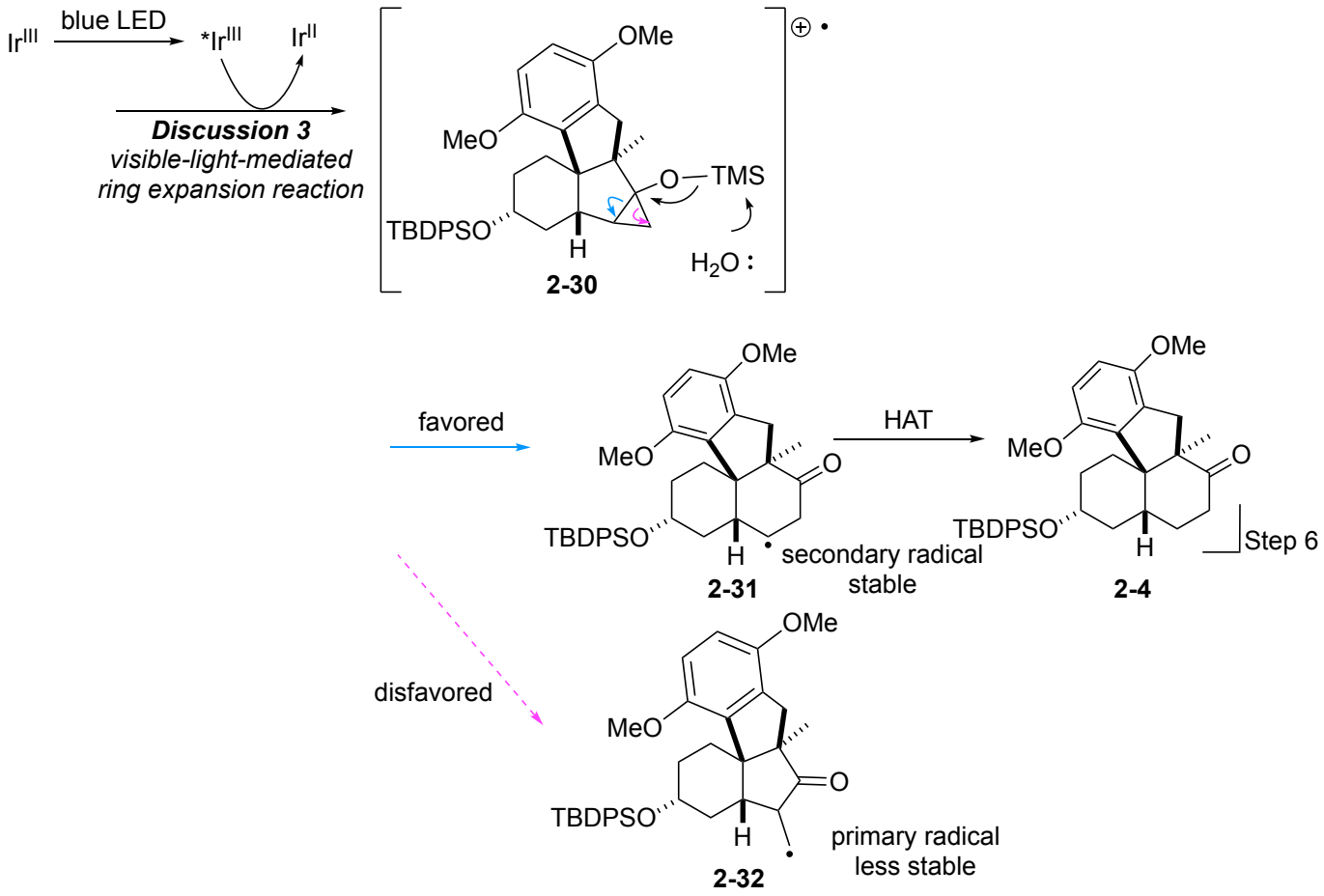
for [2+2] photocycloaddition of keteniminium salts see 221105_PS_Yuma_Komori



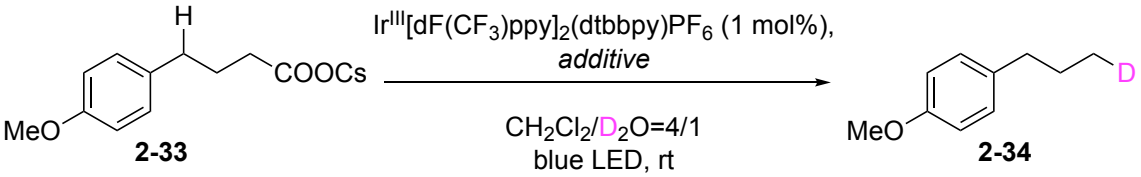




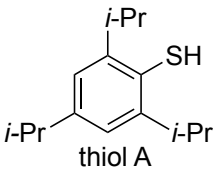
* In the paper, stereochemistry of cyclopropane is not mentioned and displayed with wavy lines. It seems that diastereomeric mixture was used in the following reaction.



