

Integration of C-C bond activation and C-H bond activation

LS. 2017.1.21.

Tsukasa Shimakawa

Contents

1. Introduction

- Definition of the word
- Overview

2. Recent research about C-C bond activation via C-H bond activation

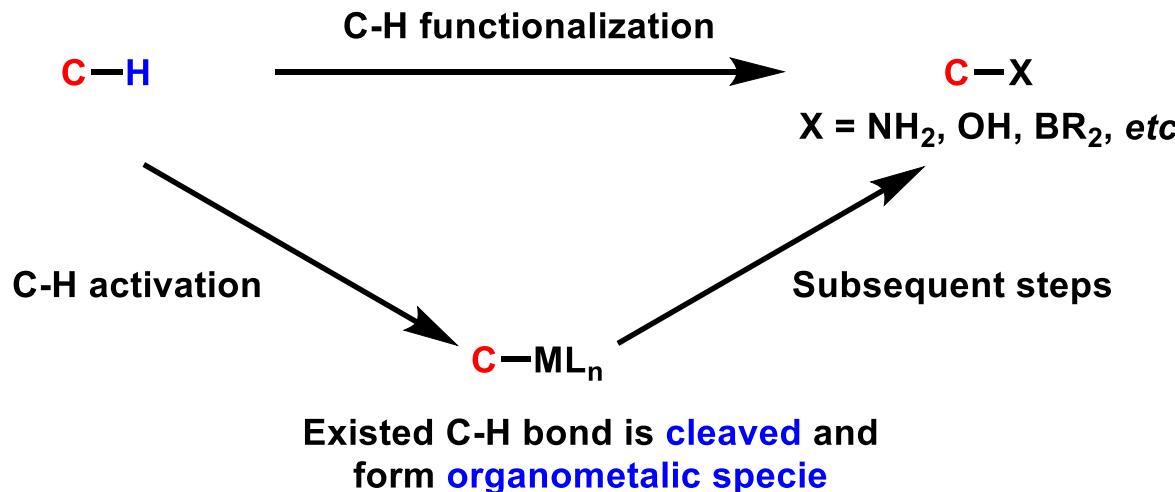
- Studies by Marek group
- C-C bond activation of highly strained cyclopropanes

3. Main Paper

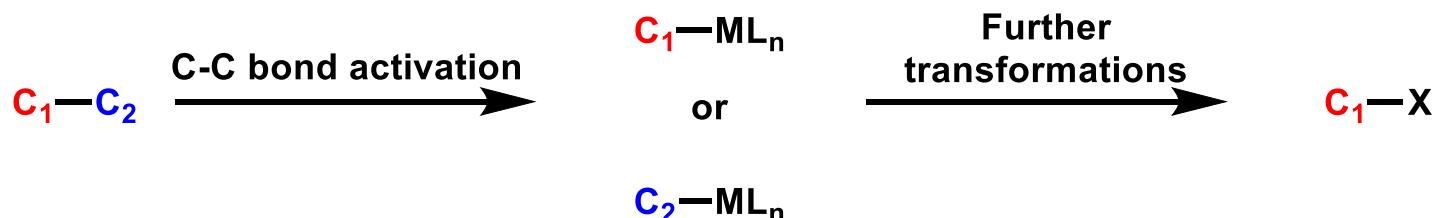
- Studies by Dong group
- C-C bond activation of less strained cyclopentanones

What is "C-C bond activation" ?

- C-H bond functionalization and C-H bond activation



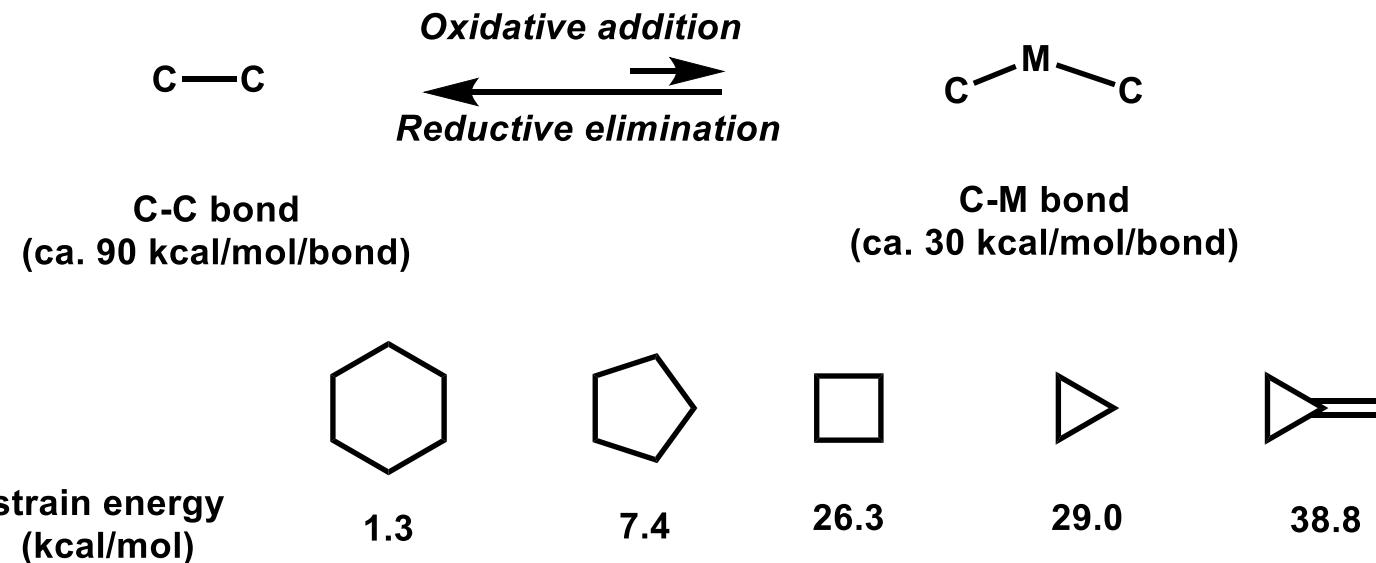
- Definition of the word "C-C bond activation"



**Existed C-C bond is cleaved and form
organometallic specie for further transformations.**

Why Oxidative Addition to C-C bond is difficult ?

1. Higher inertness of C-C bond (thermodynamic)



2. Less favorable orbital overlap (kinetic)



- 1) Jun, C. H. *Chem. Soc. Rev.* **2004**, 33, 610. 2) Halpern, J. *Acc. Chem. Res.* **1982**, 15, 238.
3) Souillart, L. and Cramer, N. *Chem. Rev.* **2015**, 115, 9410.

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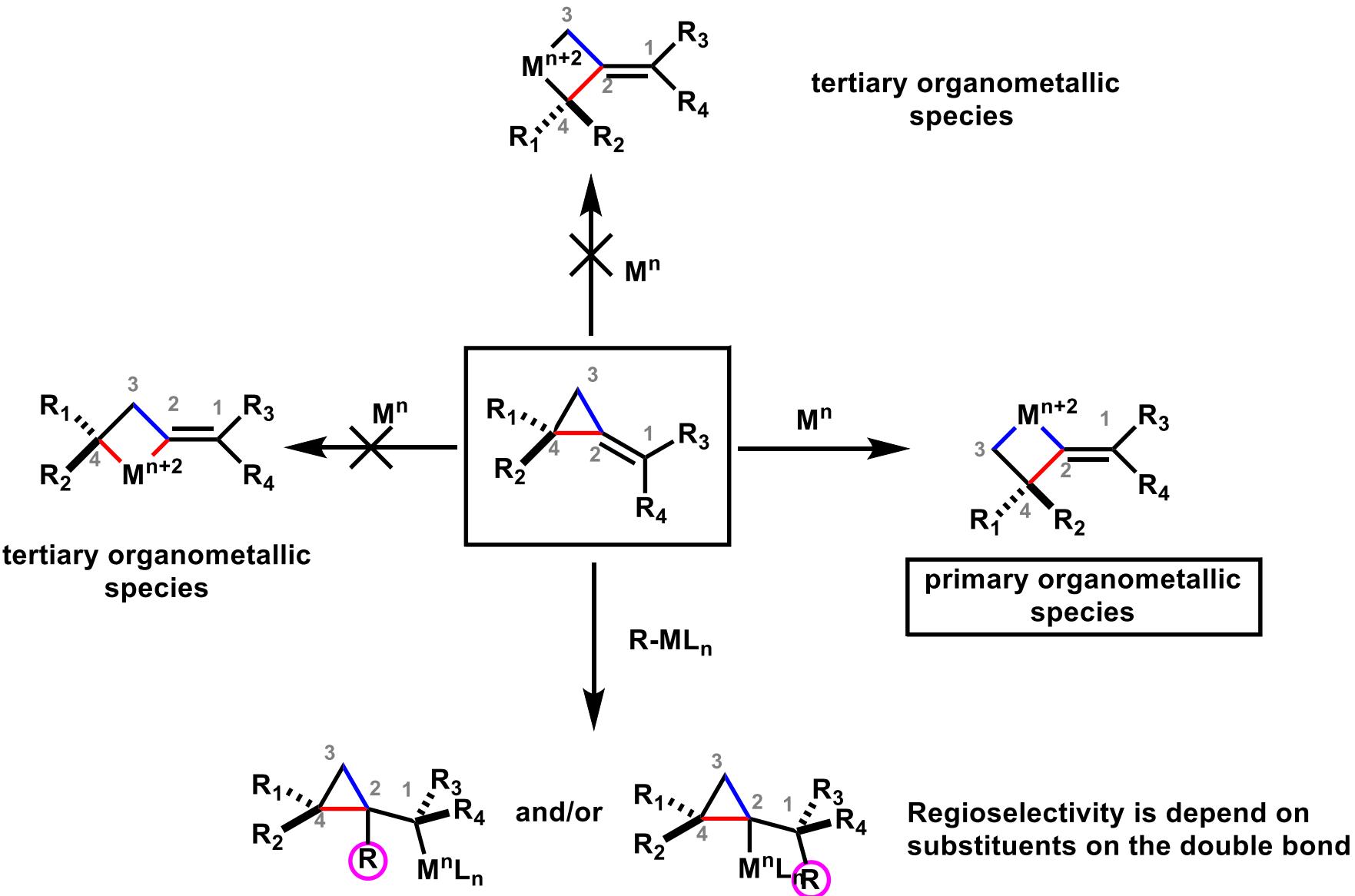
2. Recent research about C-C bond activation via C-H bond activation

- Studies by Marek group
- C-C bond activation of highly strained cyclopropanes

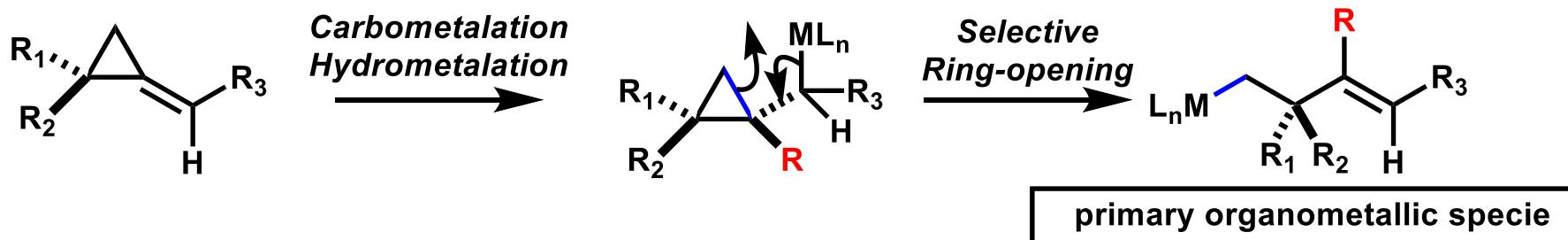
3. Main Paper

- Studies by Dong group
- C-C bond activation of less strained cyclopentanones

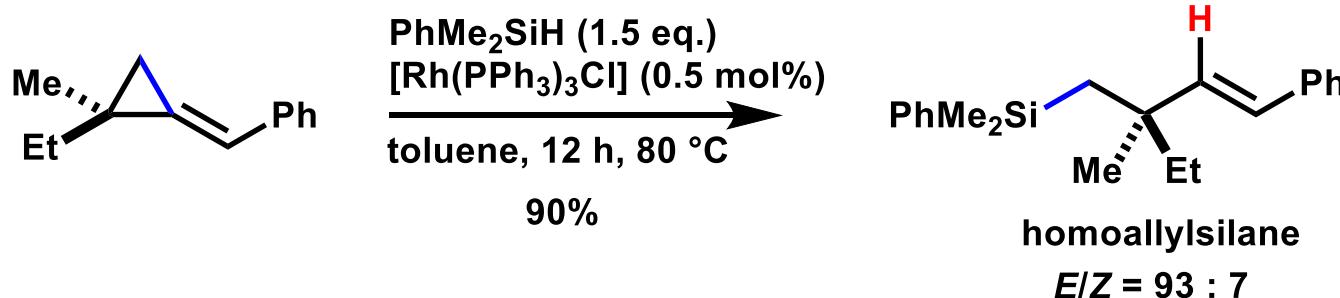
Marek's Hypothesis about Regioselectivity



