Carbon-Carbon Bond Activation

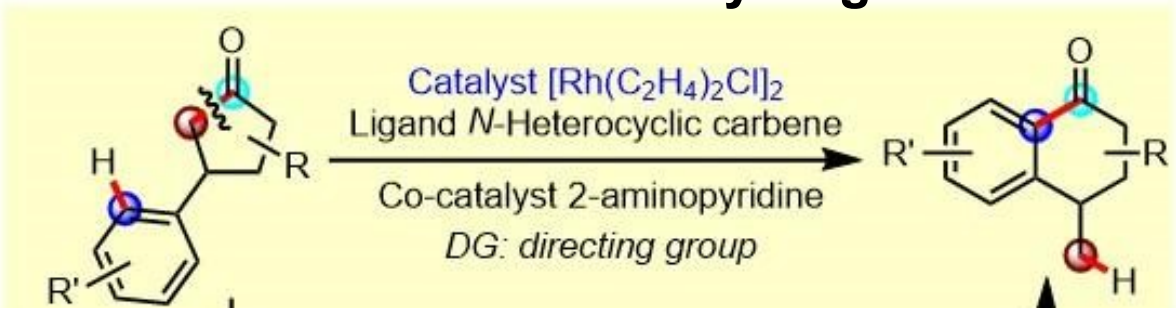
Literature seminar#3

M2 Hiromu Fuse

2018/10/06(Sat)

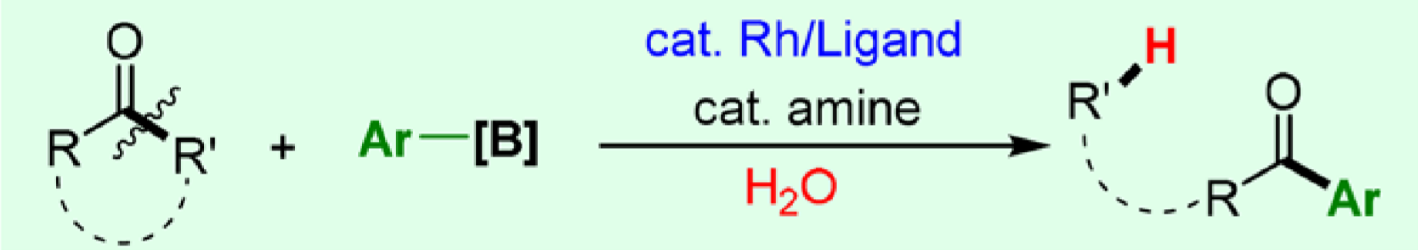
Introduction

- **Carbon-carbon bond and carbon-hydrogen bond activation**



Dong, G. *et al*. *Nature*, **2016**, *539*, 546.

- **Carbon-carbon bond activation Suzuki-Miyaura crosscoupling**



Dong, G. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 5347.

Unstrained carbon-carbon bond can be transformed to carbon-carbon bond.

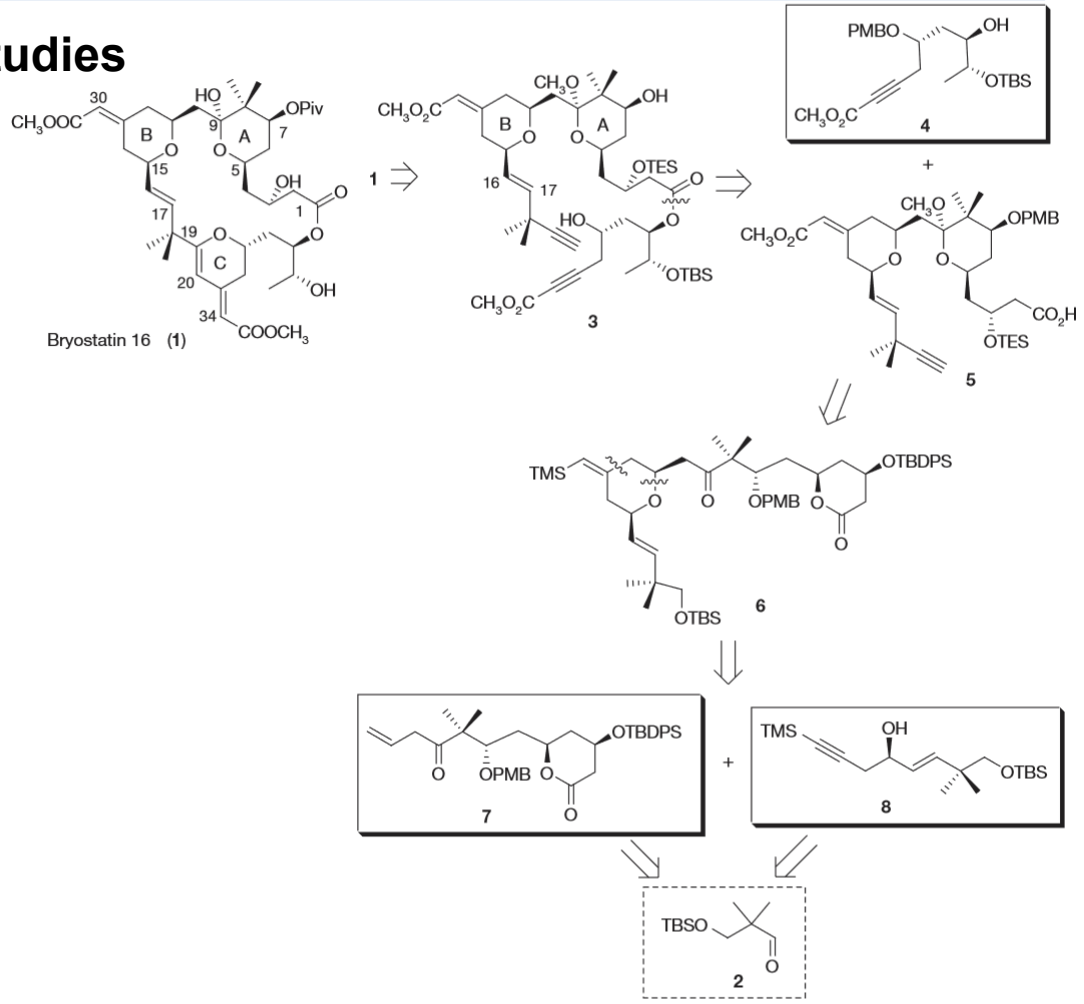
Introduction

Dr. Guangbin Dong received his B.S. degree from Peking University and completed his Ph.D. degree in Chemistry from Stanford University with Professor Barry M. Trost. In 2009, He joined the group of Prof. Robert H. Grubbs at California Institute of Technology, as a postdoctoral researcher. His expertise is in the field of organic synthesis, catalysis, organometallics and medicinal chemistry. His future research interests lie at the development of powerful chemical tools for addressing questions of biological importance. His research program will bring together the complimentary knowledge of organic synthesis, medicinal chemistry and organometallic chemistry in collaboration with scientists in the field of cellular biology and animal pharmacology to identify effective small-molecule agents that target new molecular mechanisms for cancer treatment.

