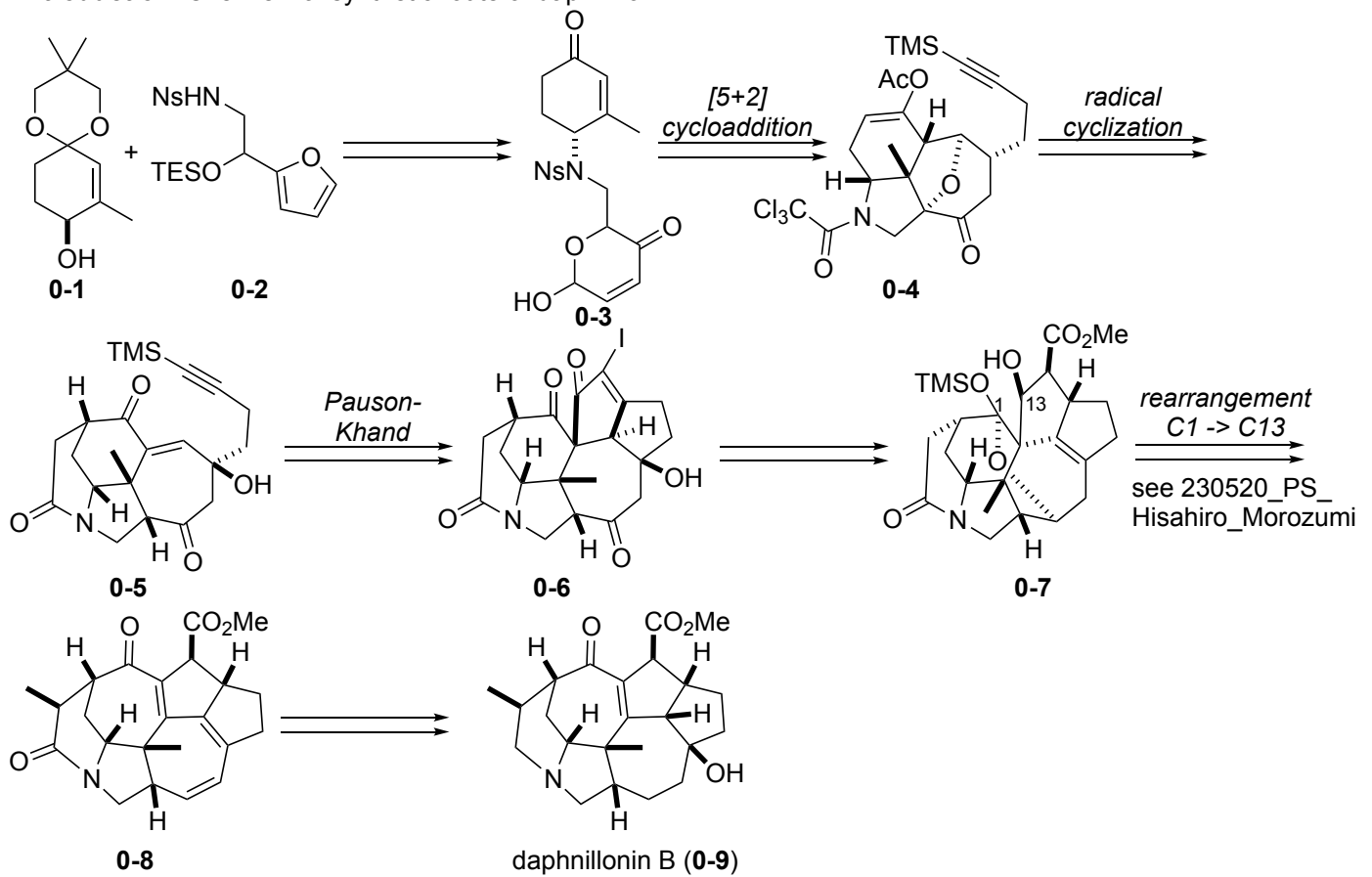


Problem session (3) -answer-

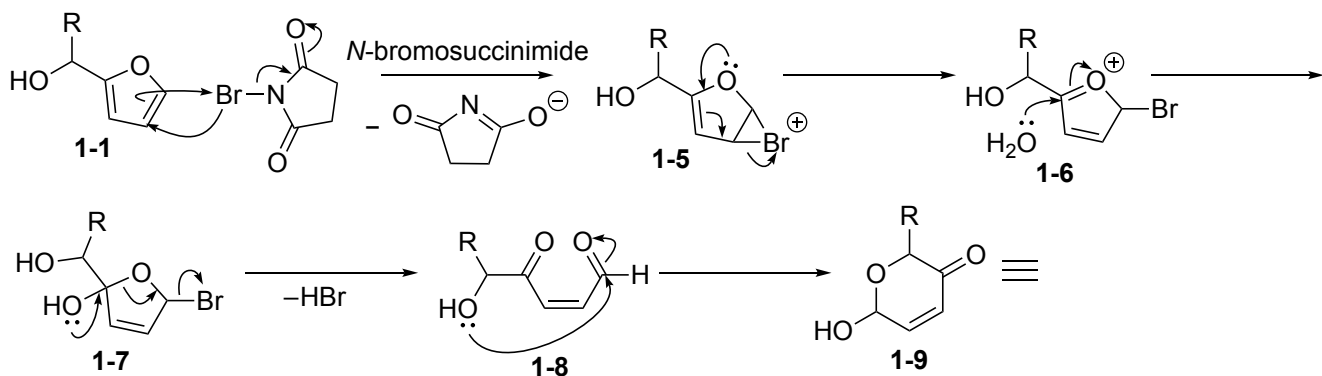
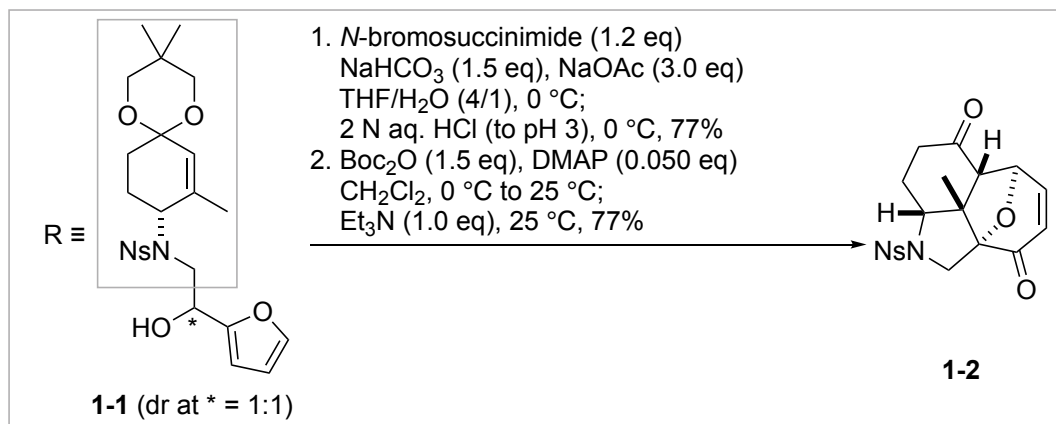
2024/06/29 Mizuki Sawada