Previous Studies about methylene cyclopropane

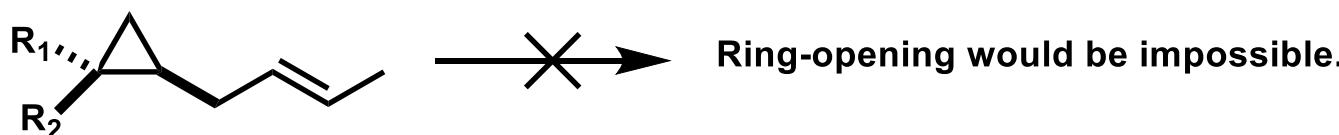


·Marek

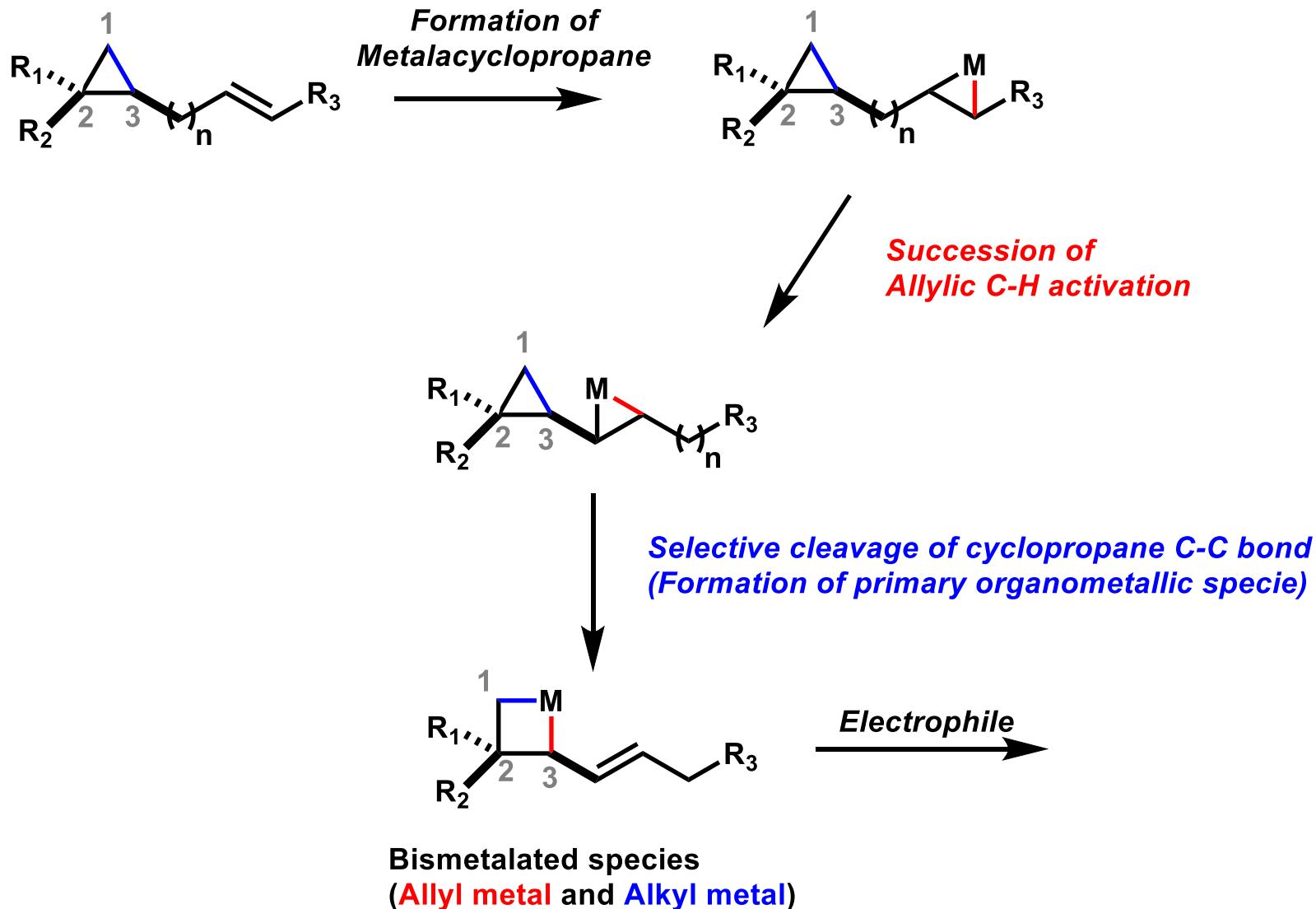


Selective ring opening is faster than reductive elimination.

·Problematic point



Working Hypothesis by Marek Group

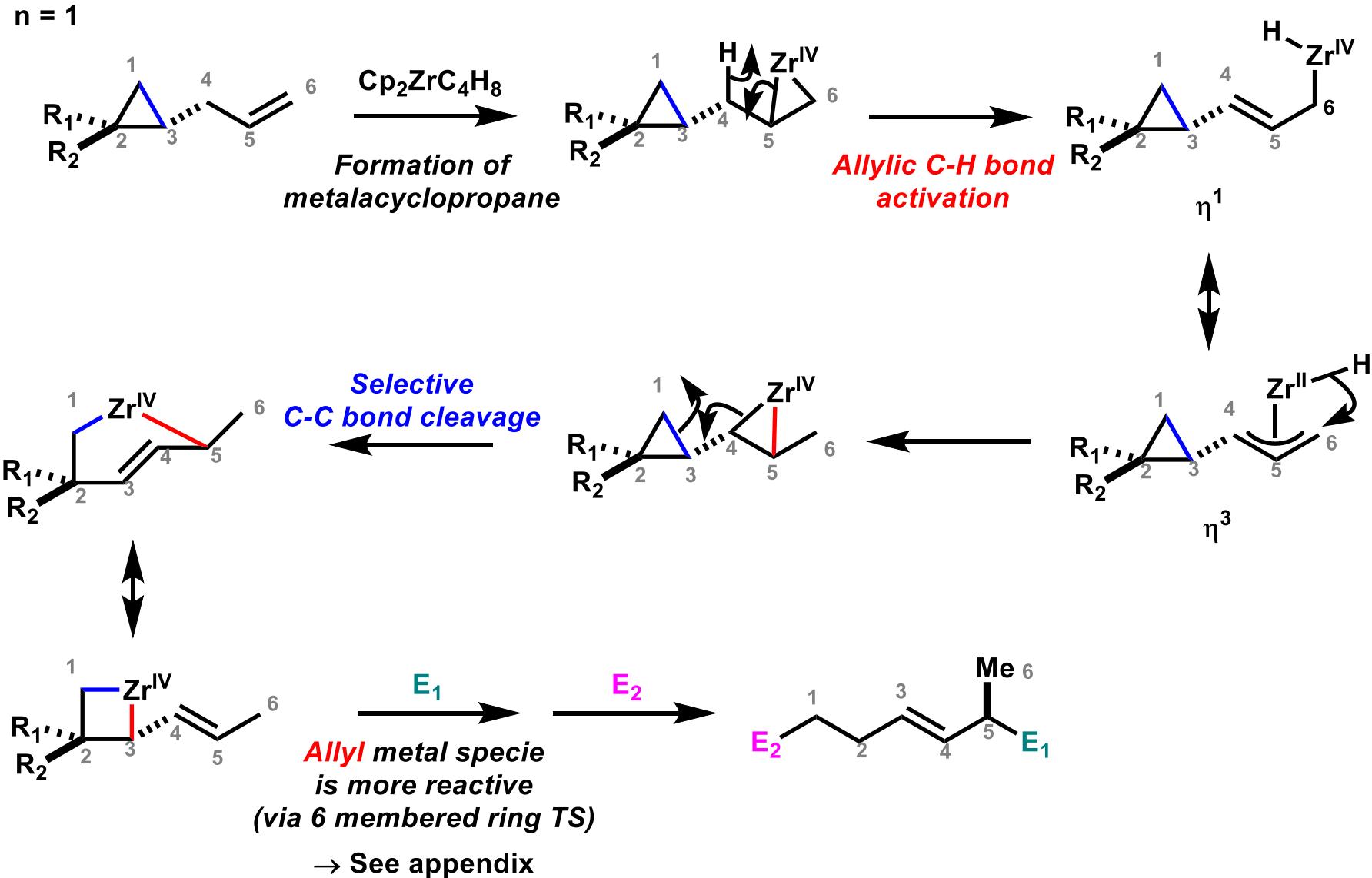


Studies by Marek Group



entry	n	R_1	R_2	E_1	E_2	result
1	1	Ph	Pr	Me_2CO	I_2	77% (dr = 98:2)
2	2	Et	Bu	Me_2CO	H_3O^+	62% (dr = 98:2)
3	3	Et	Bu	EtCOEt	H_3O^+	59% (dr = 98:2)
4	3	Me	Bu	Me_2CO	I_2	57% (dr = 95:5)
5	4	Et	Bu	Me_2CO	H_3O^+	50% (dr = 98:2)

Proposed Mechanism by Marek Group



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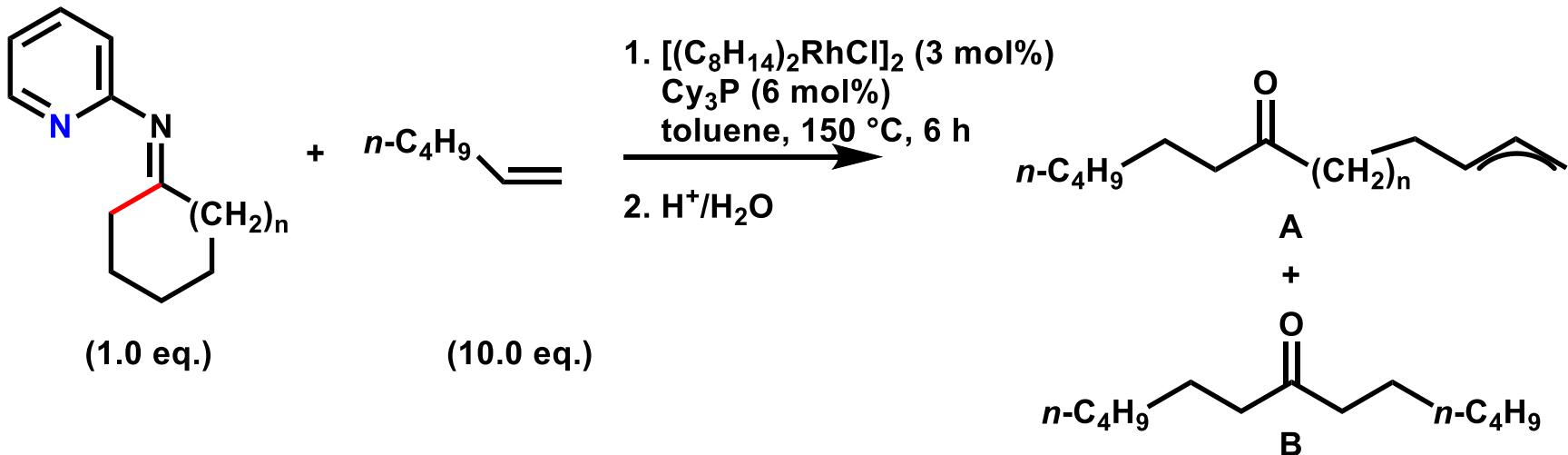
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Previous Research of Jun's Group (1)



entry	n	result
1	0	B: 9%
2	1	B: 5%
3	2	A+B: 76%
4	3	A+B: 89%
5	5	A+B: 83%

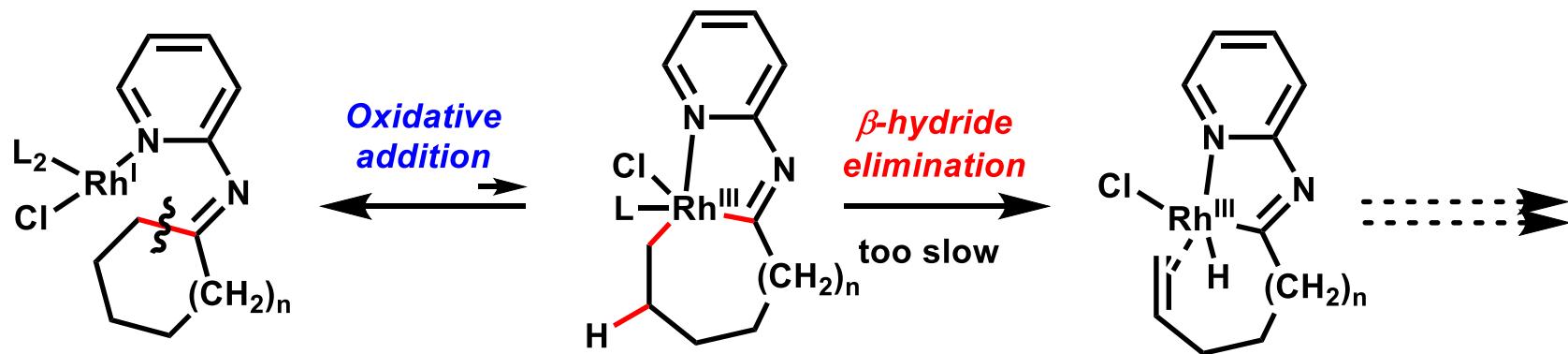
C-C bond activation is **difculty**.

What is the main factor ?

C-C bond activation is **easy**.

Previous Research of Jun's Group (2)

In case of $n = 1, 2, \dots$,



pyridine moiety is a directing group

→ Regioselective oxidative addition to C-C bond is possible.

1. Oxidative addition to C-C bond would be difficult. ← all case ($n = 0, 1, 2, 3, 5$)

2. β-hydride elimination would be very slow.