https://donggroup-sites.uchicago.edu/page/about-guangbin

Introduction

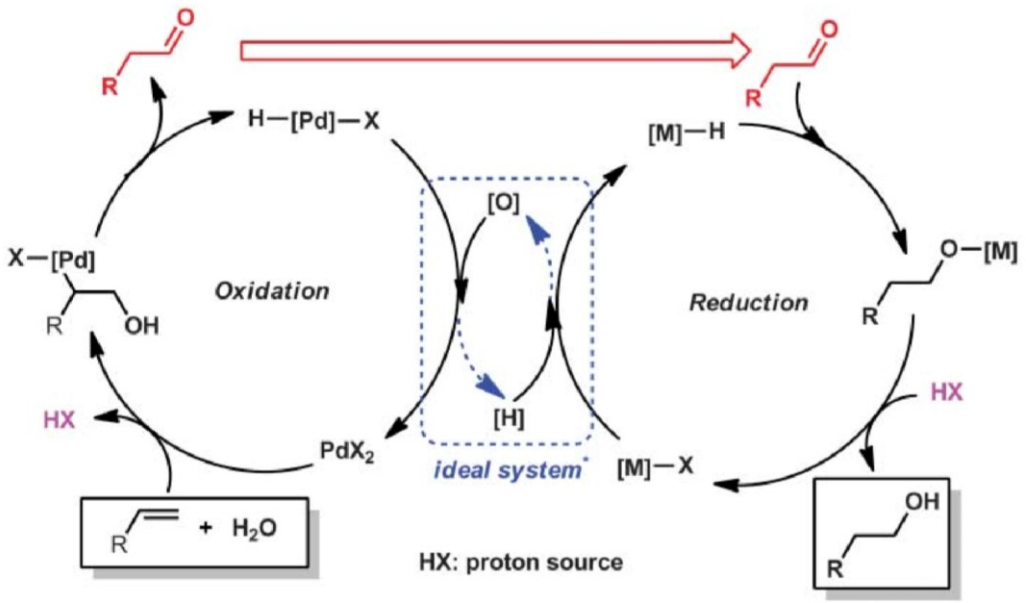
Ph. D. studies



Trost, B. M.; Dong, G. *Nature*, **2008**, *456*, 485.
https://donggroup-sites.uchicago.edu/page/about-guangbin

Introduction

postdoctoral studies



Dong, G.; Teo, P.; Wickens, Z. K.; Grubbs, R. H. *Science*, **2011**, *333*, 1609.

https://donggroup-sites.uchicago.edu/page/about-guangbin

Today's Content

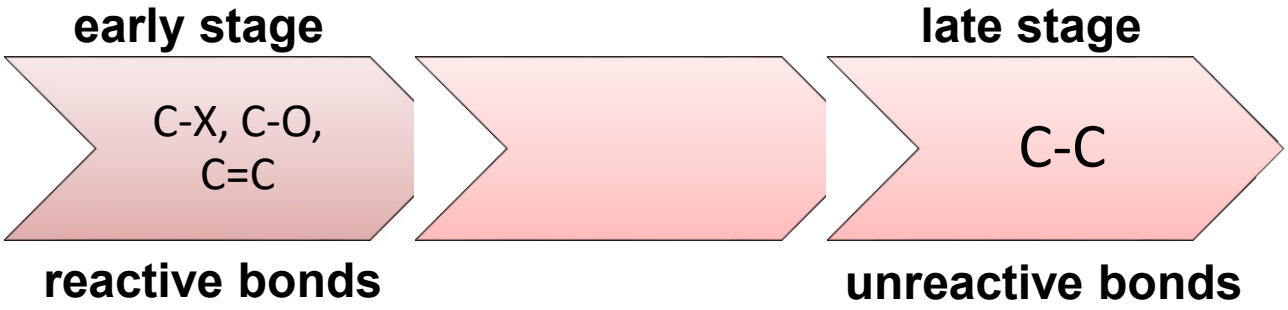
1. ***Overview of C-C activation***
2. ***C-H activation***
3. ***SMC (Suzuki-Miyaura coupling)***

Today's Content

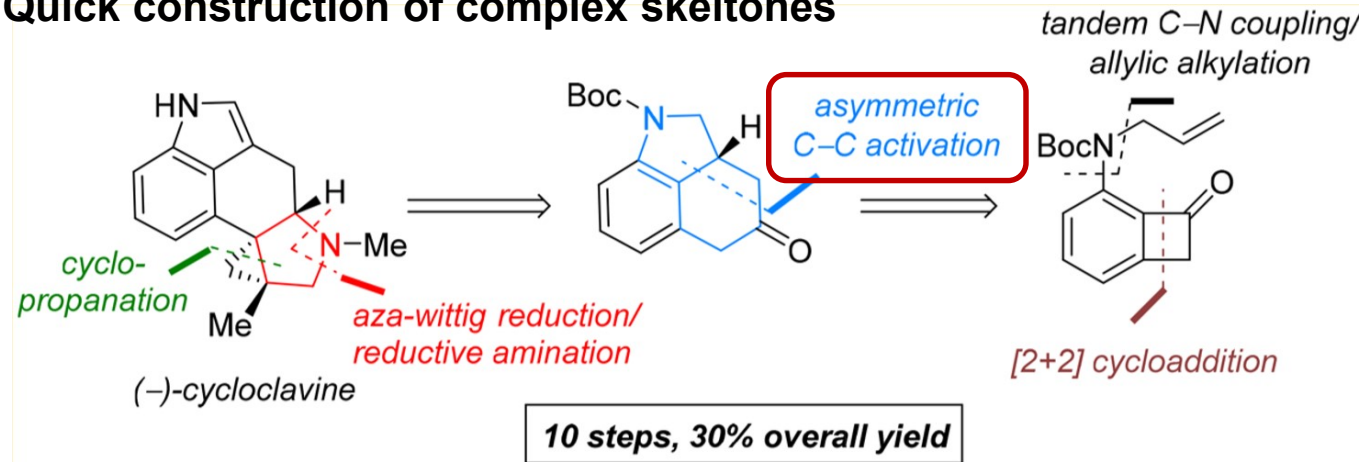
1. ***Overview of C-C activation***
2. ***C-H activation***
3. ***SMC (Suzuki-Miyaura coupling)***

Utility of C-C cleavage

- **Late stage functionalization**
  - **C-C bond is usually inert.**



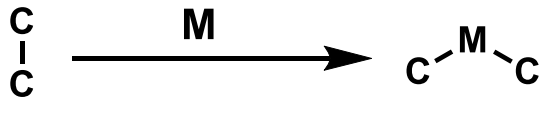
- **Total synthesis**
  - **Quick construction of complex skeltones**

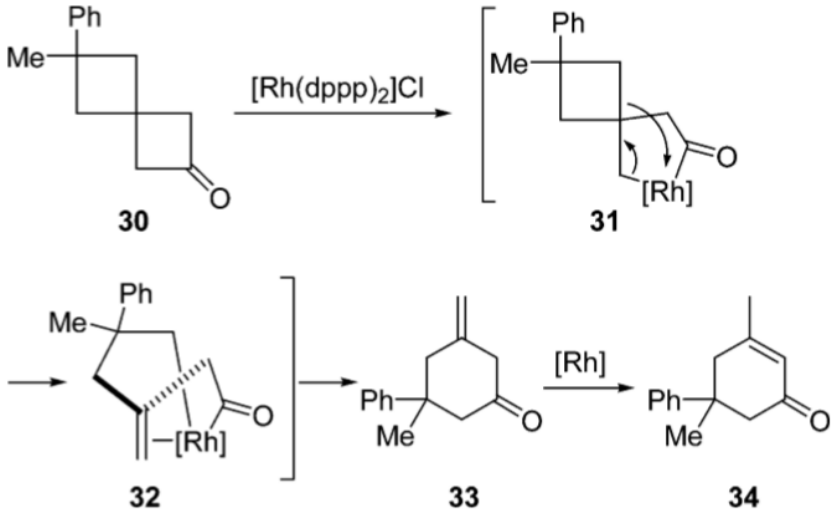


Dong, G. *et al. J. Am. Chem. Soc.* **2018**, *140*, 9652.