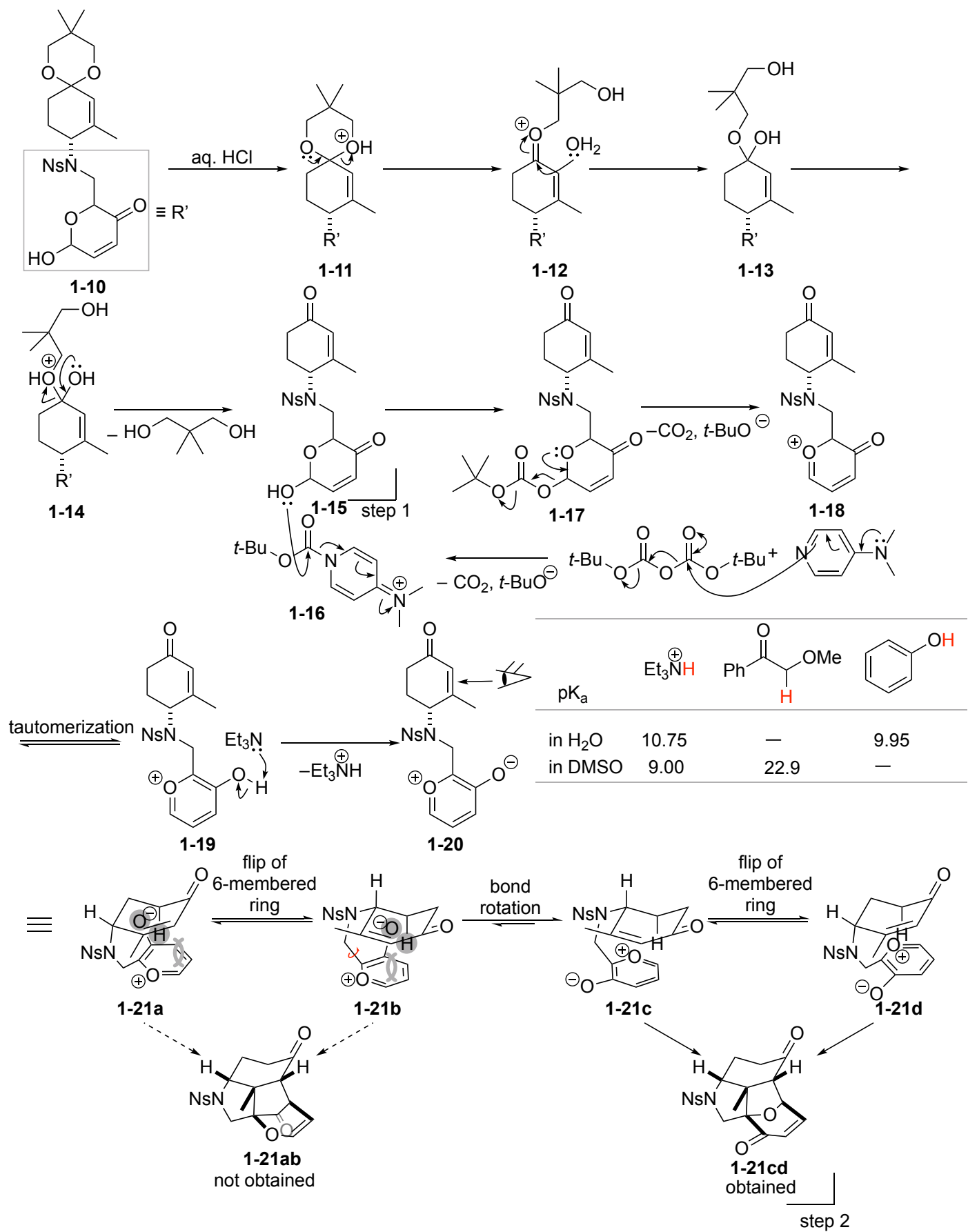
Topic: Total synthesis of daphnillonin B