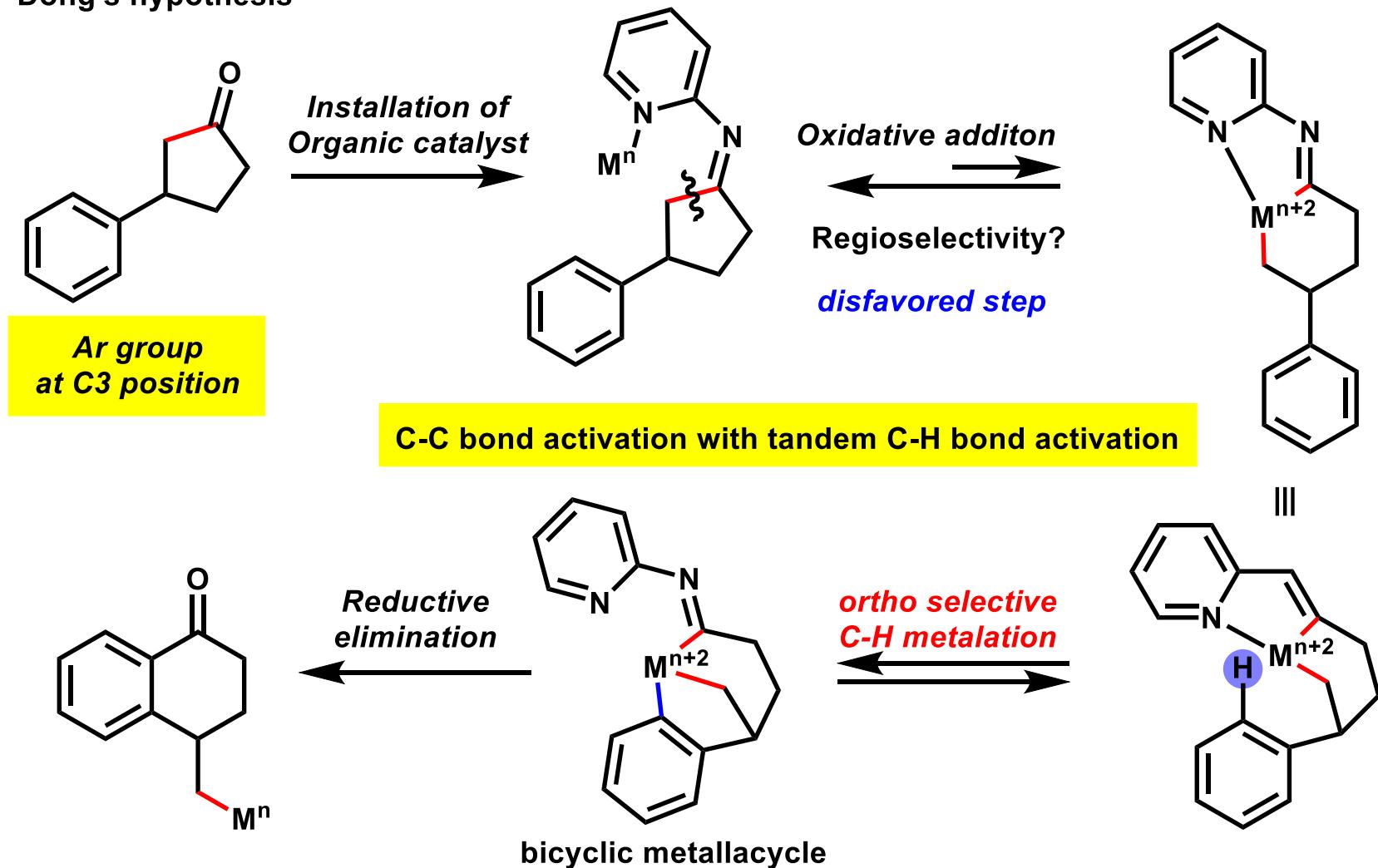
→ Overlap of C-Rh bond and C-H bond is insufficient

Main factor

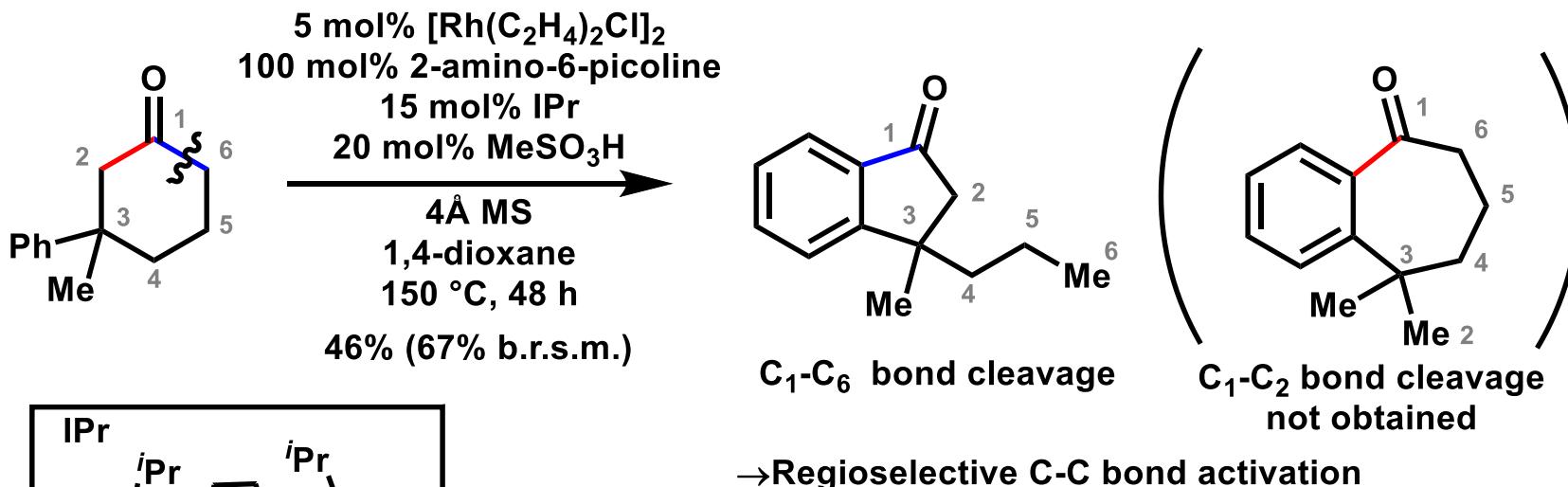
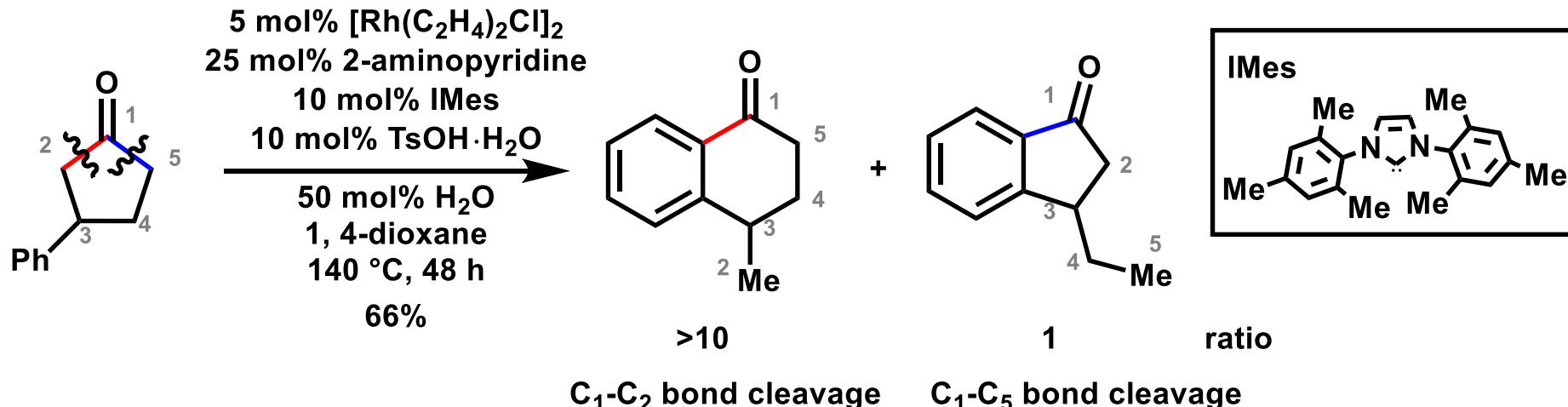
Working Hypothesis

-C-C bond activation of cyclopentanone-

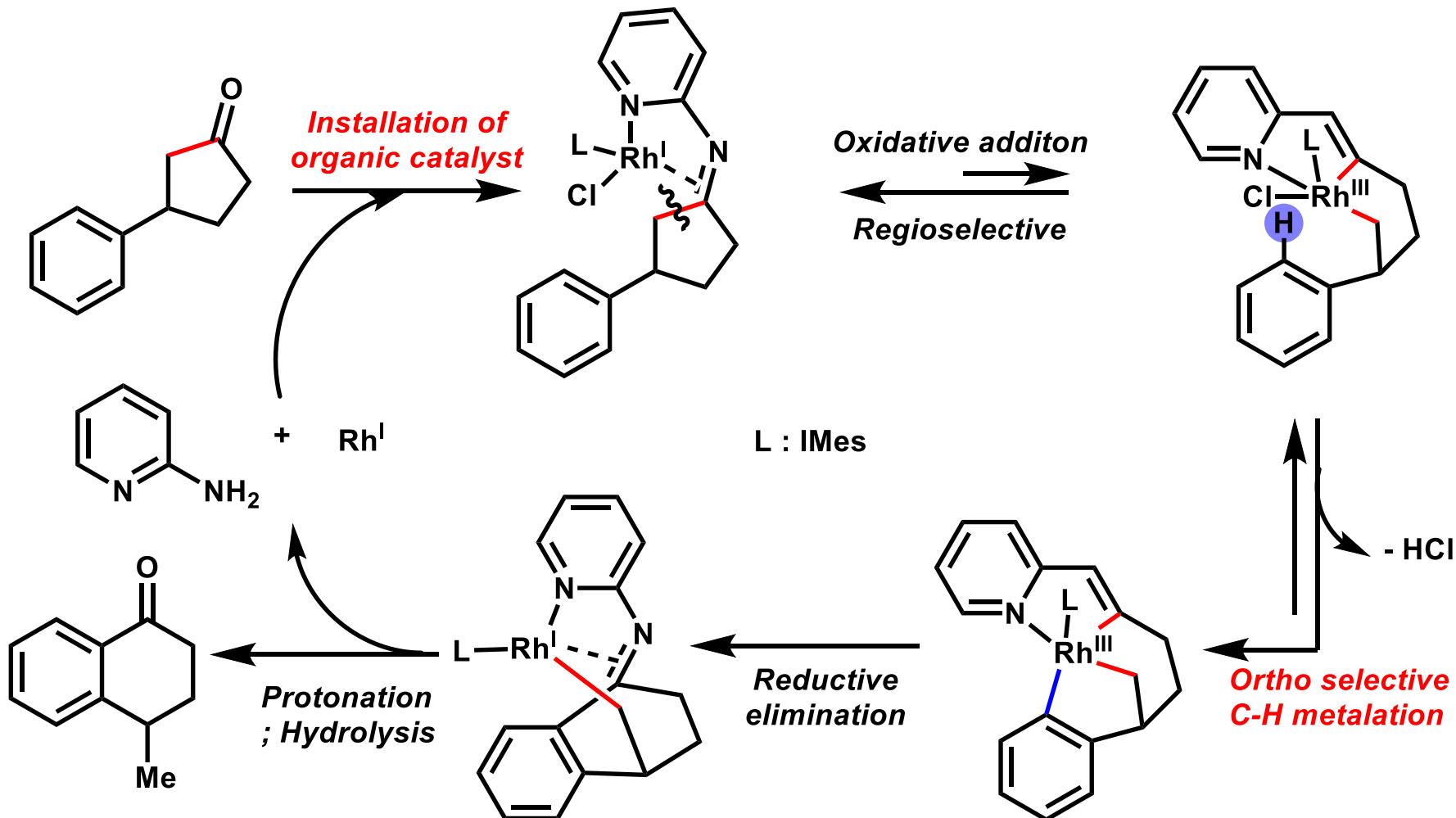
· Dong's hypothesis



Discovery of Dong Group (1)



Proposed Reaction Mechanism by Dong Group



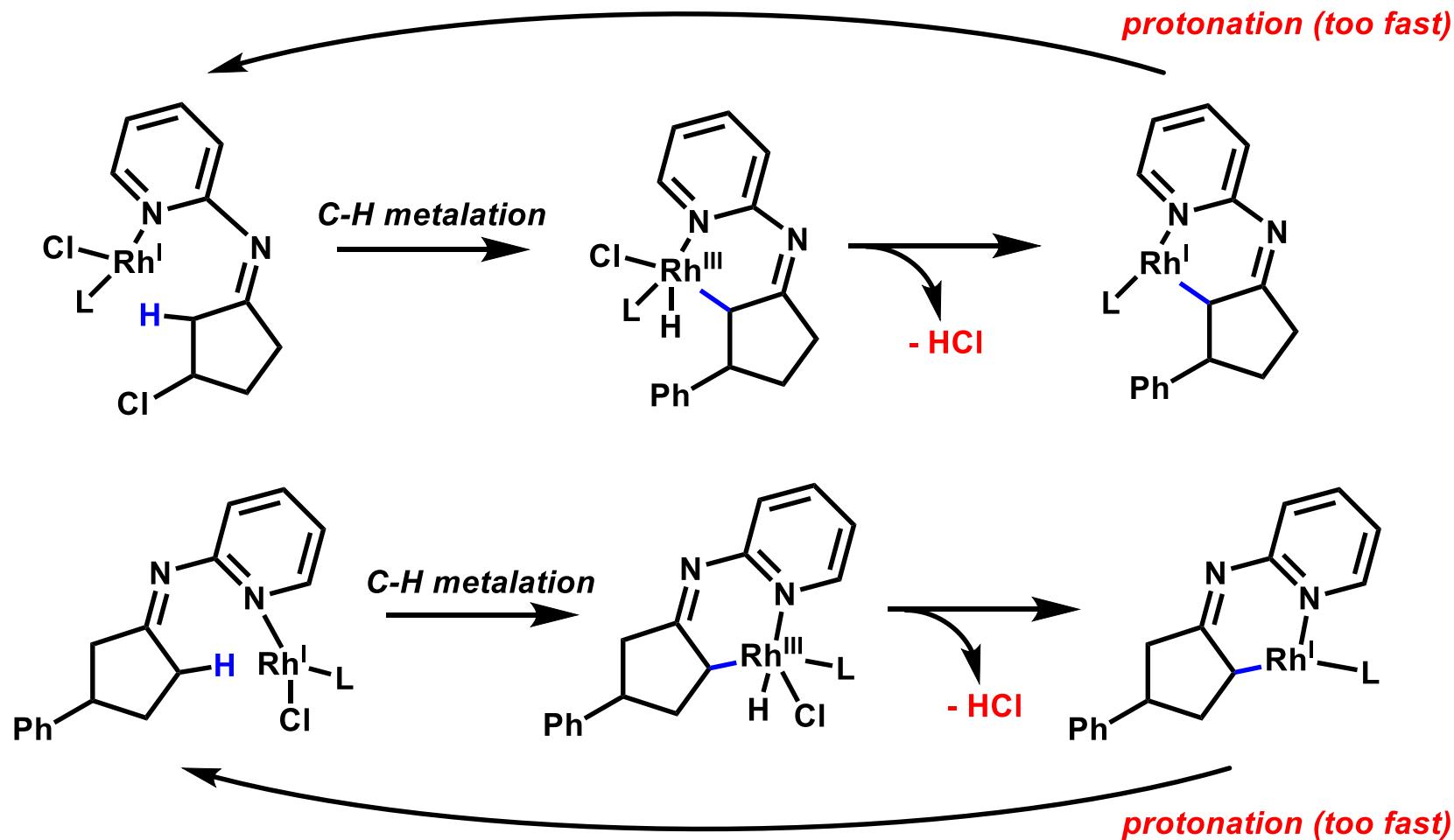
1. Oxidative addition to C-C bond vs C-H metalation