Methodologies of C-C bond activation

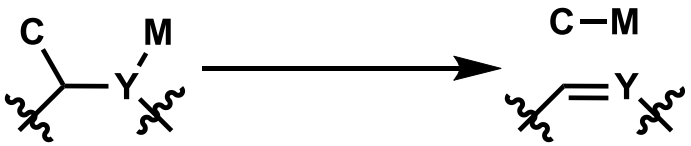
Oxidative addition

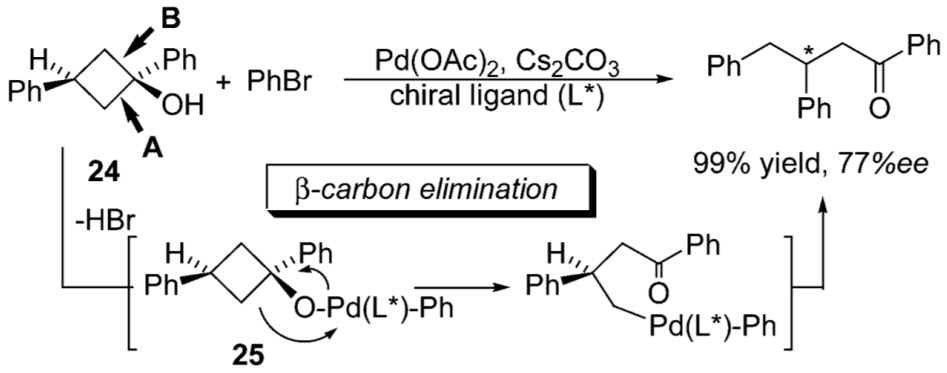




Murami, M.; Ito, Y. *et al. J. Am. Chem. Soc.* **1997**, *119*, 9307.

βcarbon elimination

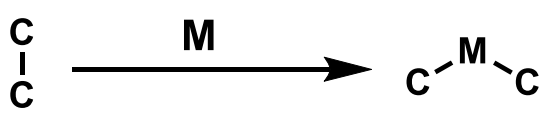




Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.

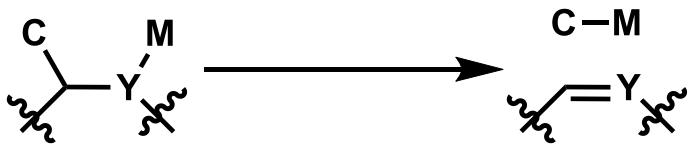
Methodologies of C-C bond activation

Oxidative addition



We mainly focus on it today.
(Prof. Dong's strategy)

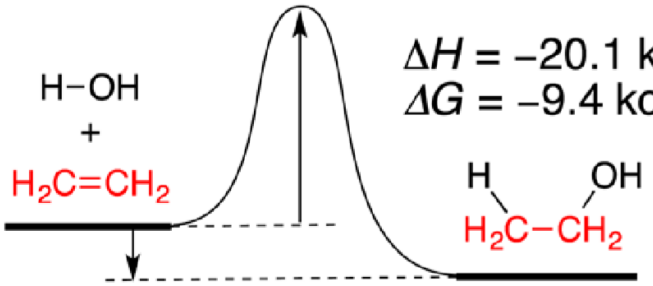
βcarbon elimination



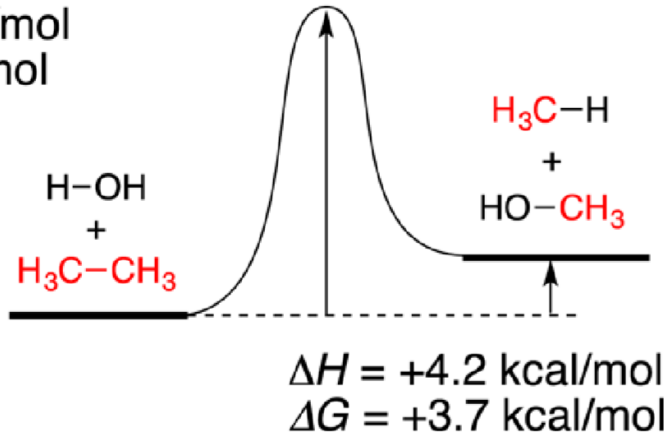
Difficulty of C-C bond cleavage

- **Thermodynamic factor**
  - **Unstability of products**

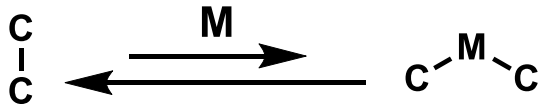
(i) hydration of ethylene



(ii) hydration of ethane



  - **Weak carbon-metal bond**



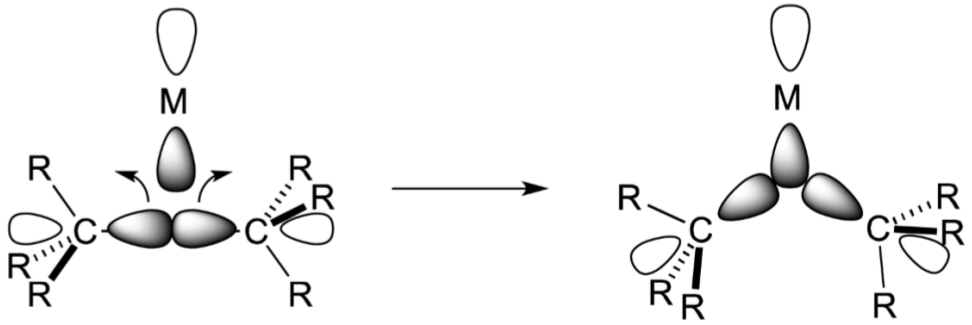
90 kcal/mol **20~30 kcal/mol ×2**

Murakami, M.; Ishida, N. *J. Am. Chem. Soc.* **2016**, *138*, 13759.

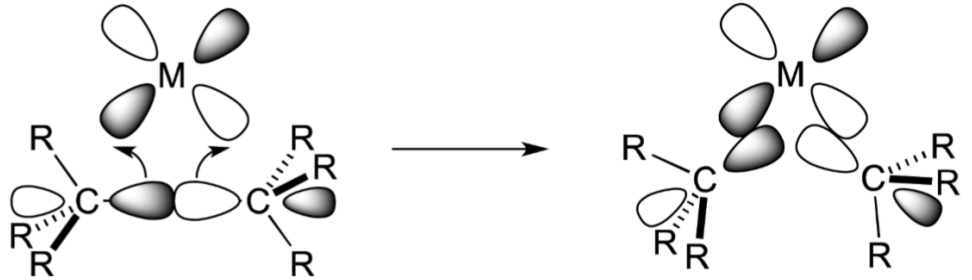
Difficulty of C-C bond cleavage

- **Kinetic factor**
  - **Interaction between metal orbitals and C-C bond**

(a) with a C–C bonding orbital



(b) with a C–C anti-bonding orbital

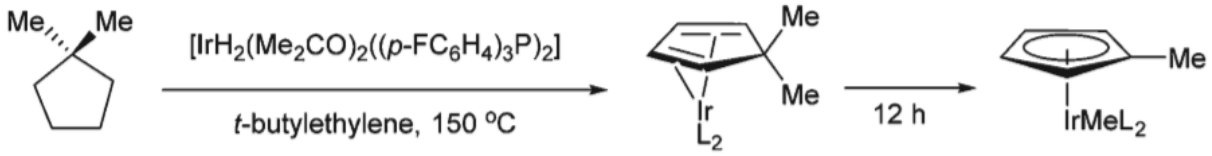


Distortion of C-C bond is needed.