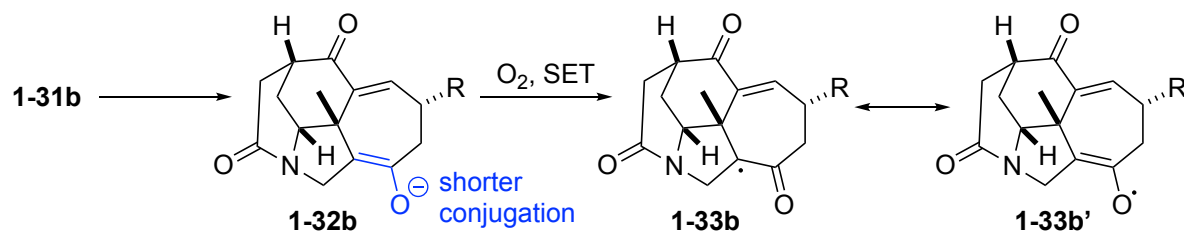
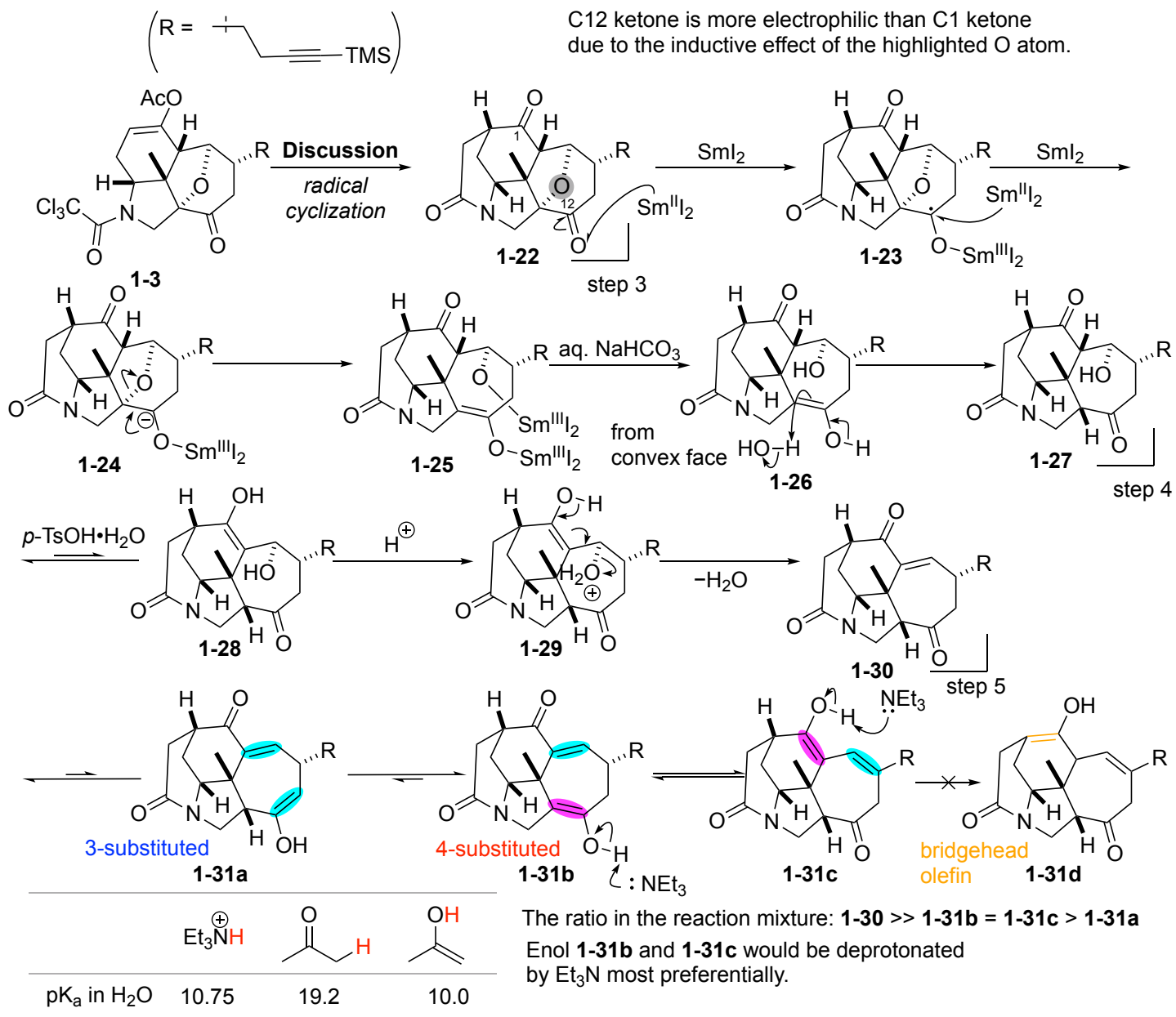
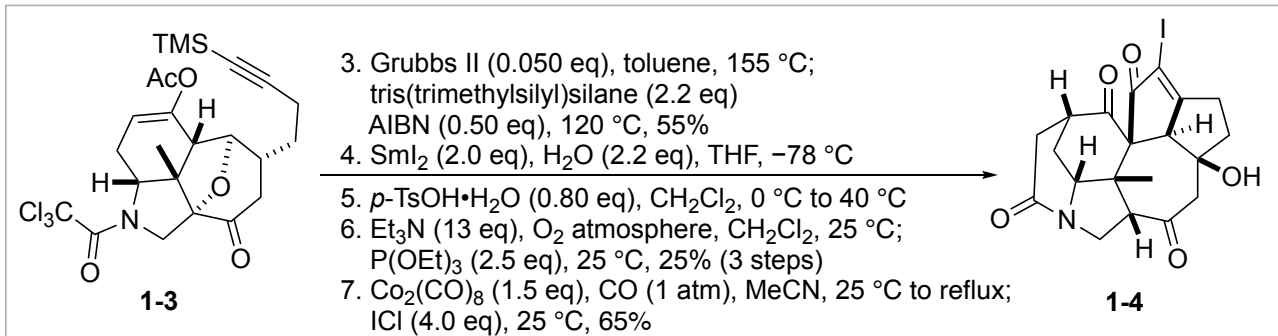
Introduction: Overview of synthetic route of daphnillonin B