2. Regioselectivity of oxidative addition

3. Mechanism of C-H metalation step

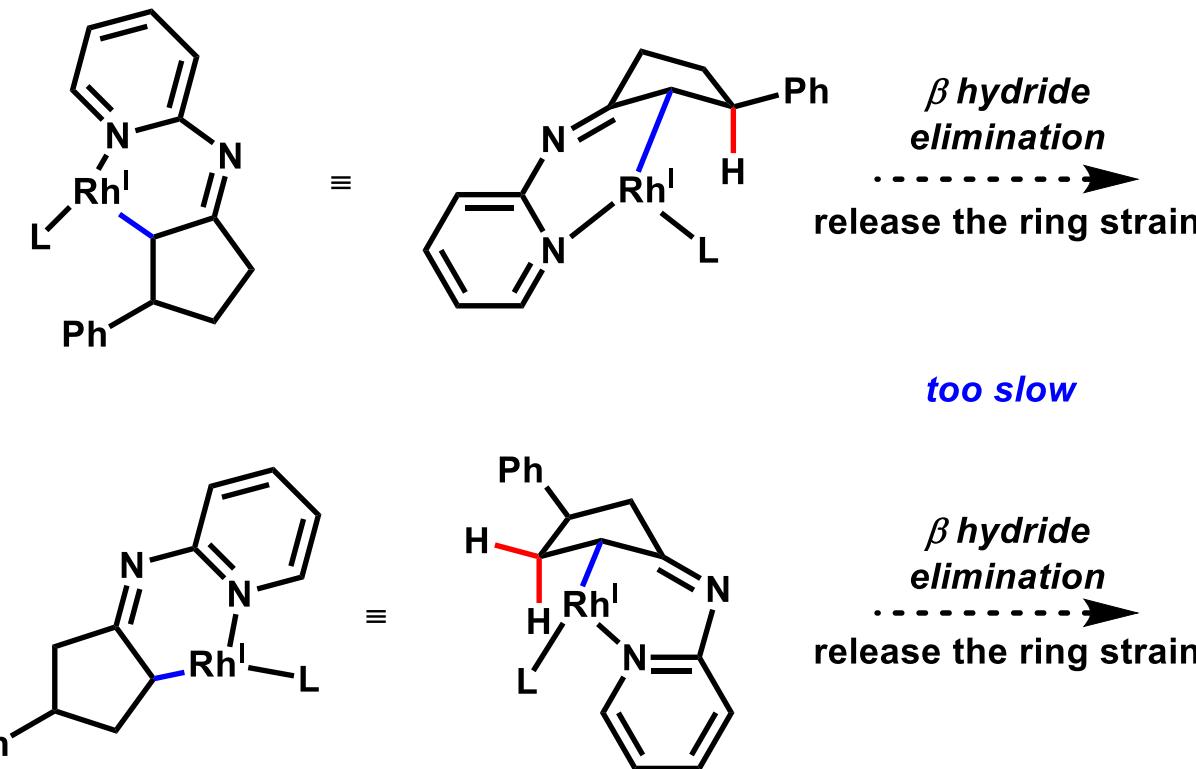
4. Turnover-Limiting-Step

Why C-C bond activation is favored ? (1) –My Opinion–



Protonation would be favored.

Why C-C bond activation is favored ? (2) -My Opinion-

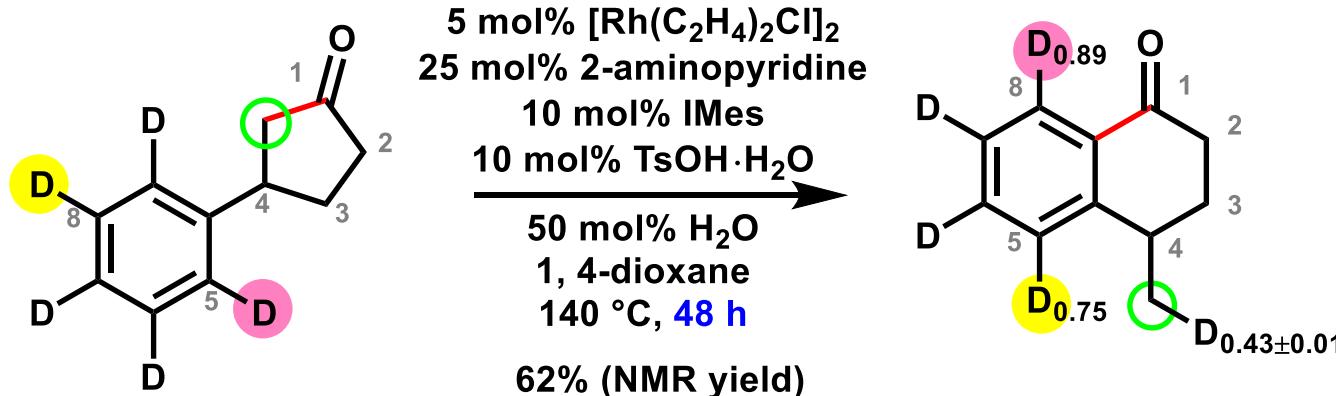


Overlap between C-Rh bond and C-H bond would be insufficient.

→ β hydride elimination would be slower than protonation.

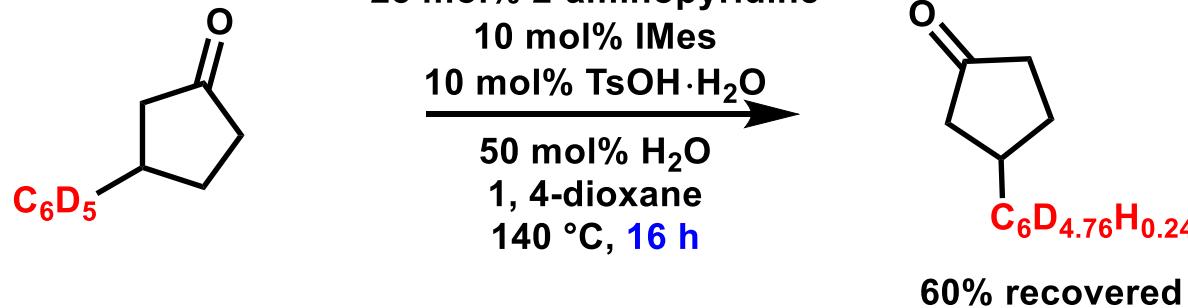
Mechanistic Study (1) -Deuterium Labeling-

A. Deuterium labeling experiment



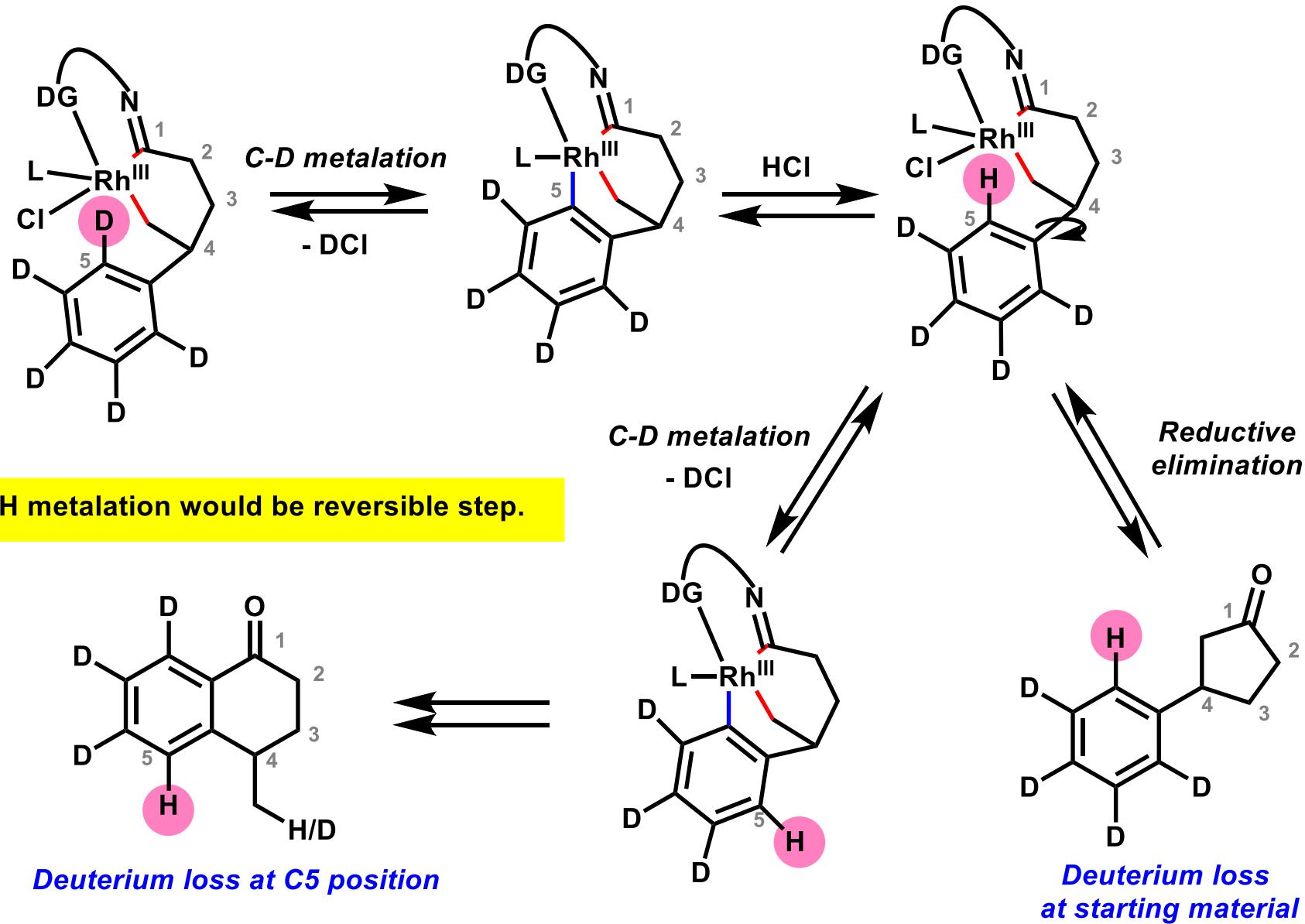
Deuterium loss at C_5 , C_8 , methyl position

B. Recovery experiment

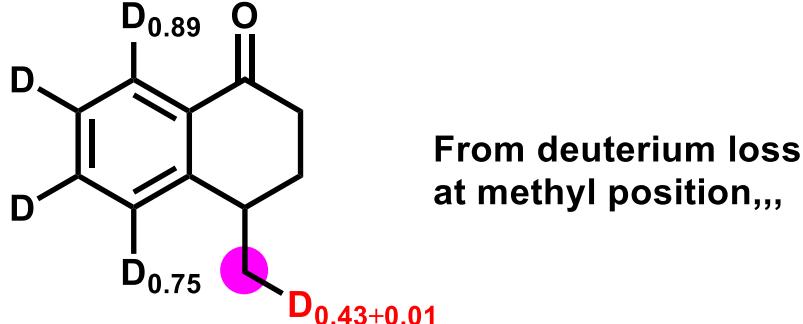


Moderate deuterium loss at Ph group

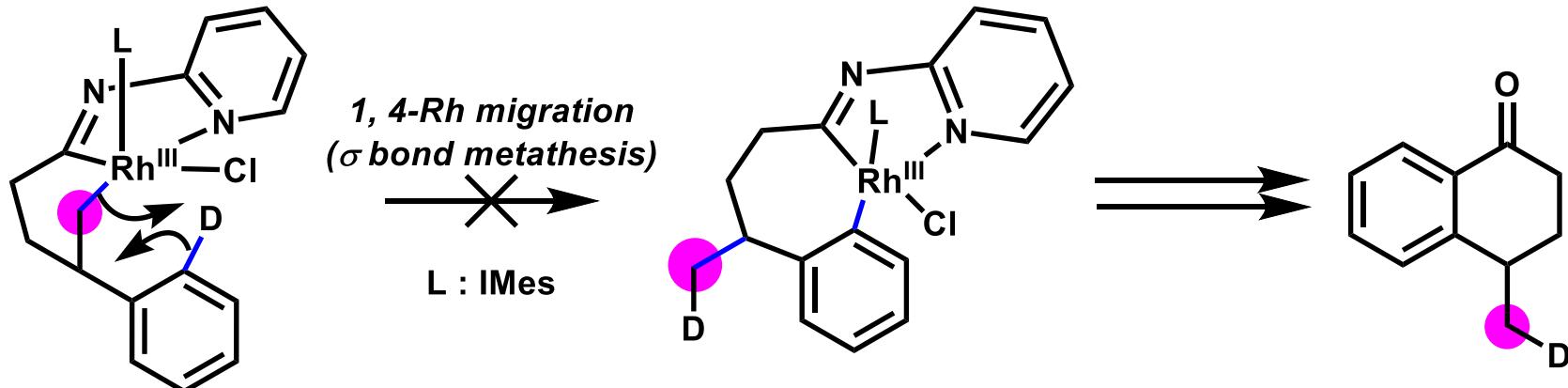
Proposed Mechanism for Deuterium Loss



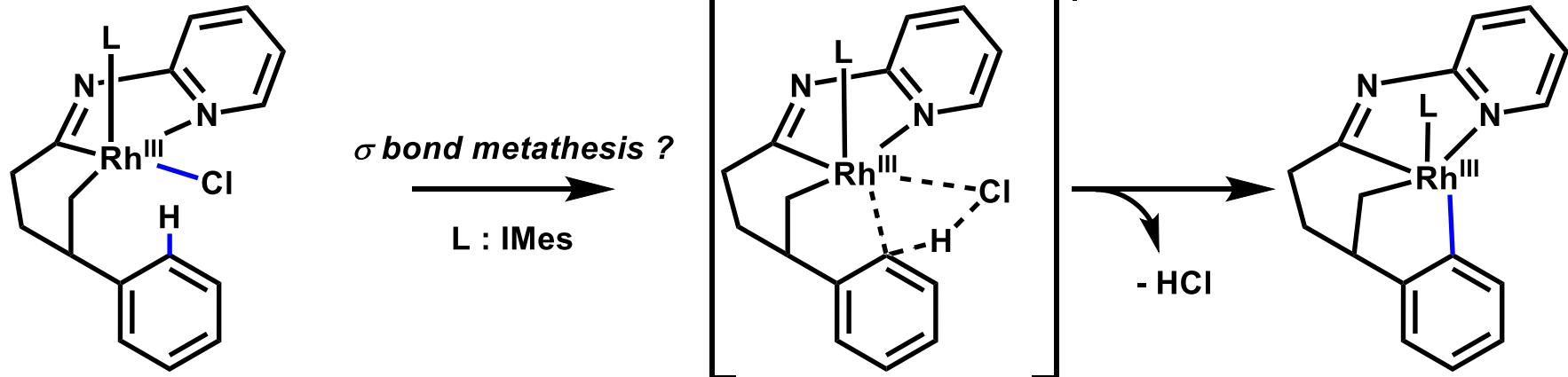
Proposed Mechanism of C-H Metalation



A.