Murakami, M.; Ishida, N. *J. Am. Chem. Soc.* **2016**, *138*, 13759.

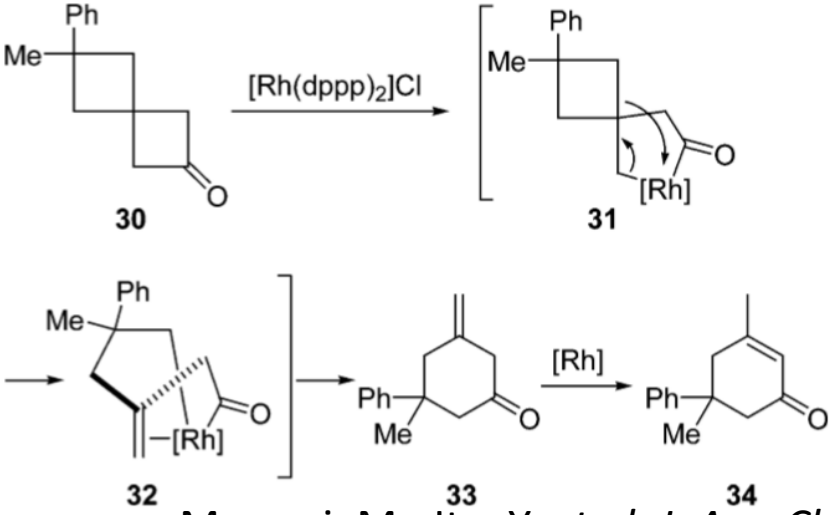
Driving force of C-C bond activation

- **Aromatization (Only stoichiometric reaction)**



Crabtree, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 7222.

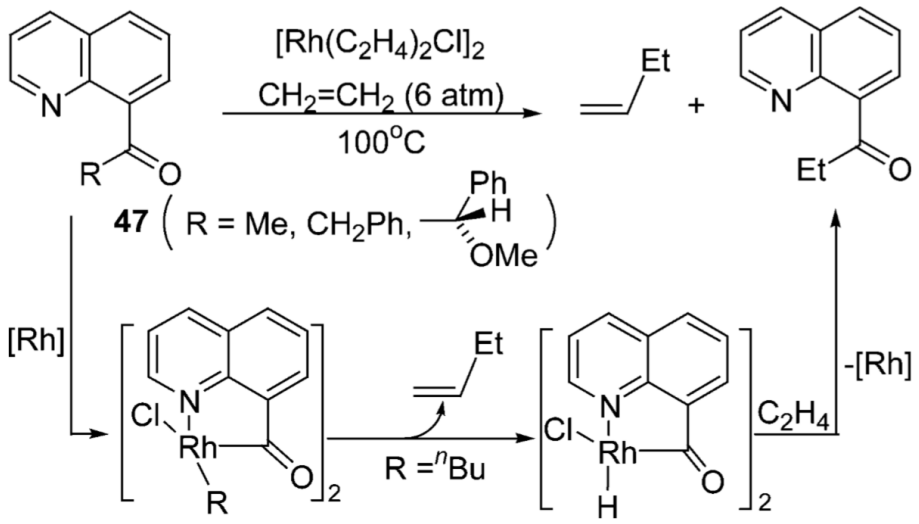
- **Strained molecules**



Murami, M.; Ito, Y. *et al. J. Am. Chem. Soc.* **1997**, *119*, 9307.

Driving force of C-C bond activation

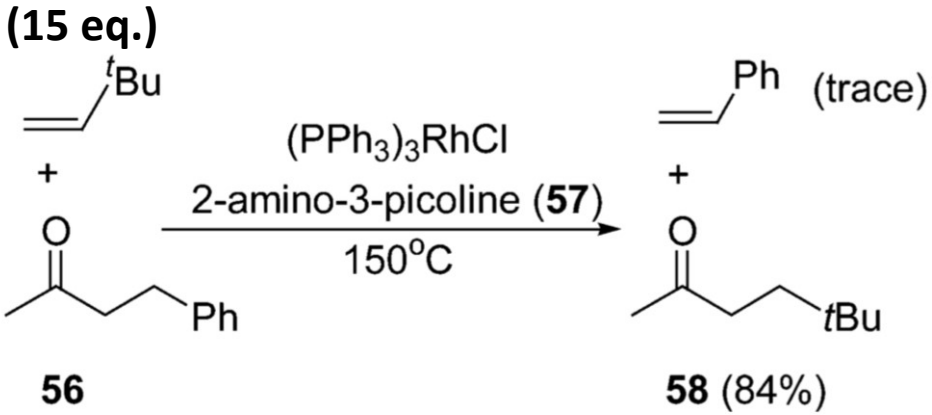
- **Directing group**

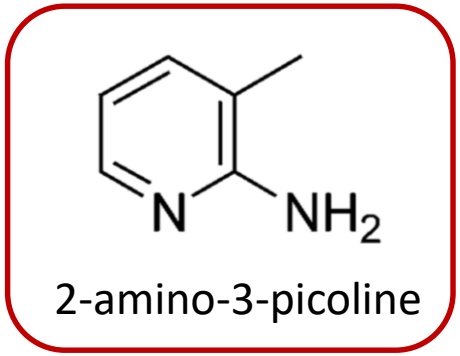


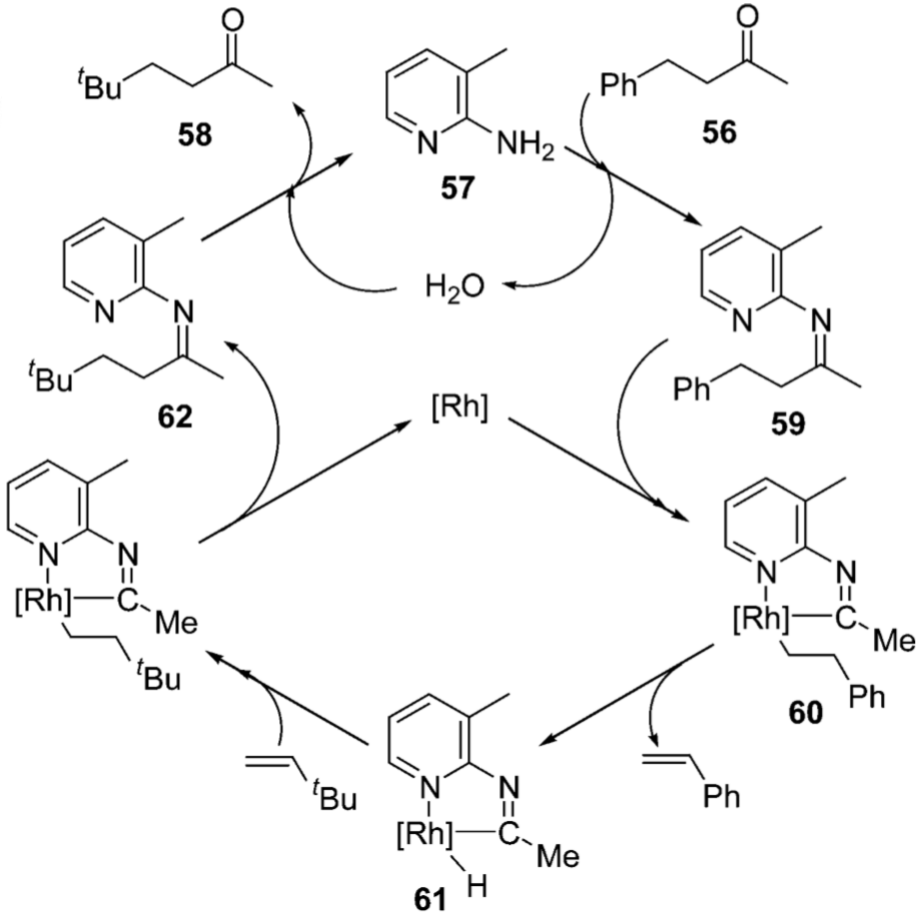
Suggs, J. W.; Jun, C. -H. *et al. J. Am. Chem. Soc.* **1984**, *106*, 3054.
Suggs, J. W.; Jun, C. -H. *et al. J. Chem. Soc., Chem. Commun.* **1985**, 92.