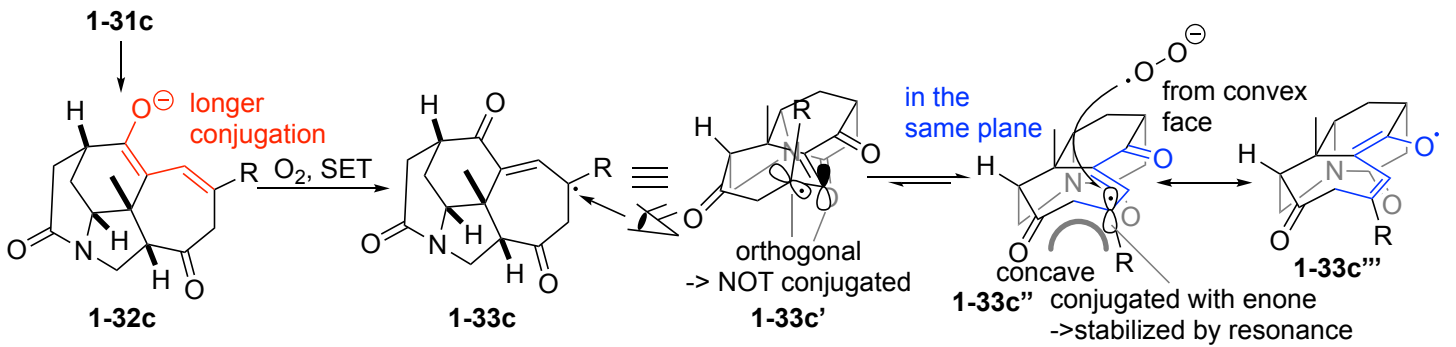


Reaction mechanism

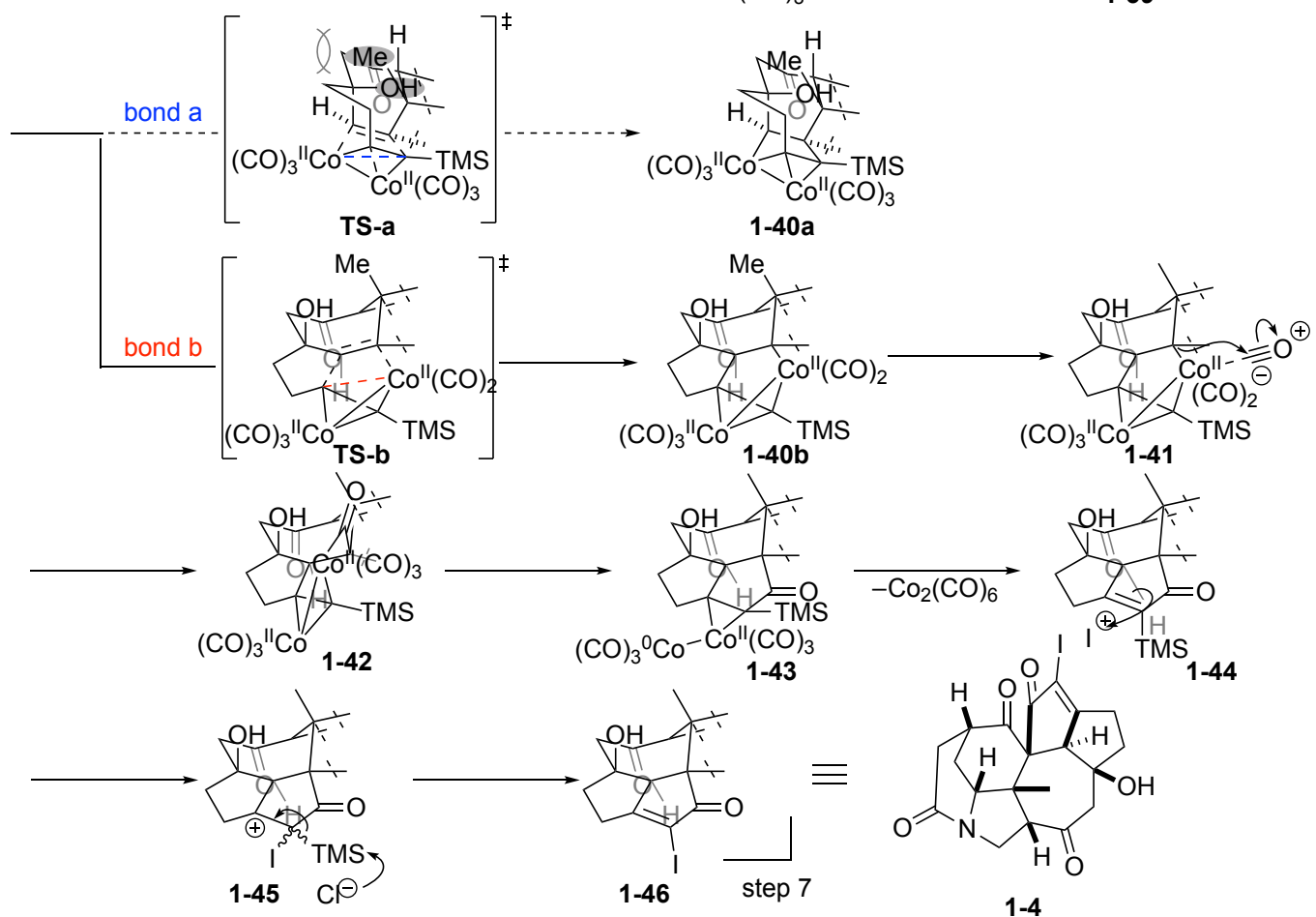
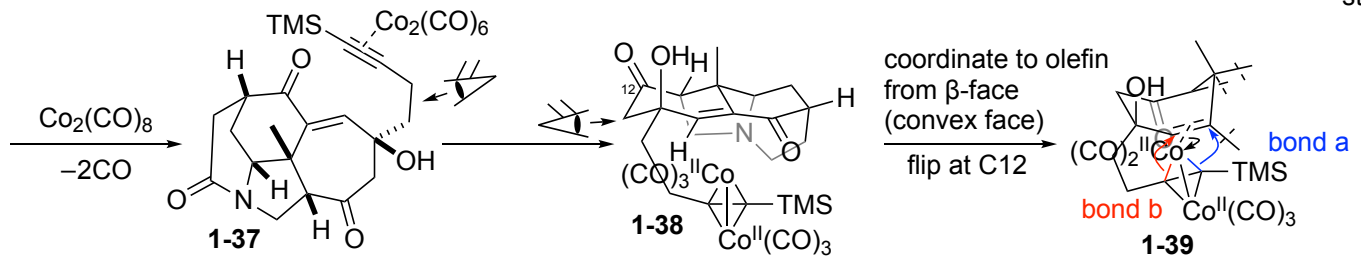
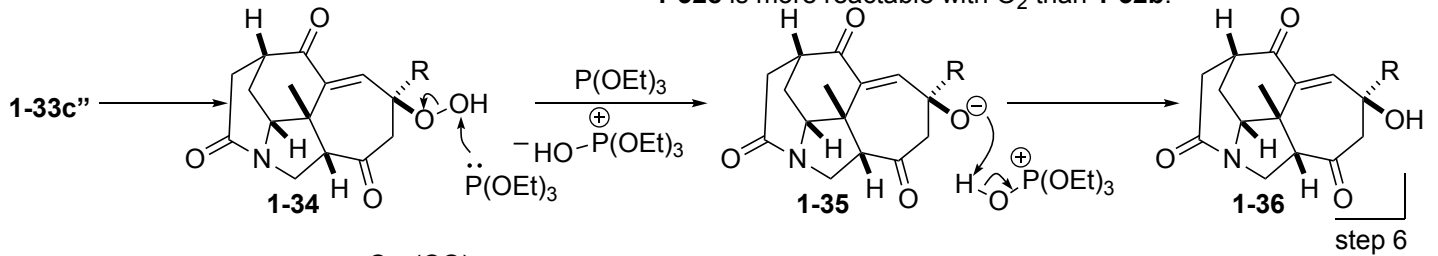








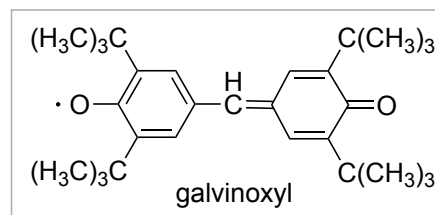
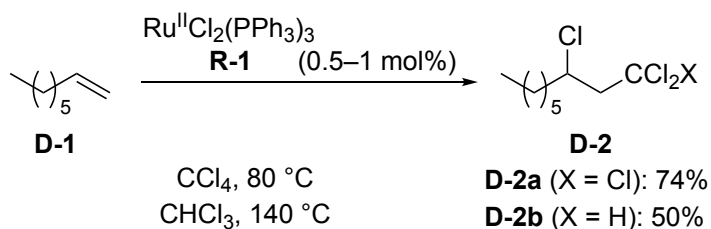
The HOMO energy of enolate of $1-32c$ is higher than that of $1-32b$.
 $1-33c$ is more stable than $1-33b$ due to the longer conjugation.
 $\rightarrow 1-32c$ is more reactive with O_2 than $1-32b$.