B.

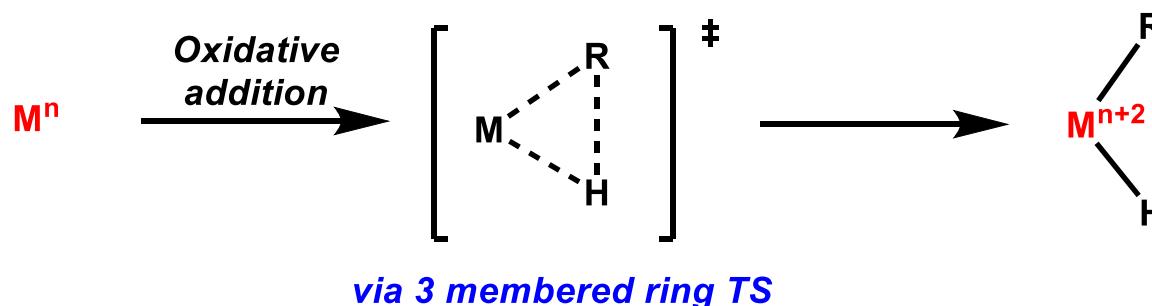


1) Xia, Y.; Lu, G.; Liu, P.; Dong, G. *Nature* 2016, 539, 546.

2) Deyonker, N. J.; Foley, N. A.; Cundari, T. R.; Gunnoe, T. B.; Petersen, J. L. *Organometallics* 2007, 26, 6604.

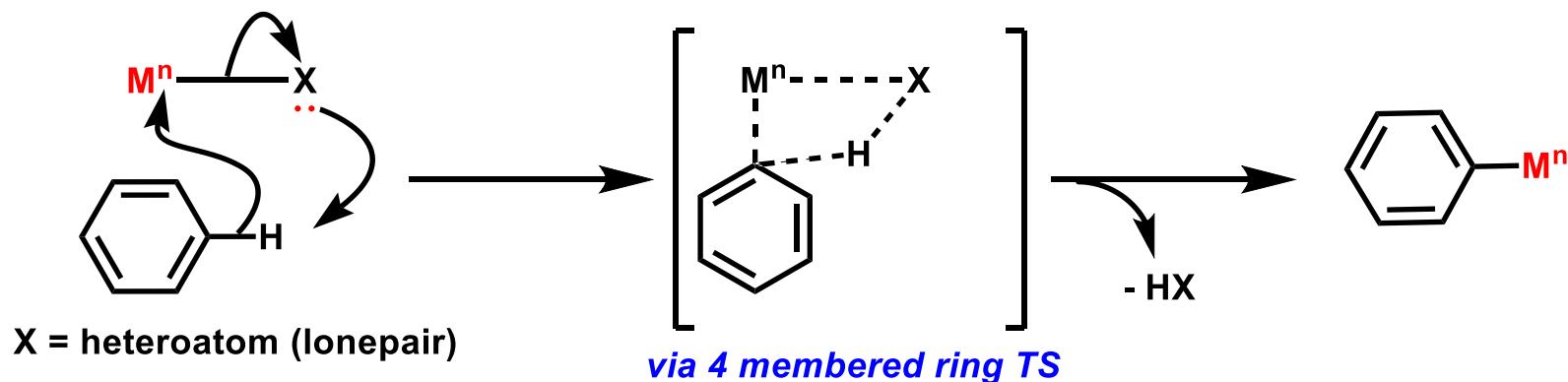
Mechanism of C-H Metalation Step (1)

- Oxidative addition



In Dong's system, $Rh(III) \rightarrow Rh(V)$ would be disfavored.

- Internal electrophilic substitution



1. Lonepair of heteroatom participates C-H metalation step.

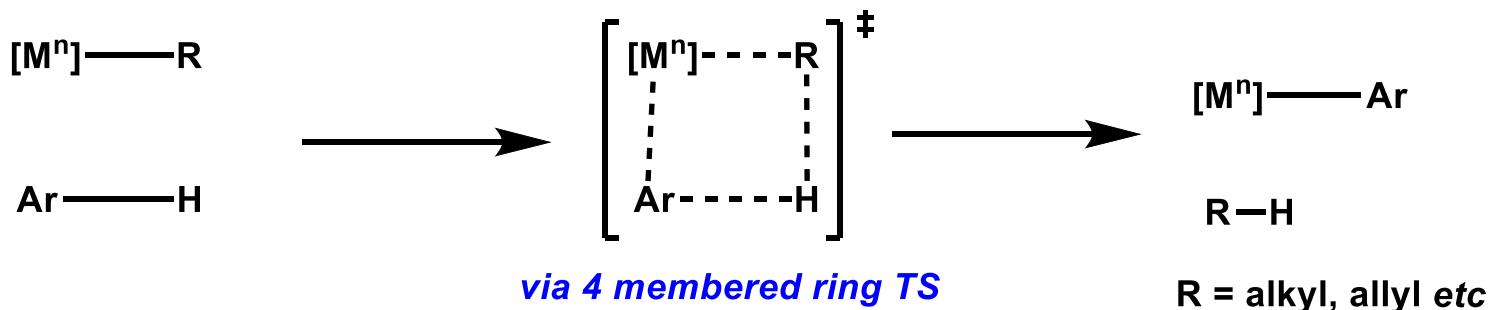
2. Electron density of metal would be a key factor.

1) Periana, R. A. et al *J. Am. Chem. Soc.* **2005**, 127, 14172.

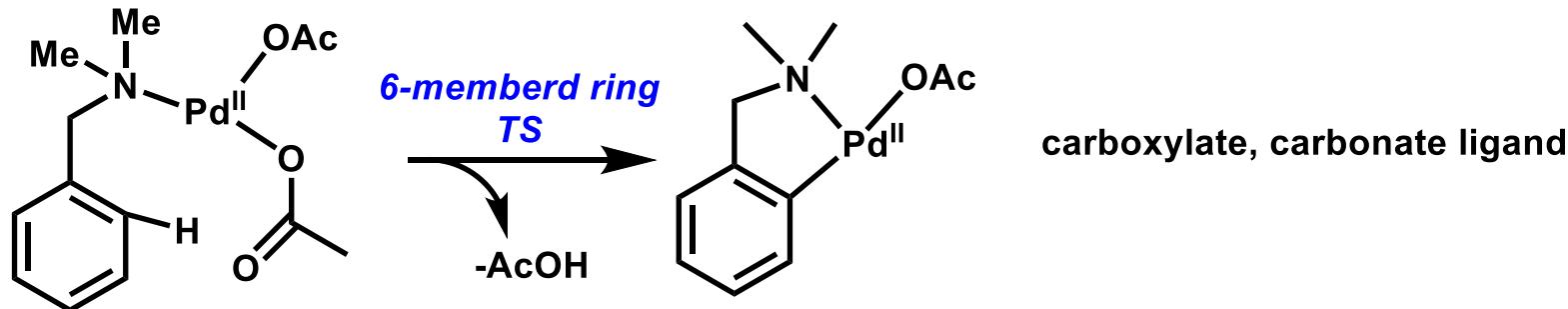
2) Goddard, W. A. et al *Organometallics* **2007**, 26, 1565.

Mechanism of C-H Metalation Step (2)

- σ -bond metathesis



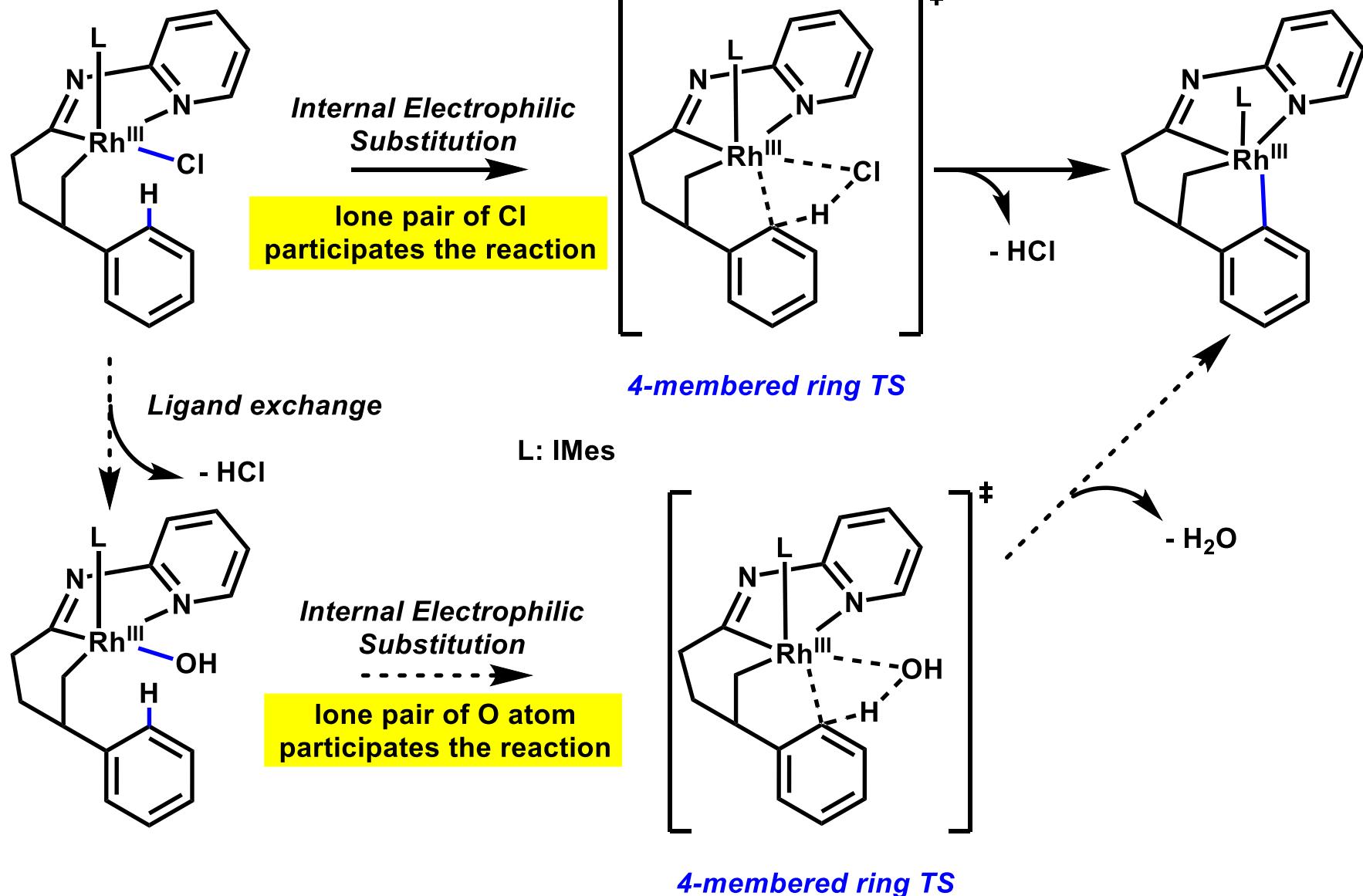
- Concerted metallation-deprotonation (Proposed by Fagnou)



In Dong's system, ligand exchange would be necessary.

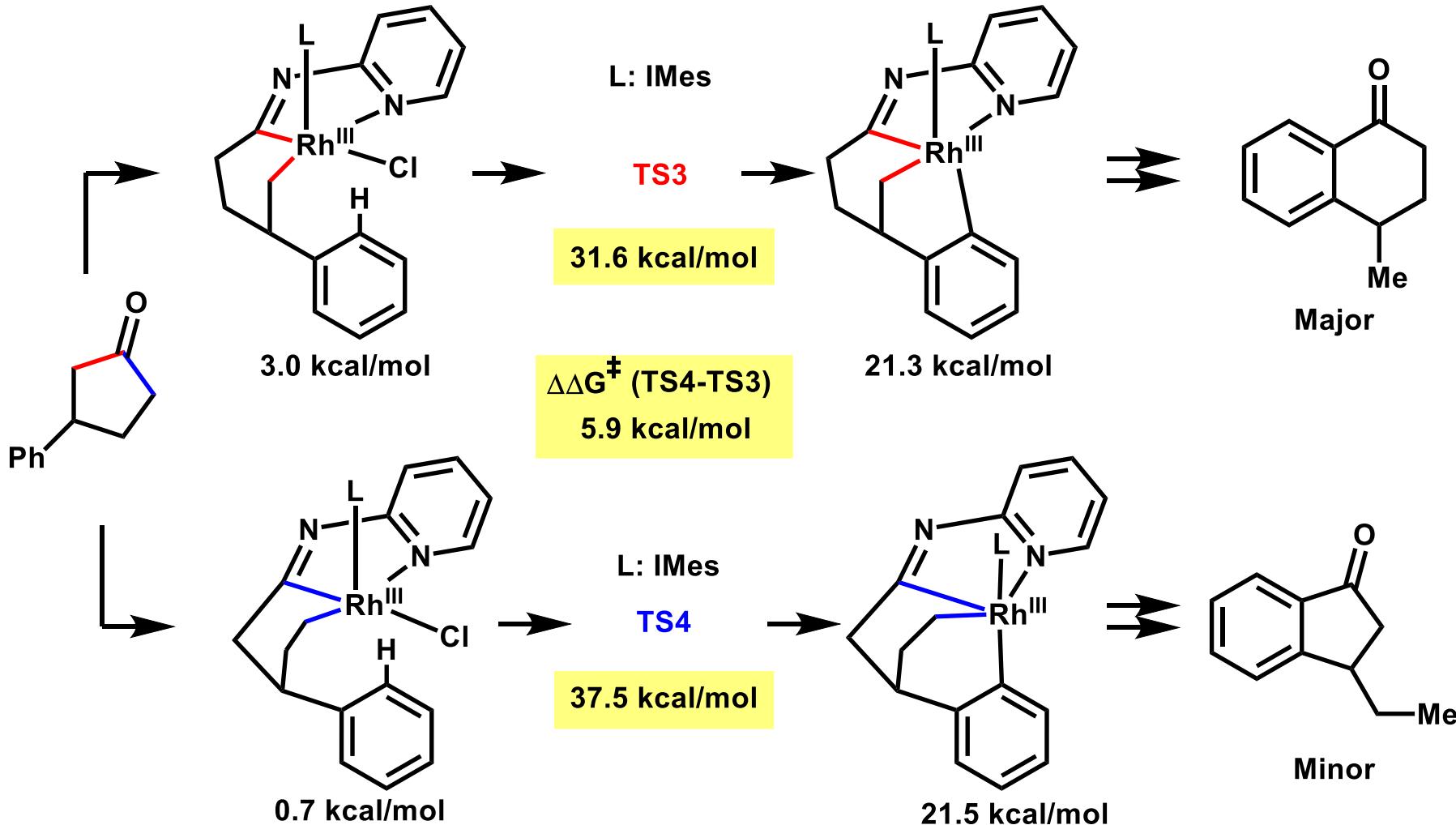
→ from Cl to OTs (disfavored)

C-H Metalation Step -My Opinion-



- 1) Periana, R. A. et al *J. Am. Chem. Soc.* **2005**, 127, 14172.
 2) Goddard, W. A. et al *Organometallics* **2007**, 26, 1565.