Driving force of C-C bond activation

- **Temporary directing group**







Jun, C. -H. *et al. J. Am. Chem. Soc.* **1999**, *121*, 880.

Short summary

- **Carbon –carbon activation is a promising reaction for organic synthesis.**
  - **Late-stage functionalization**
  - **Total synthesis**
- **But, it has difficulty about both thermodynamics and kinetics factor.**
  - **Unstability of products**
  - **Weak C-M bond**
  - **Interaction between metal orbitals and C-C bond.**
- **Therefore, some strategies for driving force were developed.**
  - **Aromatization**
  - **Strained molecules**
  - **Directing group**
  - **Temporary directing group**

Today's Content

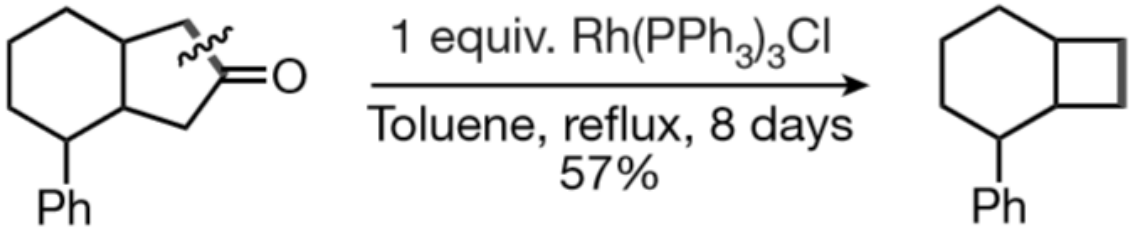
1. *Overview of C-C activation*
2. ***C-H activation***
3. *SMC (Suzuki-Miyaura coupling)*

C-H activation type reaction

- **Carbon-carbon bond and carbon-hydrogen bond activation**

Dong, G. *et al*. *Nature* **2016**, *539*, 546.

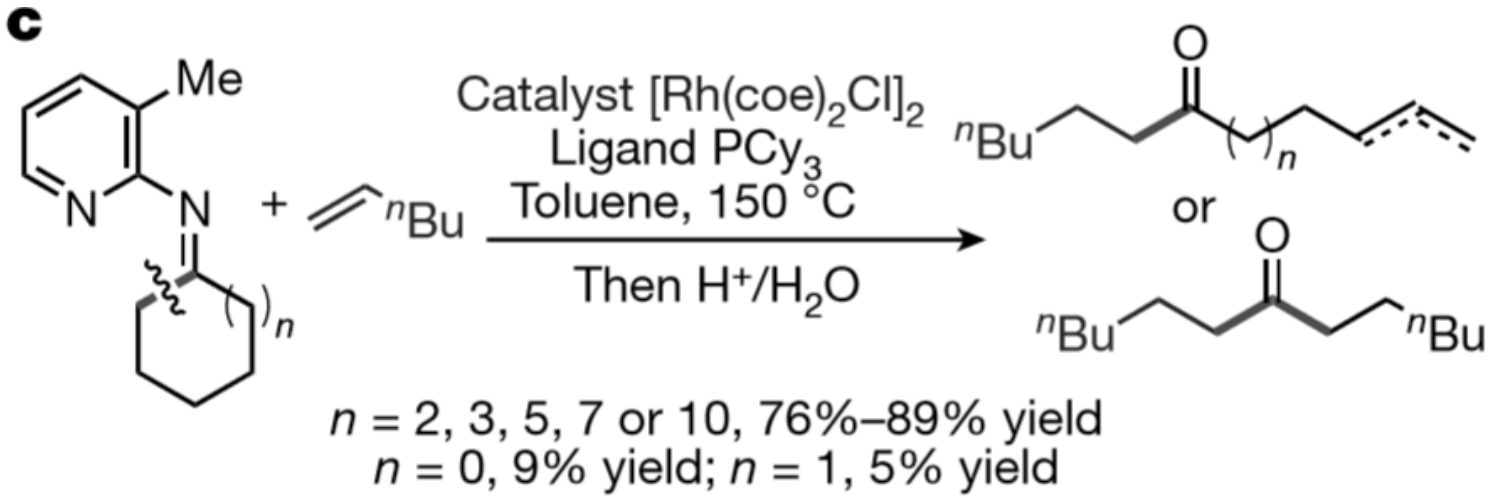
C-C bond cleavage of unstrained molecule



Murakami, M.; Amii, H.; Ito, Y. *Nature* **1994**, *370*, 540.

- **Low efficiency (8 days)**
- **C-C bond activation of unstrained molecule is usually difficult.**

Temporary directing group

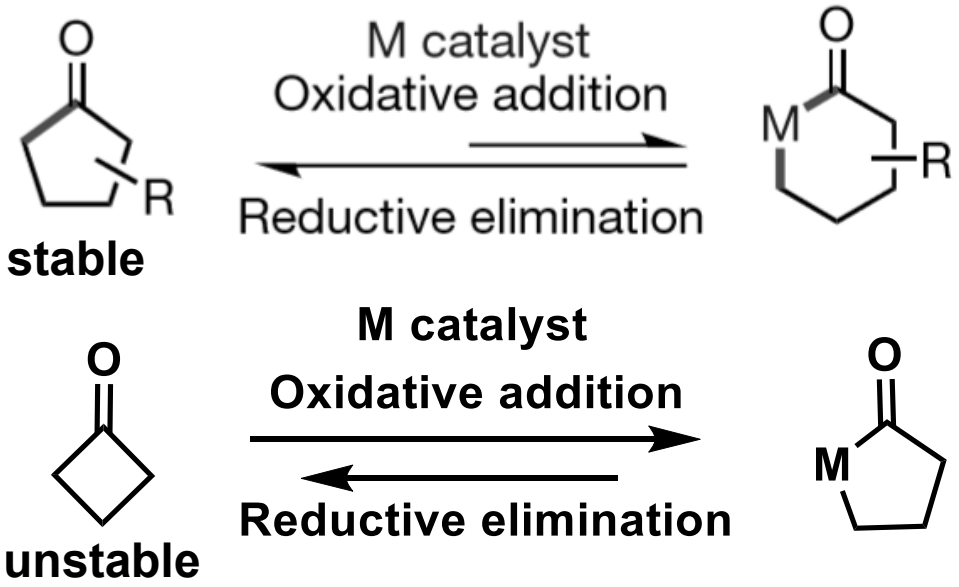


Jun, C.-H.; Lee, H.; Lim, S.-G. *J. Am. Chem. Soc.* **2001**, *123*, 751.