Discussion 3: Proposed catalytic cycle of visible-light-mediated ring expansion reaction[8)]

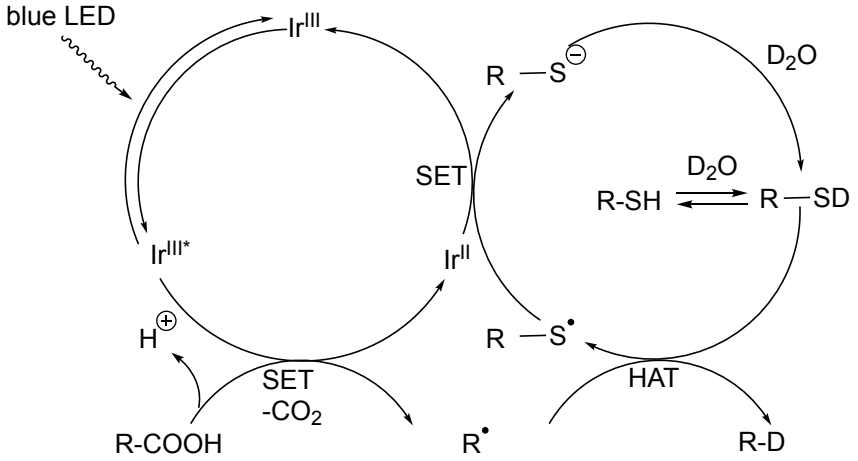


additive	yield	D rate
none	3%	-
thiol A (10 mol%)	75%	96%

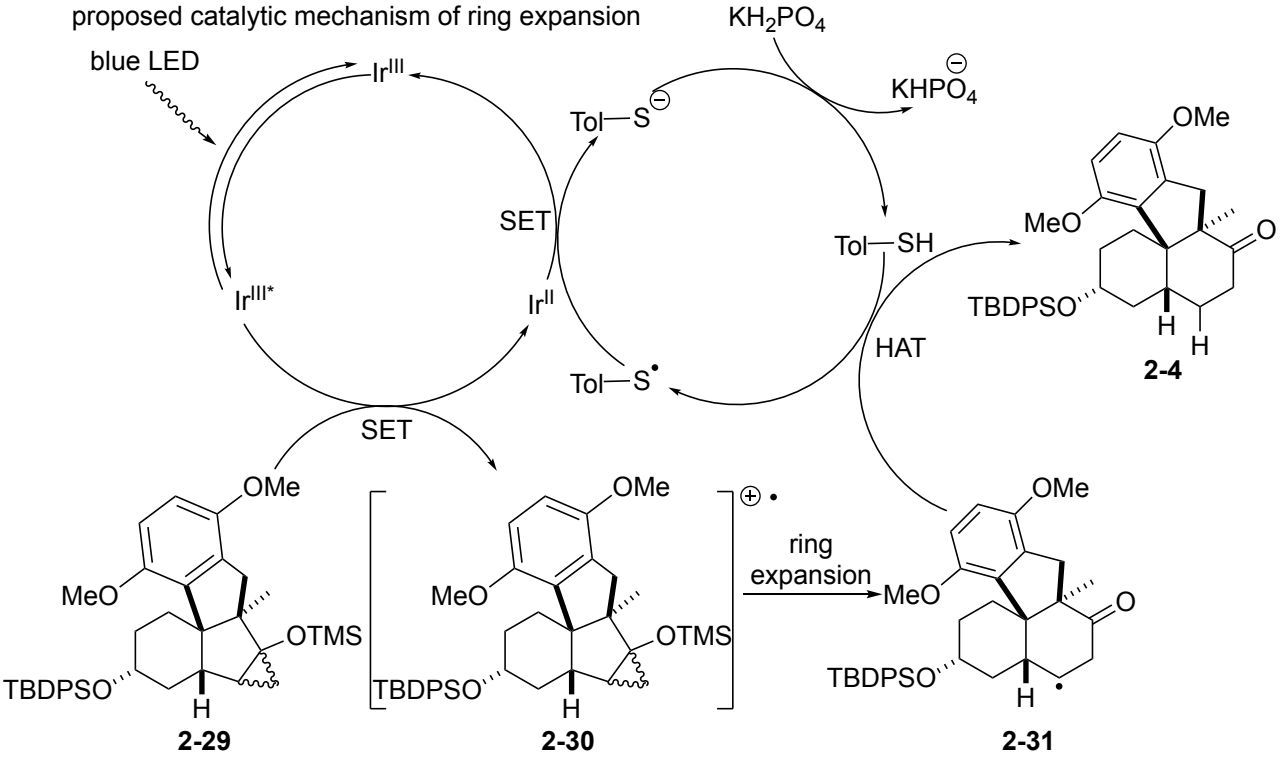


It is reported that addition of thiol A as HAT catalyst improved the yield of decarboxylative deuteration reaction using the same Ir catalyst as problem 2.
The role of TolSH and KH_2PO_4 is not stated, but it is possible that the thiol acts as HAT catalyst like the above reaction, and KH_2PO_4 is proton source.

Catalytic mechanism of decarboxylative deuteration



proposed catalytic mechanism of ring expansion



Reference:

8) Li, N.; Ning, Y.; Wu, X.; Xie, J.; Li, W.; Zhu, C. *Chem. Sci.* **2021**, *12*, 5505.