Mechanistic Study (2) -DFT Calculation-

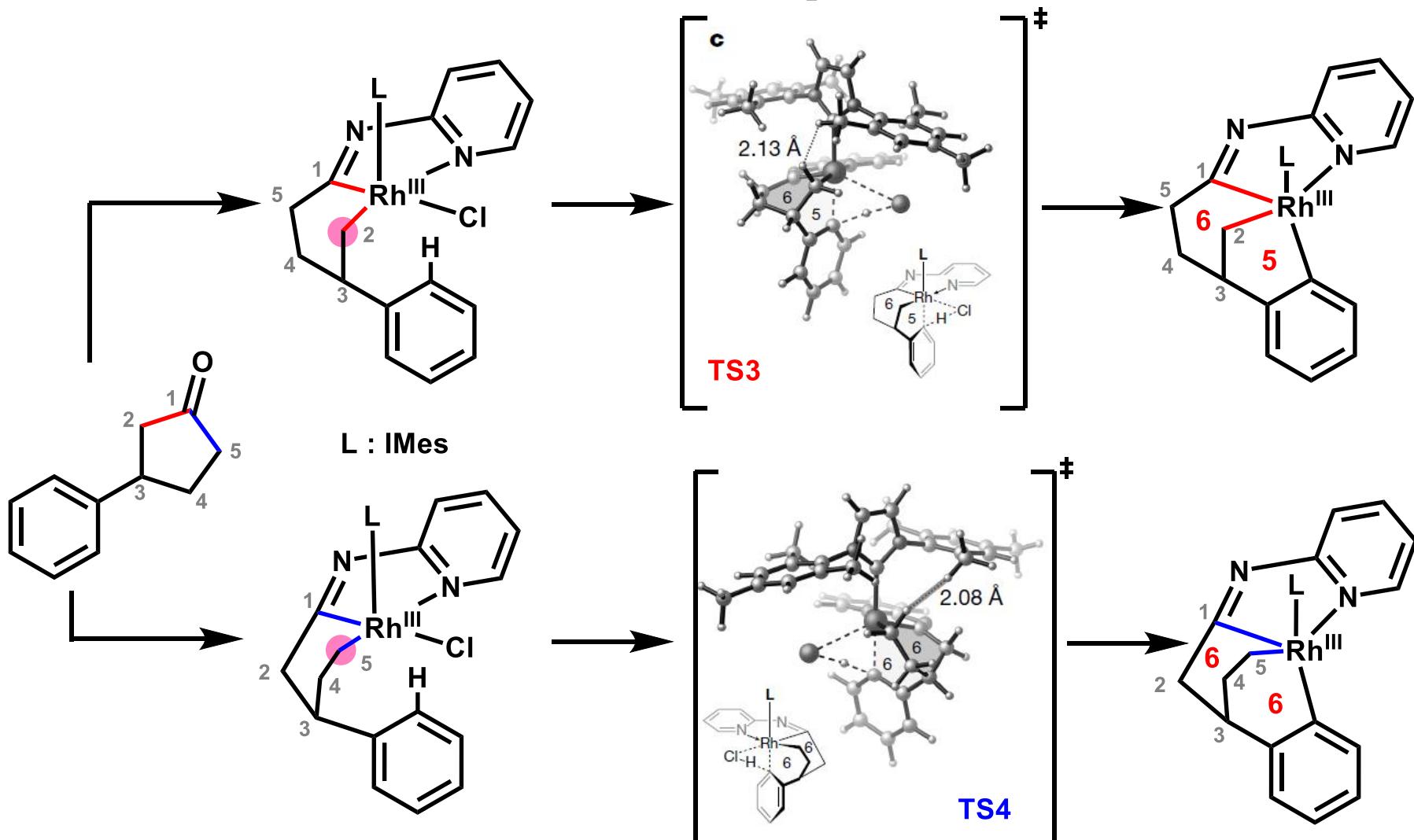


TS4 >> TS3 → C-H metatlation step plays a significant role ?

Method: M06/SDD-6-311+G(d,p)/SMD

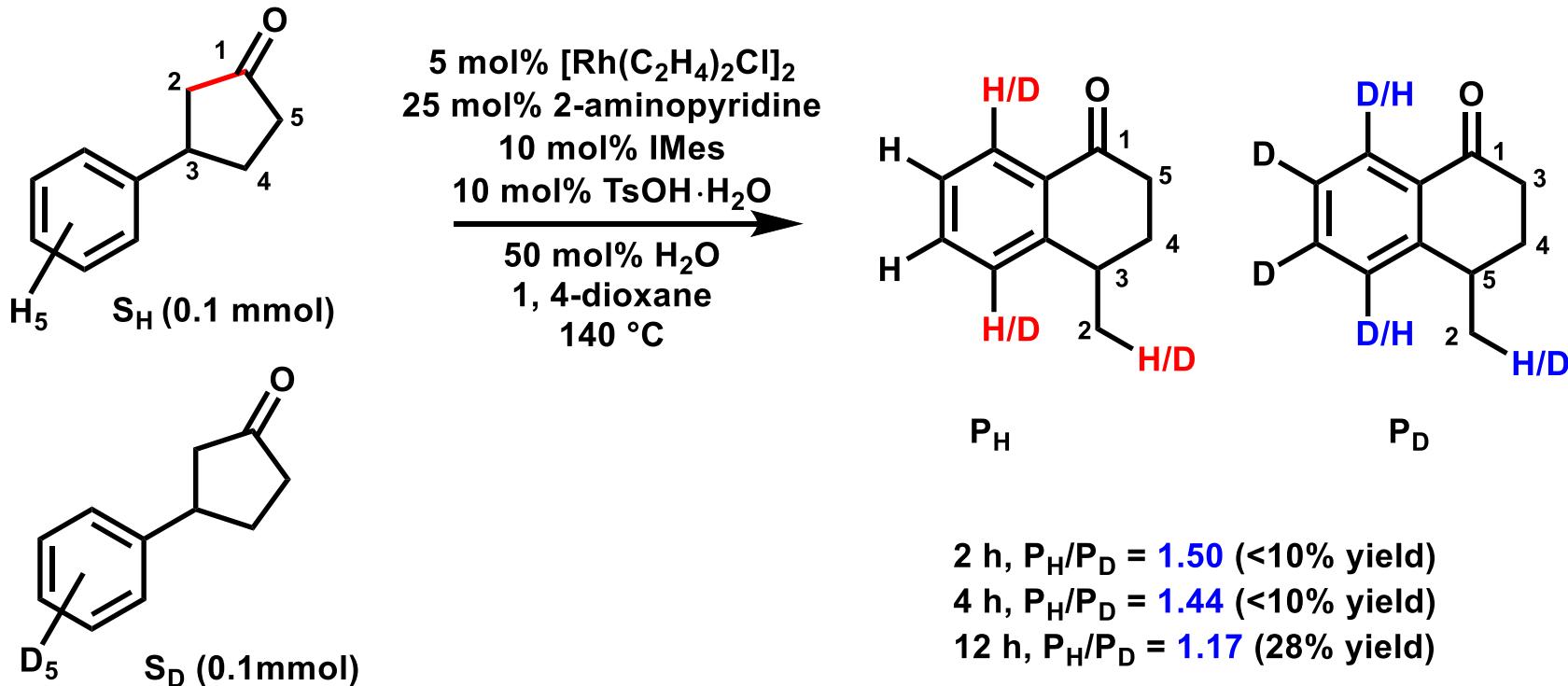
Regioselectivity of C-C bond activation

-Author's Proposal-



Steric repulsion between **methylene proton** and **methyl proton of IMes ligand**.

Mechanistic Study (3) -KIE-



1. Smaller than typical primary KIE

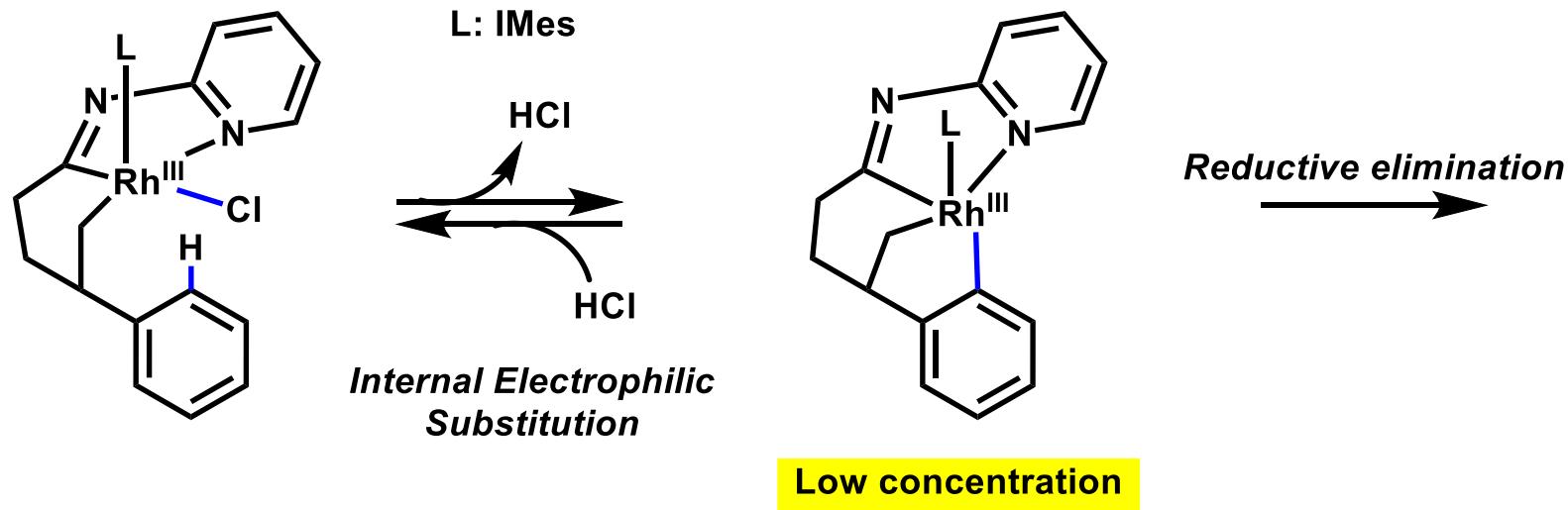
→ C-H metalation step cannot be the Turnover-Limiting Step ?

2. Product ratio (P_H/P_D) decreased as the reaction proceeds.

→ Consistent with reversible C-H metalation step

Mechanistic Study (4) -KIE-

"Reductive elimination step" would be the TLS in this catalytic reaction.

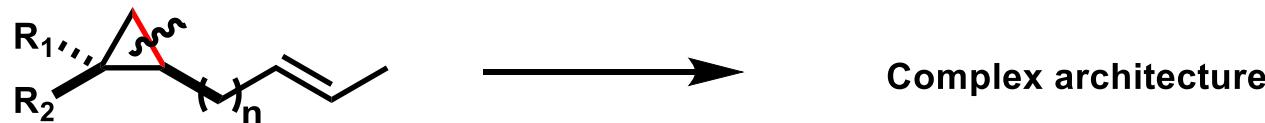


Reversibility of C-H metallation step lowers the concentration of bycyclic intermediate.

- 1) Xia, Y.; Lu, G.; Liu, P.; Dong, G. *Nature* **2016**, 539, 546.
- 2) Cheng, C. and Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, 136, 12064.