- **For stable 5 or 6-membered ring, low reactivity was observed.**

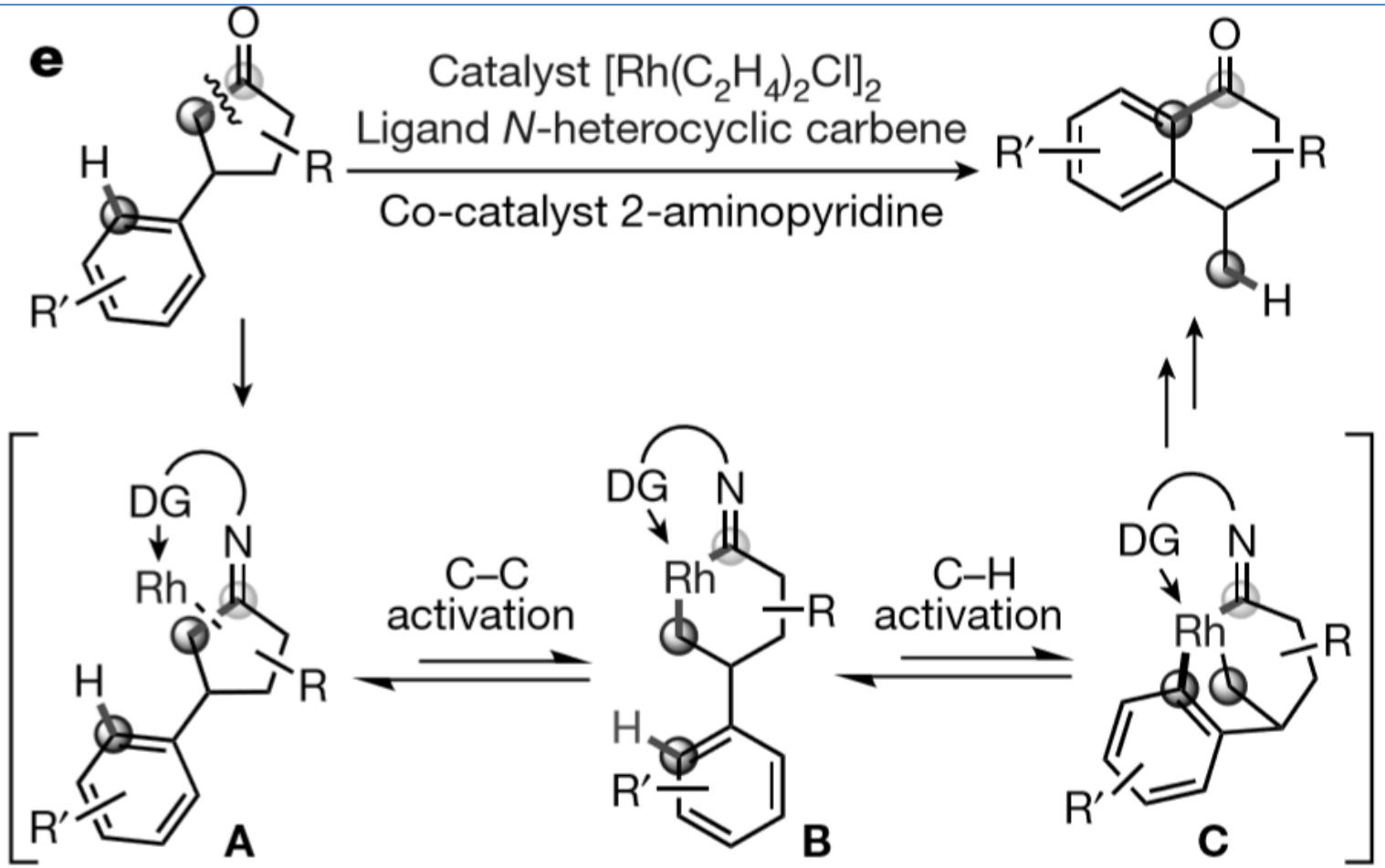
Problematic point

- **Reversibility of oxidative addition step**



- **Due to stability of cyclopentanones, thermodynamic driving force is lacked.**

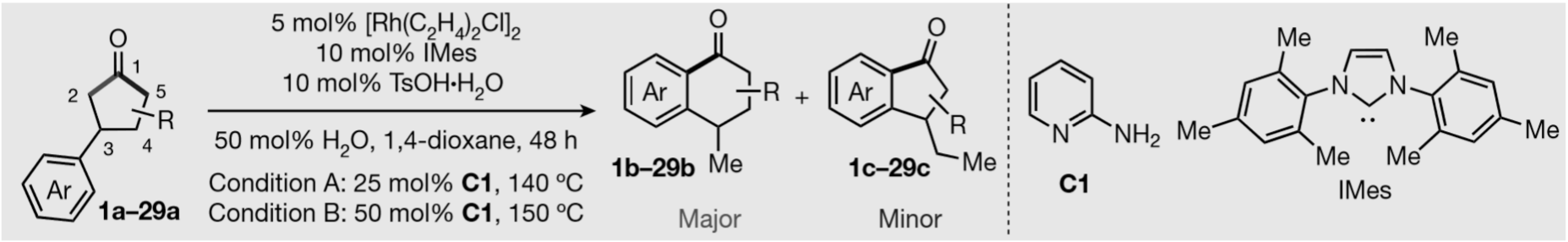
Reaction design



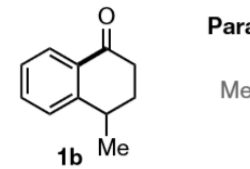
- **Overall thermodynamically favored transformation ($\Delta G \simeq -6$ kcal/mol)**

Dong, G. *et al*. *Nature* **2016**, *539*, 546.

Substrate scope

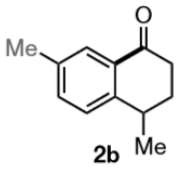


C1-C2 **C1-C5**

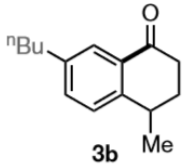


Condition A
66% (>10:1)
68% (1 mmol scale)
Condition B, 73% (5.8:1)

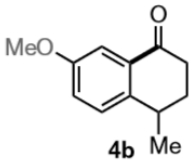
Para-substituted aryl



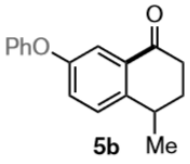
Condition A
64% (>10:1)



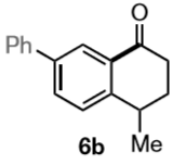
Condition A
65% (>10:1)



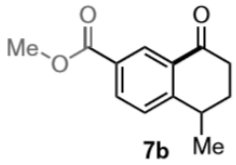
Condition A
75% (>10:1)



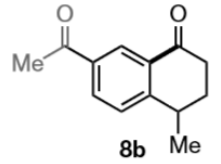
Condition A
69% (>10:1)



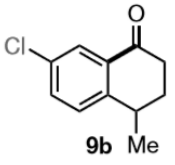
Condition A
64% (>10:1)



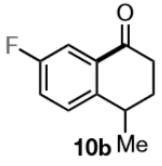
Condition A, 43% (>10:1)
Condition B, 63% (>10:1)



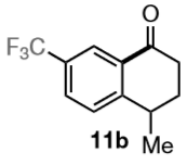
Condition A, 54% (>10:1)
Condition B, 71% (>10:1)



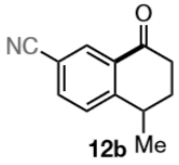
Condition B
72% (>10:1)



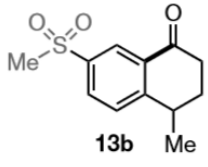
Condition B
82% (>10:1)



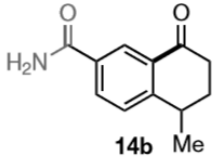
Condition B
73% (>10:1)



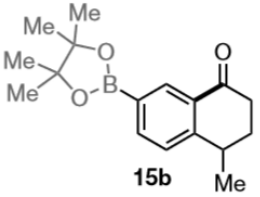
Condition B
66% (>10:1)



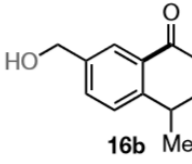
Condition B
85% (>10:1)