Discussion: Radical cyclization with Grubbs catalyst

1. Atom transfer radical addition (ATRA) with Ru(II) catalyst

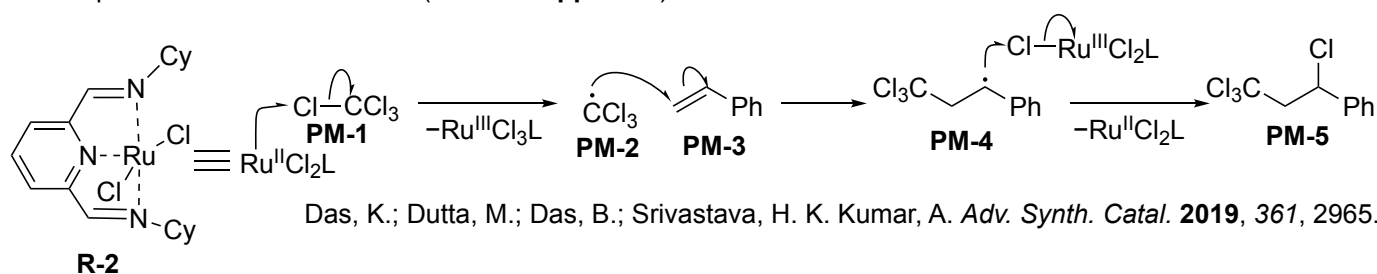
The first report of Ru(II) catalyzed ATRA



It was reported that the addition of small amount of galvinoxyl was completely inhibited the above reaction.

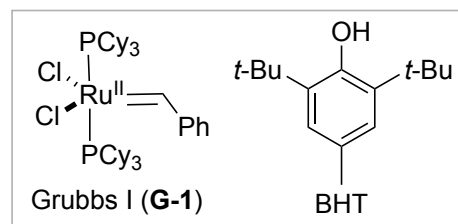
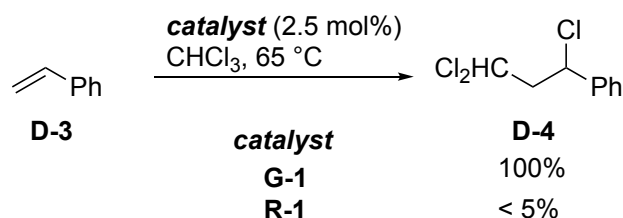
Matsumoto, H.; Nakano, T.; Nagai, Y. *Tetrahedron. Lett.* **1973**, *51*, 5150.

Proposed reaction mechanism (see also **Appendix**)



2. ATRA with ruthenium benzylidene complex

One of the first reports of Grubbs catalyst catalyzed ATRA

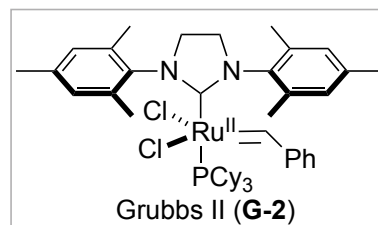
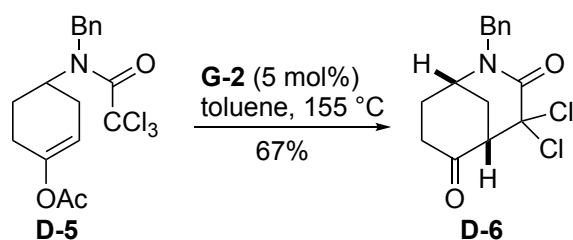


Compound **D-4** was obtained in better yield with **G-1** than **R-1**.

It was reported that the addition of BHT or galvinoxyl severely limited the formation of **D-4**.

Tallarico, J. A.; Malnick, L. M.; Snapper, M. L. *J. Org. Chem.* **1999**, *64*, 344.

An example of radical cyclization of trichloroacetamide to enol acetate



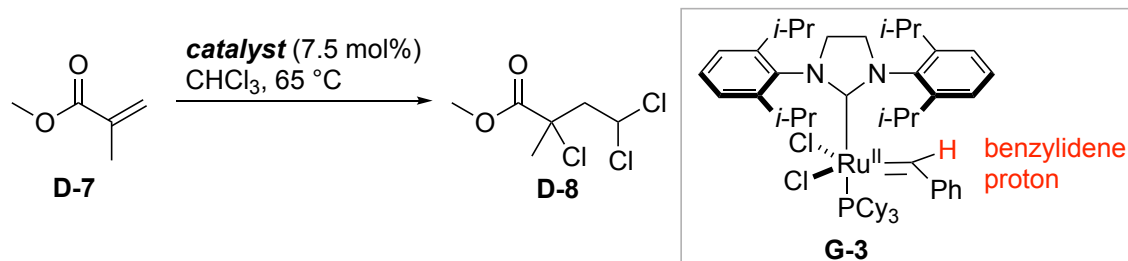
Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem.* **2014**, *79*, 9365.

3. The active Ru species for ATRA with ruthenium benzylidene complex

3-1. Investigation of active Ru species for ATRA by Grubbs's group

Lee, J.; Grandner, J. M.; Engle, K. M.; Houk, K. N.; Grubbs, R. H. *J. Am. Chem. Soc.* **2016**, *138*, 7171.