Summary

· Marek



1. Succession of allylic C-H activation

2. Introduction of R₁, R₂ group.

· Dong



Installation of Ar group
at C3 position

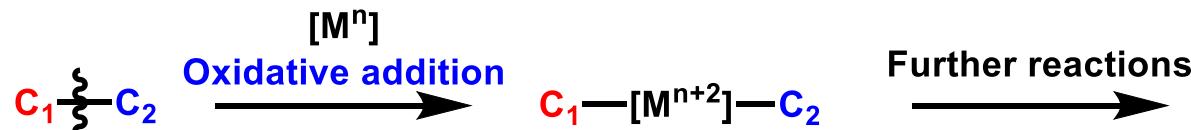
1. Temporary directing group

2. C-C activation and tandem sp² C-H activation

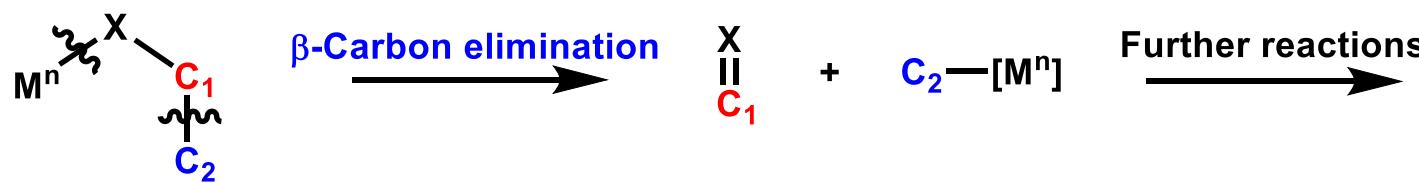
Appendix

Mechanistic Categories of C-C bond activation

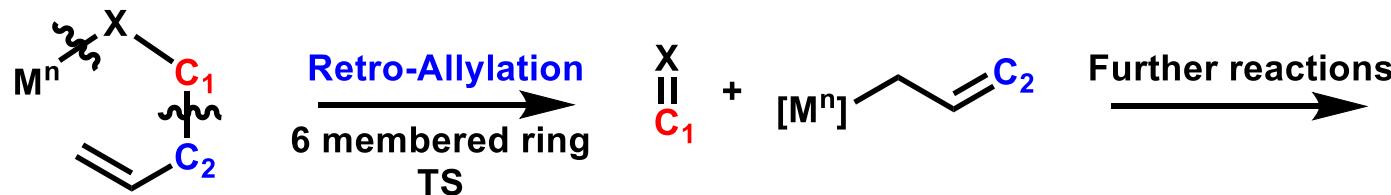
- Oxidative addition



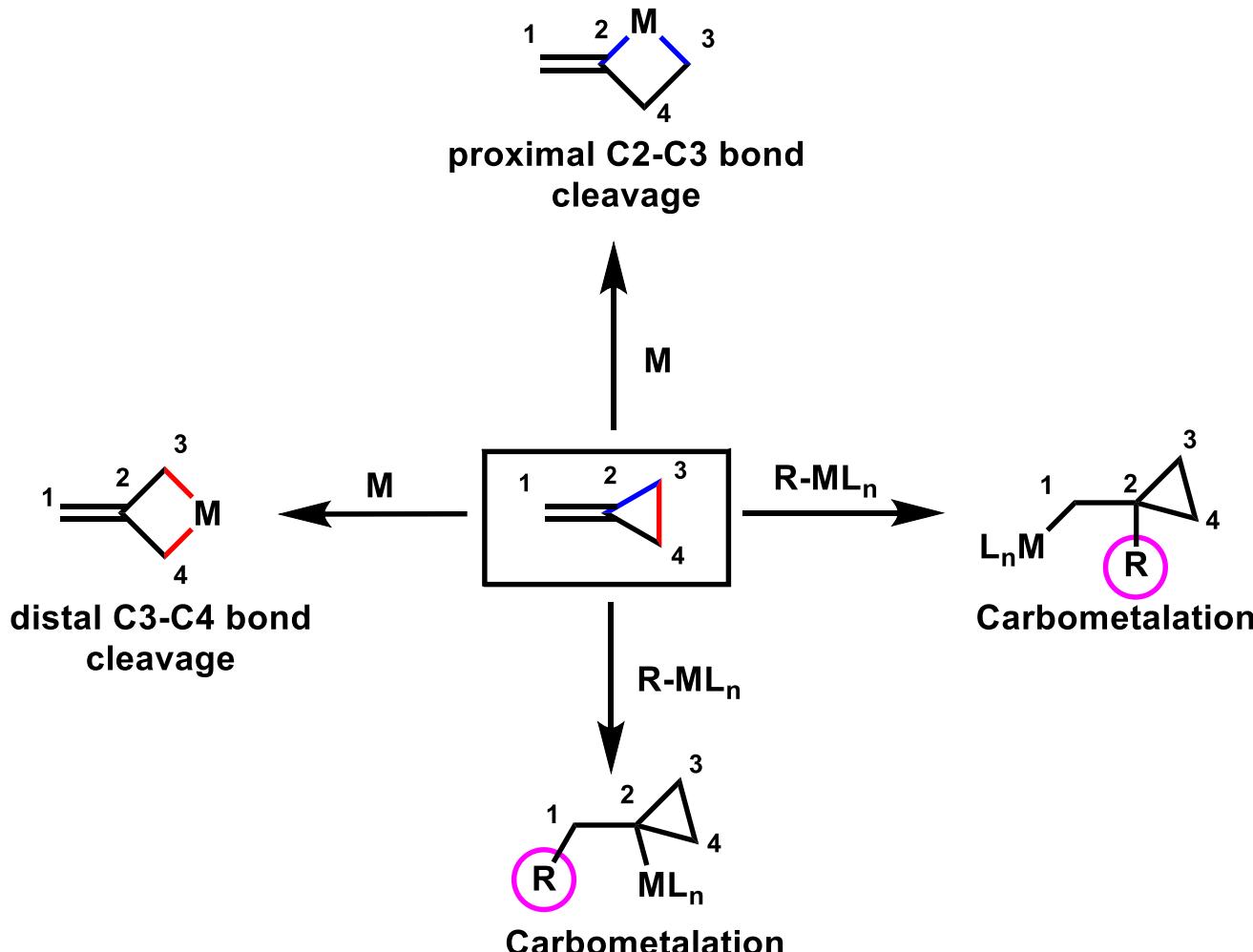
- β -Carbon elimination



- Retro-Allylation



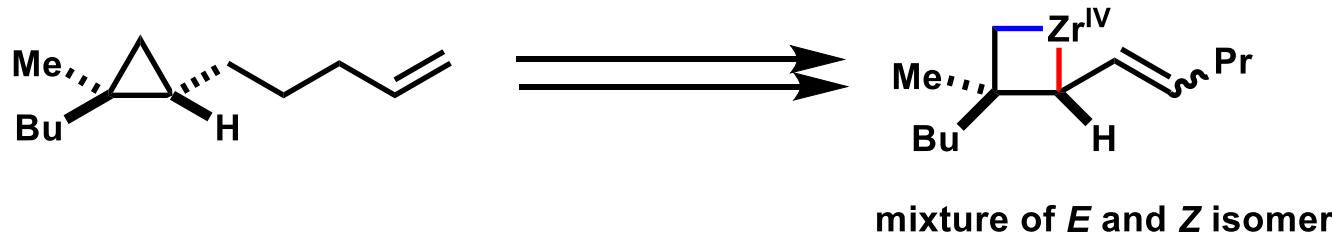
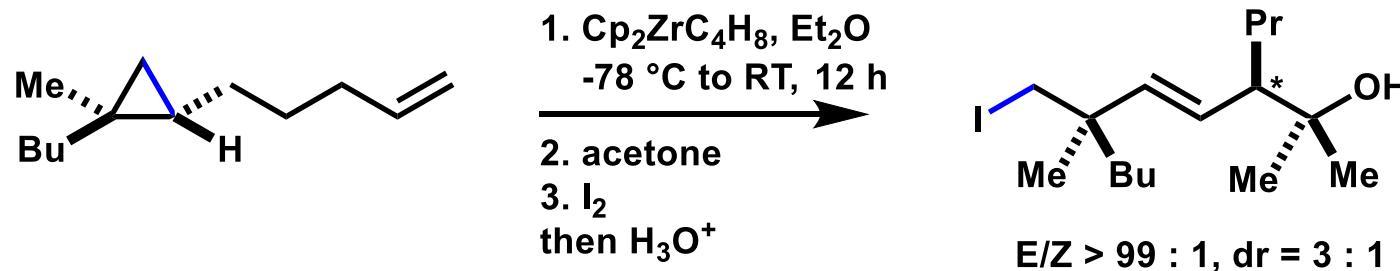
Regioselectivity of C-C bond activation



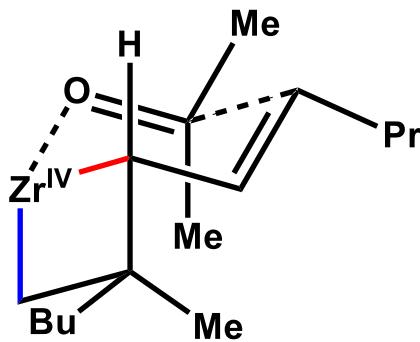
Methylenecyclopropanes have multiform reactivities.
However, the control is inherent to the structure of substrate.

Diastereo Selectivity

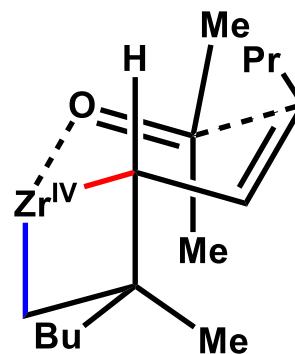
Zimmermann-Traxler transition state



TS from E isomer



TS from Z isomer

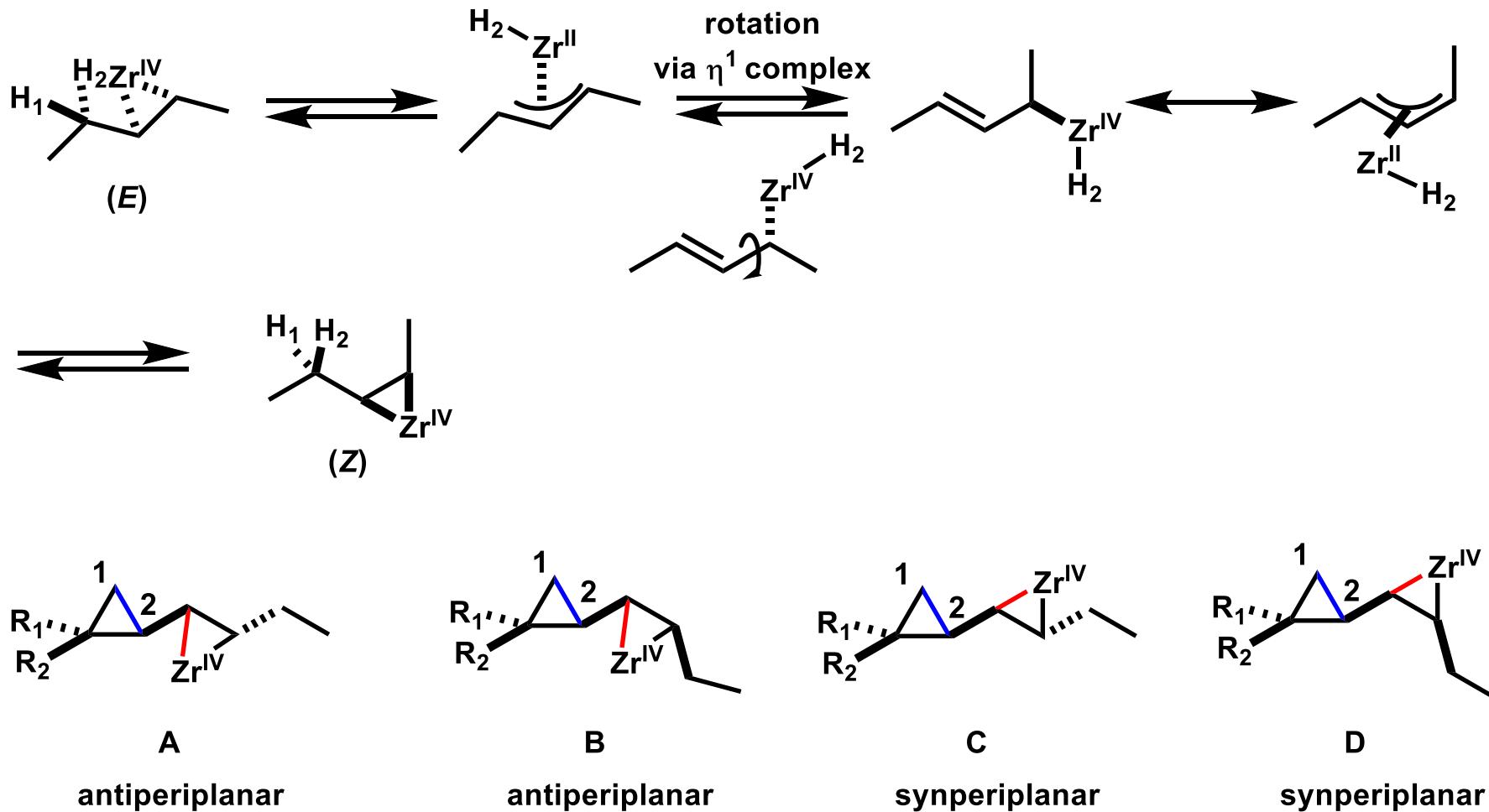


Vasseur, A.; Perrin, L.; Eisenstein, O.; Marek, I. *Chem. Sci.* **2015**, *6*, 2770.