Condition B
53% (>10:1)



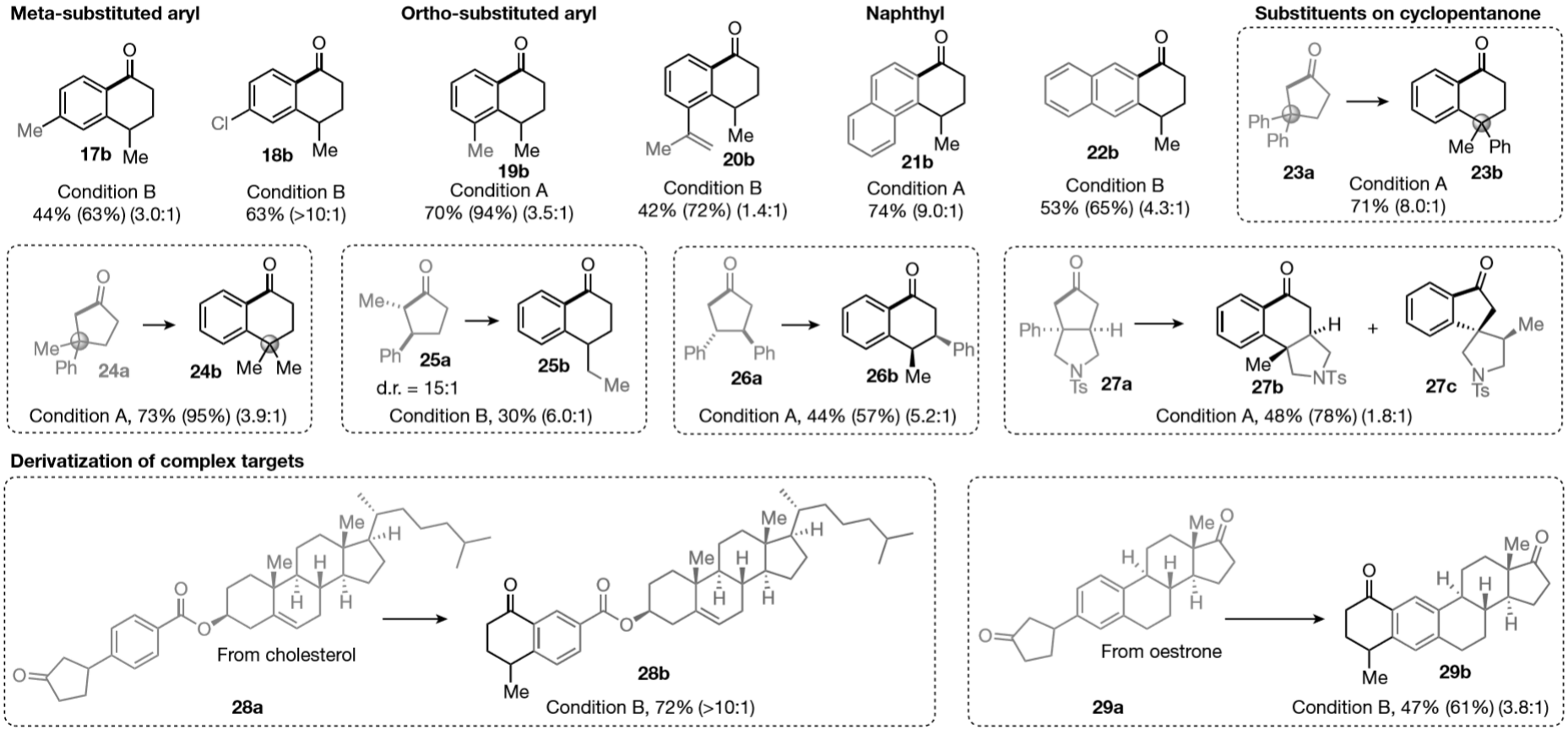
Condition A
45% (>10:1)



Condition A
66% (8.2:1)

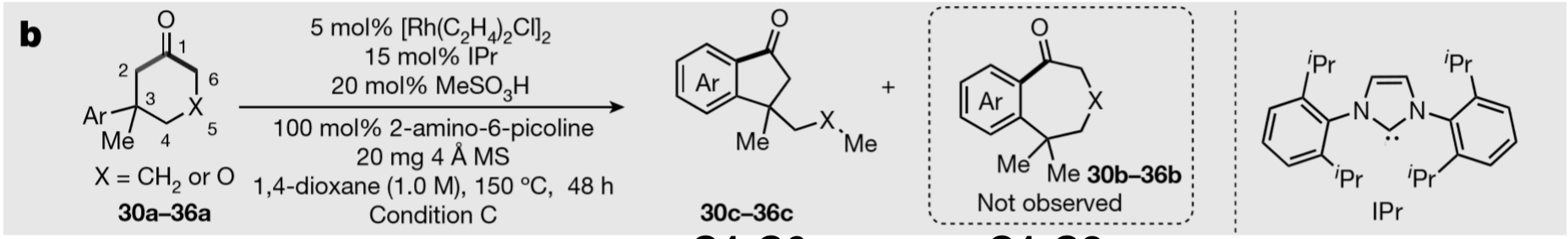
Dong, G. *et al*. *Nature* **2016**, *539*, 546.

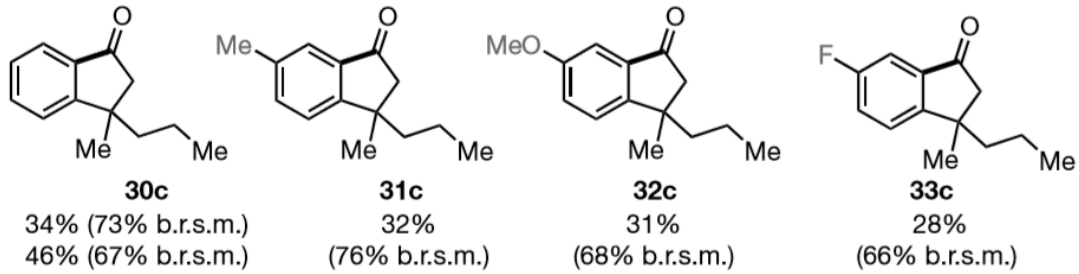
Substrate scope

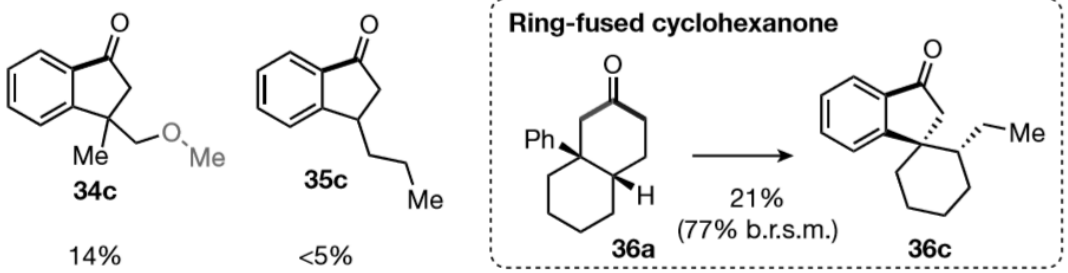


Dong, G. *et al*. *Nature* **2016**, *539*, 546.