3-1-1. ATRA with Ru benzylidene catalysts **G-1**, **G-2** and **G-3**

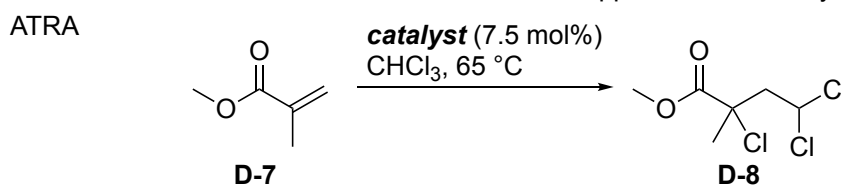
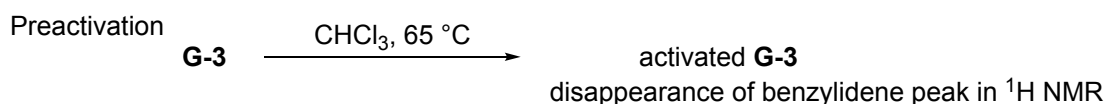


catalyst	decomp. of catalyst (%)*		conv. of D-7 (%)		yield of D-8 in 2 h (%)
	30 min	90 min	30 min	2 h	
G-1	~15	~50	~30	89	89
G-2	< 5	~10	~20	45	7
G-3	~40	~100	~70	95	94

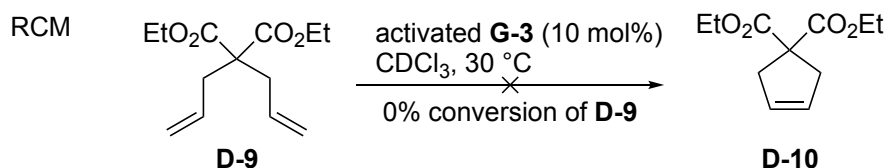
* Decomposition of the catalysts was monitored by the disappearance of ^1H NMR peak of benzylidene proton.

faster decomposed catalyst \rightarrow faster conversion of **D-7** and better yield of **D-8**

3-1-2. ATRA and ring closing metathesis (RCM) with activated **G-3**



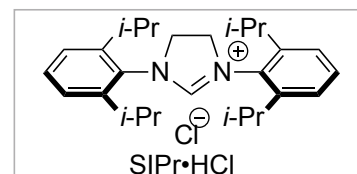
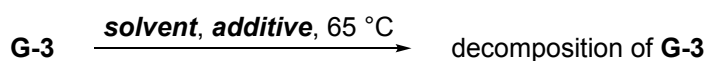
catalyst	conv. of D-7 in 30 min (%)	yield of D-8 in 2 h (%)
G-3	~70	94
activated G-3	~85	93



The results shown in sections 3-1-1 and 3-1-2 indicate that new Ru species (= activated **G-3**) without benzylidene moiety catalyzes the ATRA.

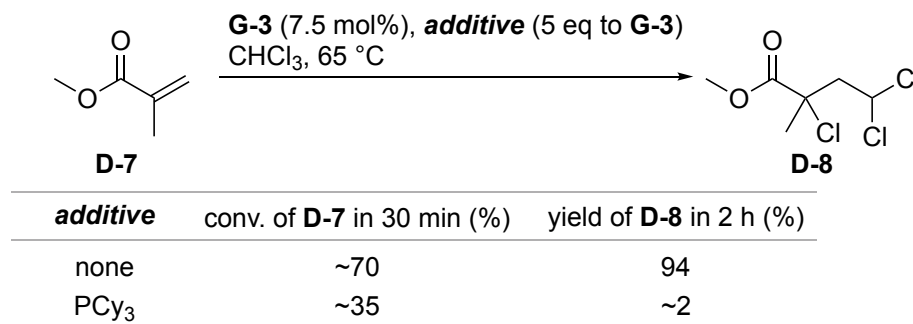
3-1-3. Proposed new ATRA-active Ru species and supporting experimental results

(1) Alkyl halide triggered the decomposition of **G-3**.

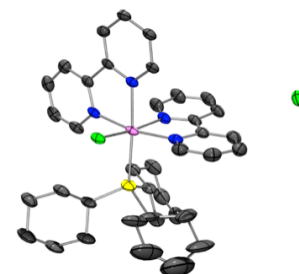
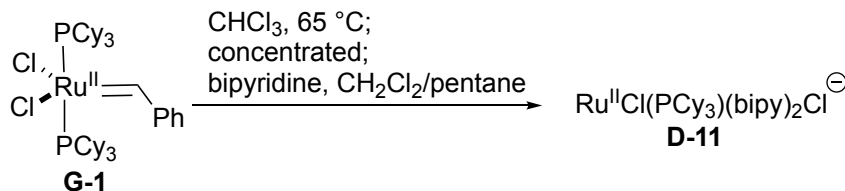


solvent	additive	decomp. of G-3 in 1 h (%)	note
CDCl_3	none	~100	SIPr•HCl was isolated.
C_6D_6	none	~0	

(2) The excess PCy₃ suppressed the ATRA.

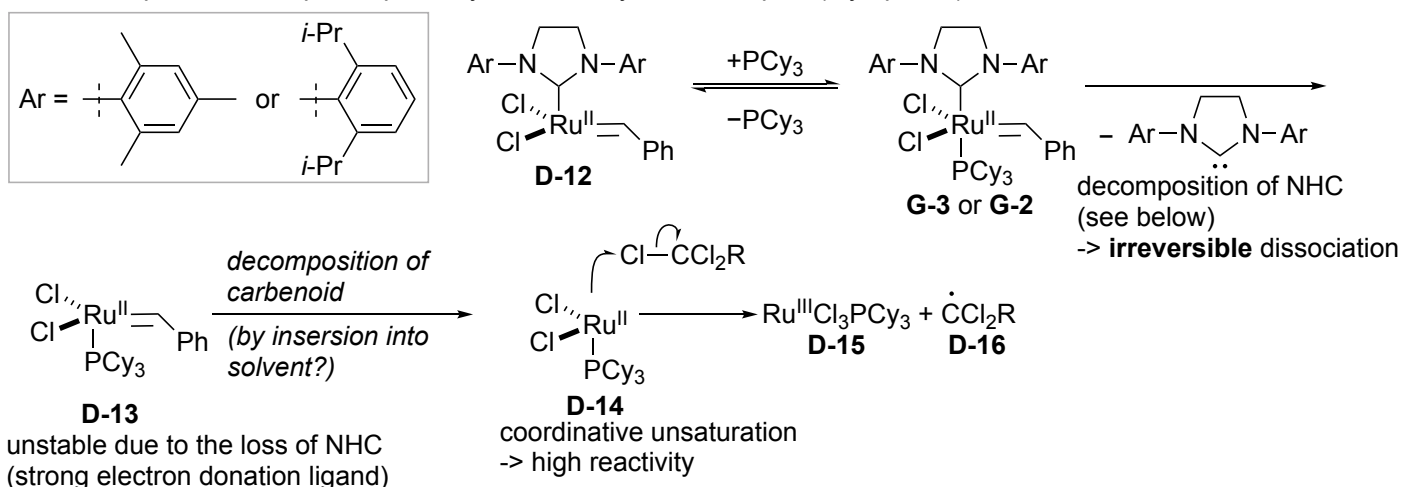


(3) X-ray structure of decomposed **G-1**



(4) Proposed new ATRA-active Ru species: **Ru_xCl_y(PCy₃)_z**

3-2. Proposed decomposed pathway of Ru benzylidene complex (my opinion)