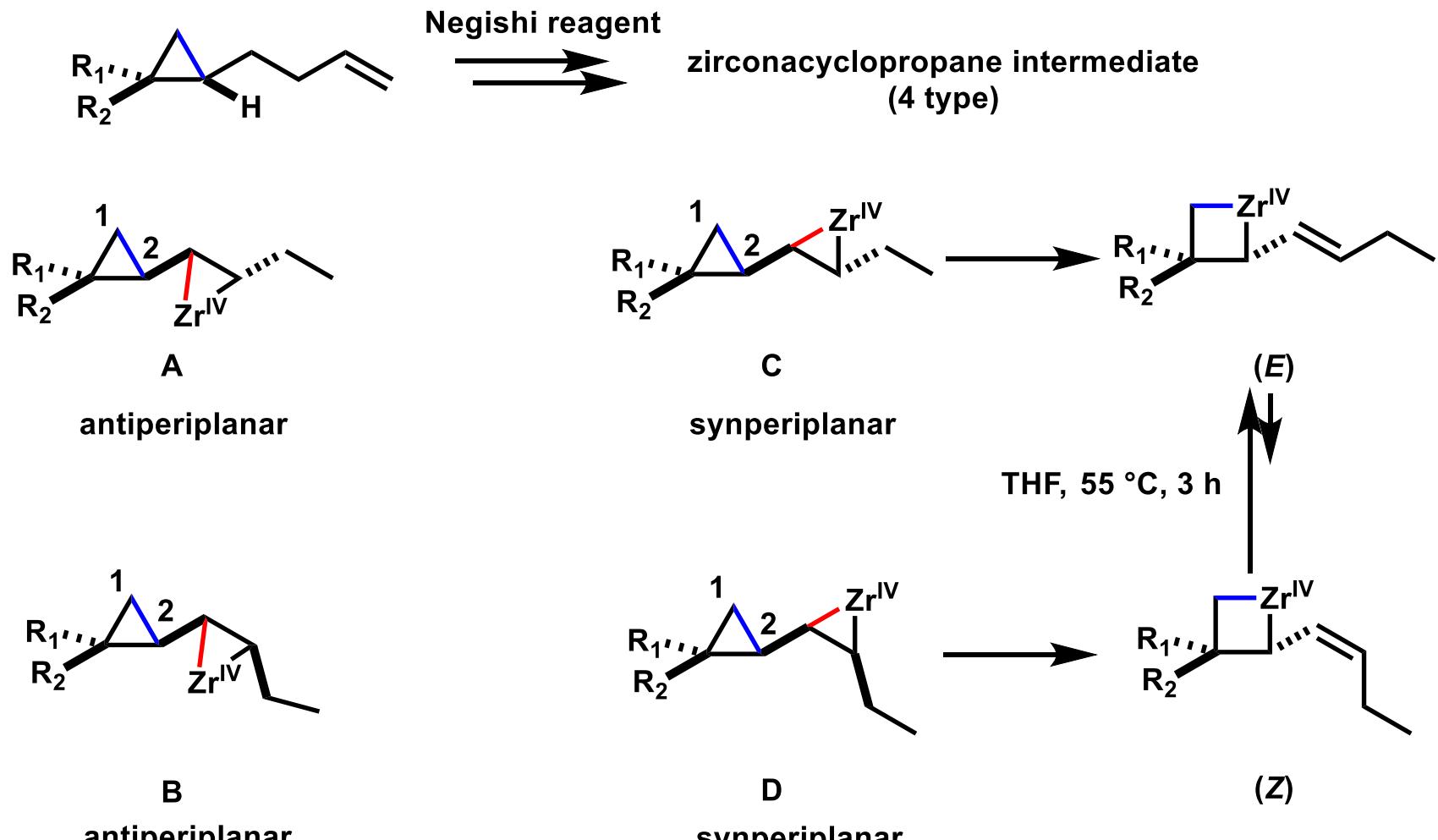
Harada, S.; Kiyono, H.; Nishio, R.; Taguchi, T.; Hanazawa, Y. *J. Org. Chem.* **1997**, *62*, 3994.

Chemistry about Allylic C-H bond Activation

· Olefin isomerization



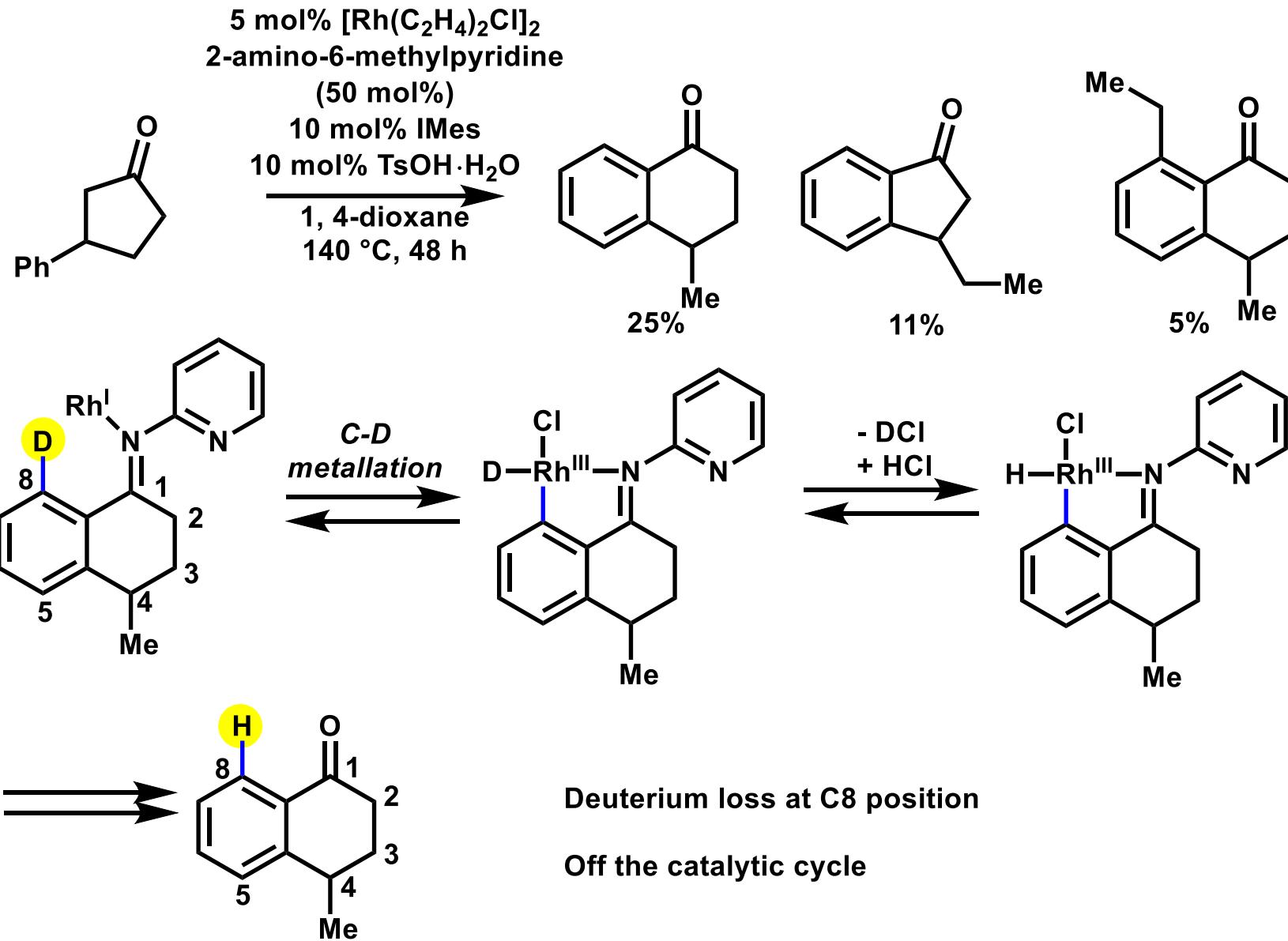
Proposed Mechanism by Marek Group (2)



C₁-C₂ bond cleavage is **impossible**.

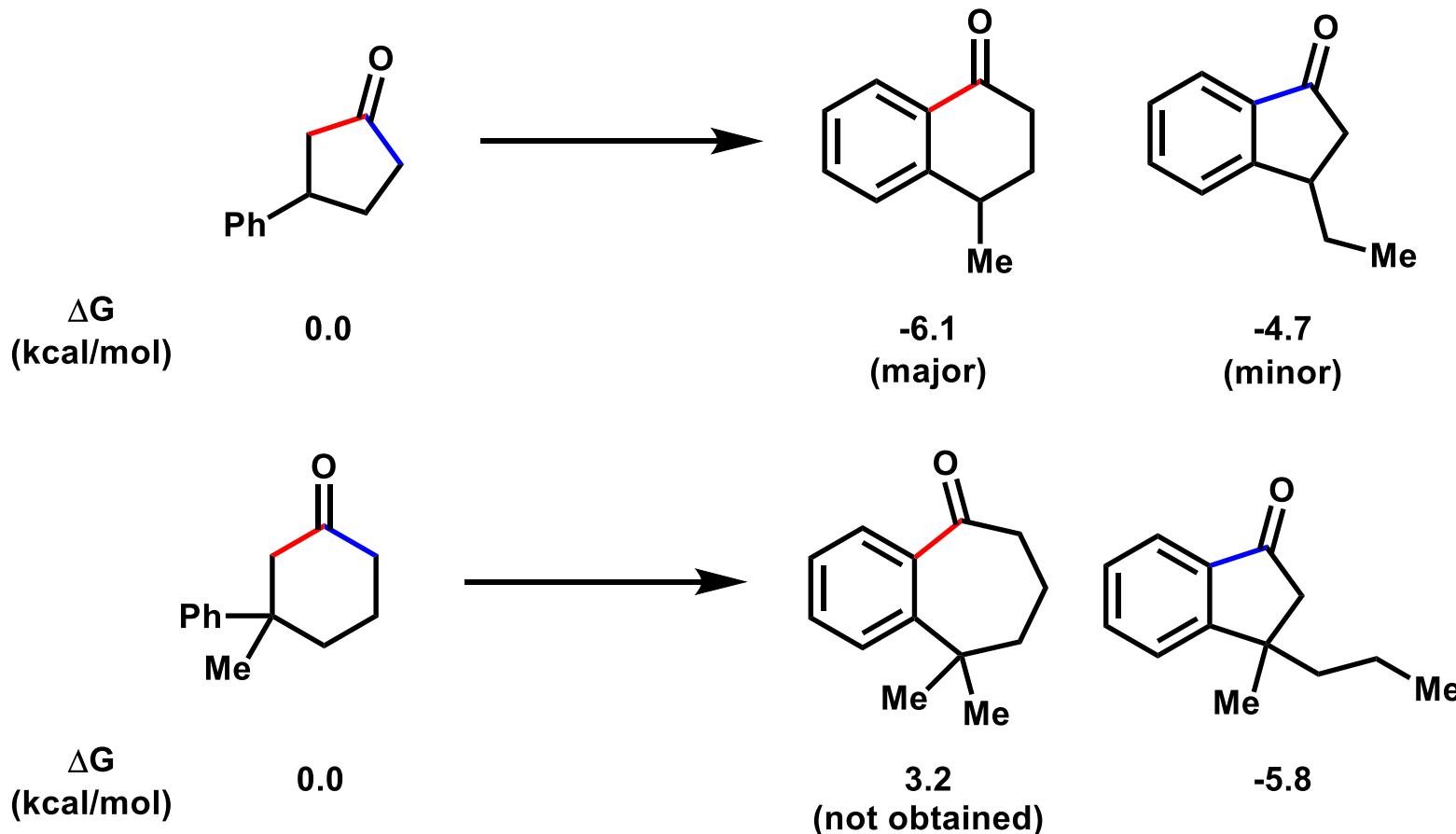
C₁-C₂ bond cleavage is **possible**.

Proposed Mechanism for Deuterium Loss (2)



Regioselectivity of C-C bond activation

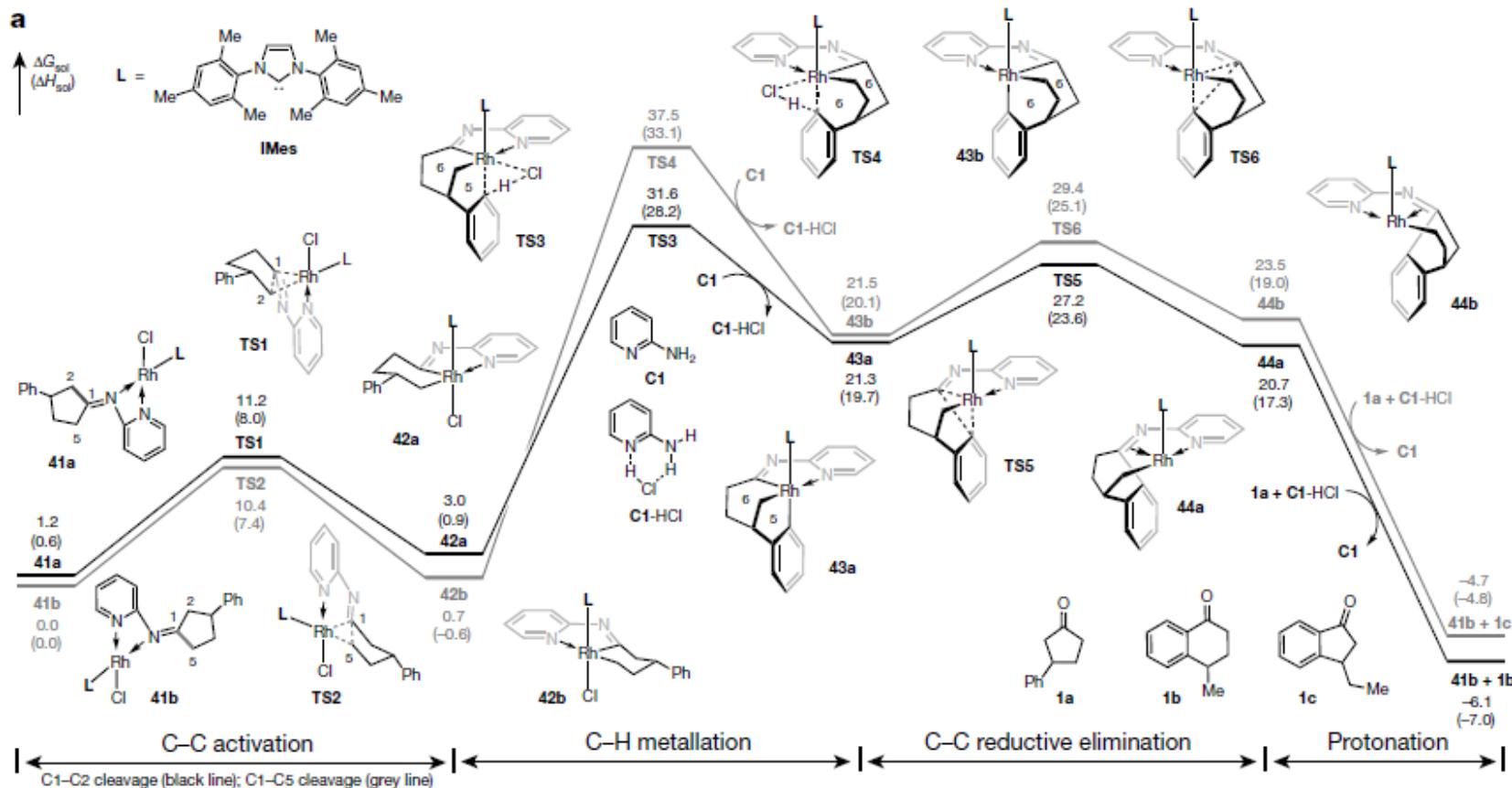
-Another Interpretation-



Both reactions afford the thermodynamically more stable product.

→ Thermodynamic control reaction ?

DFT Calculation



Application of Dong's Research

- Derivatization of complex targets