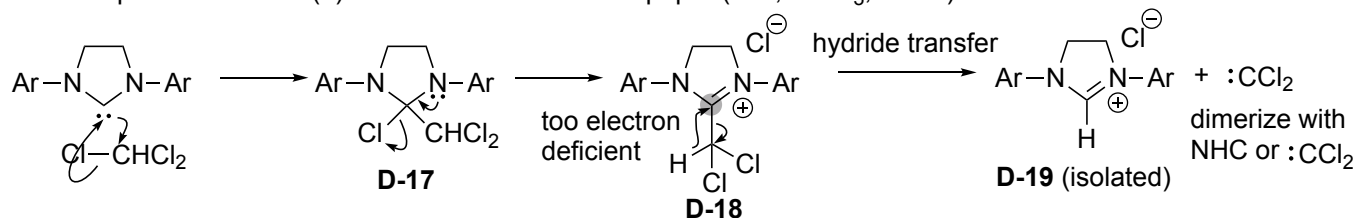


Irreversible dissociation of NHC ligands seem to trigger the decomposition of carbenoid complex **D-13**.

In section 3-3-1 (2), excess PCy₃ would be coordinate to **D-13** and prevent the decomposition of **D-13**.

The irreversible dissociation of ligands may contribute to the higher reactivity of Ru benzylidene catalysts than Ru complex without carbene ligands.

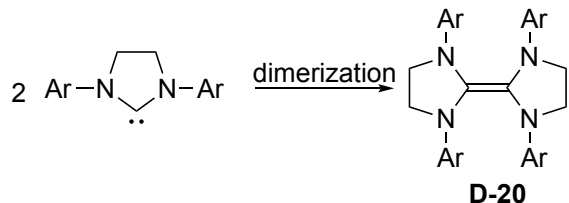
Decomposition of NHC (1): in the case of Grubbs's paper (**G-3**, CHCl₃, 65 °C)



In the case of low reaction temperature (65 °C), the dissociation of NHC ligands would be slow and the concentration of the free ligands would be low.

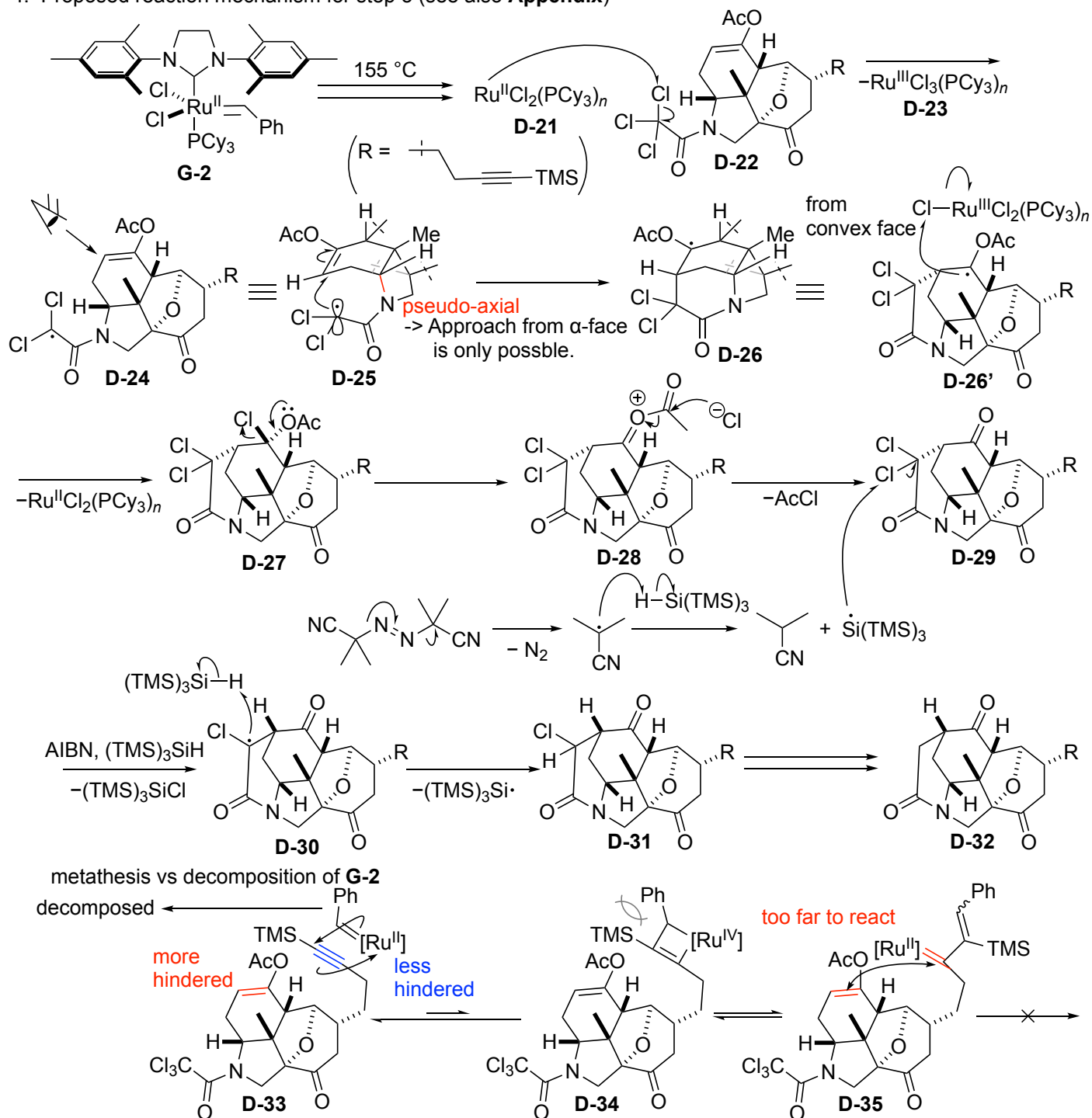
Therefore, it is seemed that carbene insertion into abundant CHCl₃ proceeds rather than dimerization.

Decomposition of NHC (2): In the case of Grubbs's paper (G-2, toluene, 155 °C)



In the case of high reaction temperature (155 °C), the dissociation of NHC ligands would proceed quickly and the free ligands would be abundant in the reaction mixture. Therefore, it is estimated that carbenes can dimerize easily.

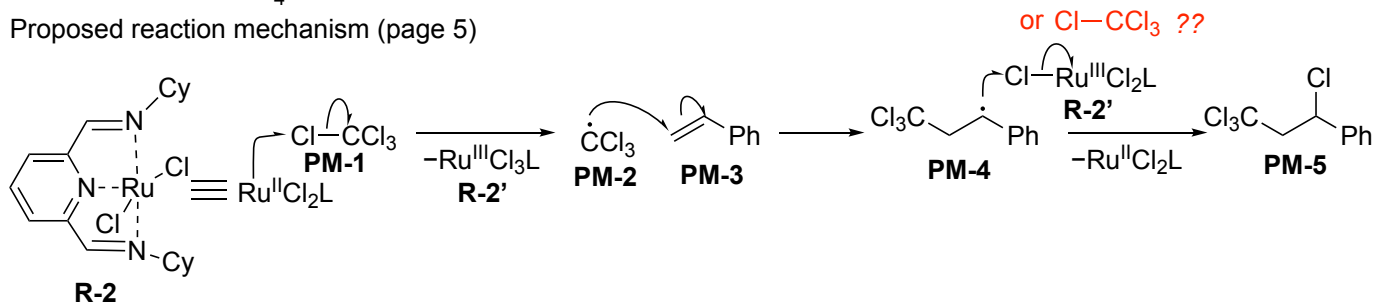
4. Proposed reaction mechanism for step 3 (see also **Appendix**)



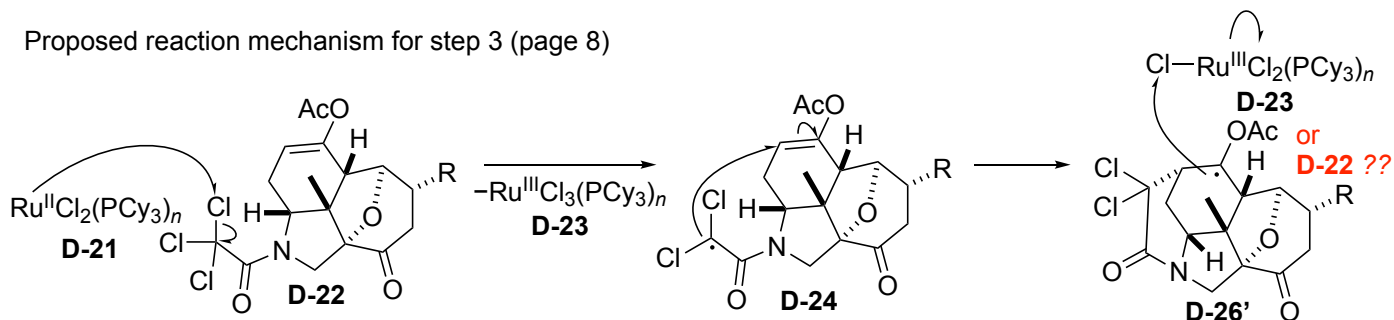
Appendix: BDE of Ru^{III}-Cl bond

Question: In the following proposed reaction mechanisms, do **PM-4** and **D-26'** abstract Cl from **R-2'** or **D-23**, not from CCl₄ or **D-22**?

Proposed reaction mechanism (page 5)

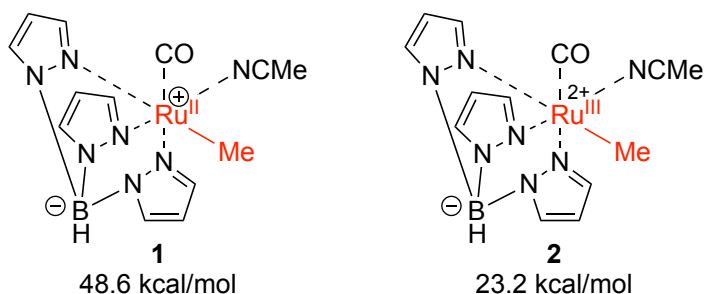


Proposed reaction mechanism for step 3 (page 8)



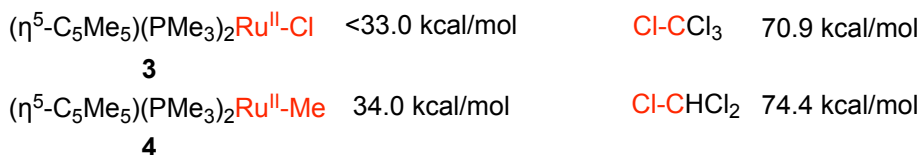
Calculated BDEs of red bond

Lail, M.; Gunnoe, T. B.; Barakat, K. A.; Cundari, T. R. *Organometallics* **2005**, *24*, 1301.

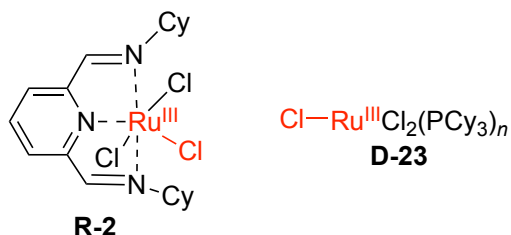


Calculation level:
B3LYP/SBK(d)

Reported BDEs of red bond



Estimation BDEs of Ru^{III}-Cl bond of **R-2'** and **D-23**



(1) comparison of **3** and **4** -> The BDE of Ru^{II}-Cl bond is similar to that of Ru^{II}-Me.

-> The BDE of Ru^{III}-Cl bond of **R-2'** and **D-23** can be assumed to be around 23.2 kcal/mol (the BDE of Ru^{III}-Me of **2**).

(2) comparison of **1** and **2** -> The BDE of Ru^{III}-Me bond is lower than that of Ru^{II}-Me.

-> The BDE of Ru^{III}-Cl bond of **R-2'** and **D-23** can be assumed to be lower than 33.0 kcal/mol (the BDE of Ru^{II}-Cl of **3**).

Judging from estimations (1) and (2), the BDE of **R-2'** and **D-23** can be assumed to be lower than about 30 kcal/mol.

Since the estimated BDE of Ru^{III}-Cl bond of **R-2'** and **D-23** is much lower than that of C-Cl bond of CCl₄ or CHCl₃, in terms of BDEs, it seems that **PM-4** and **D-26'** abstract Cl from **R-2'** or **D-23**, not from CCl₄ or **D-22**.