Scope of 6-membered ring

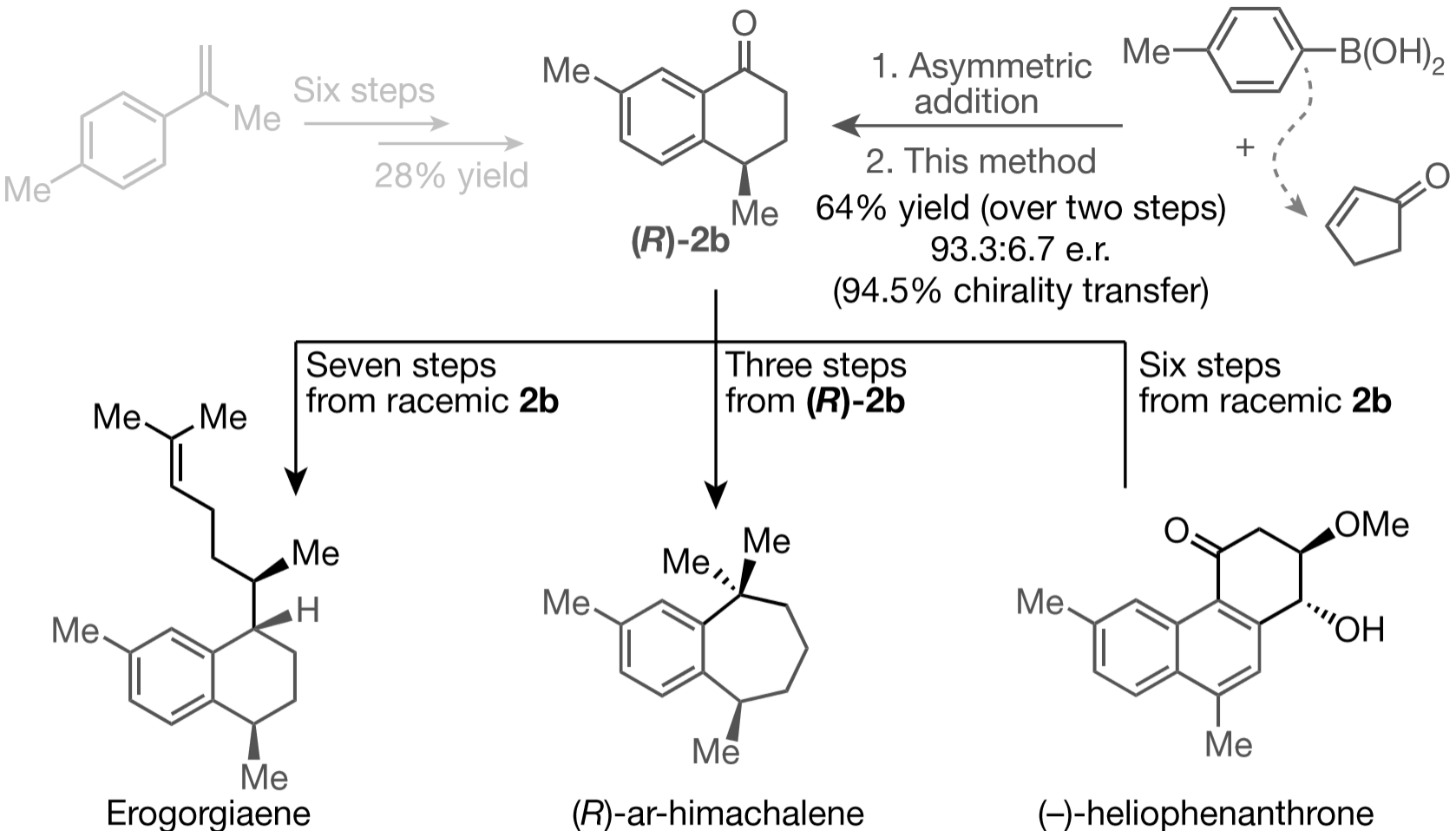






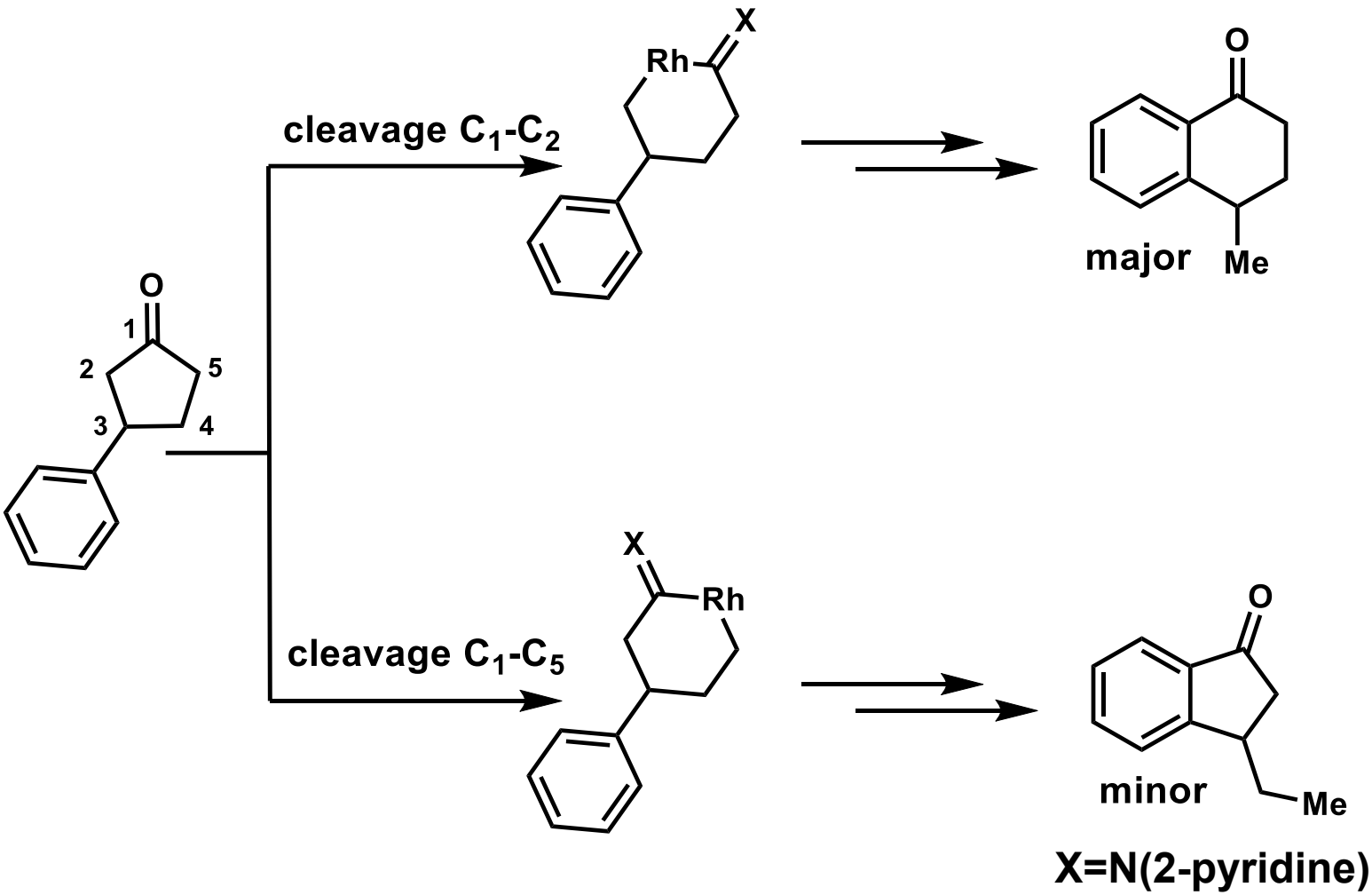
Dong, G. *et al*. *Nature* **2016**, *539*, 546.

Asymmetric synthesis of terpenoids



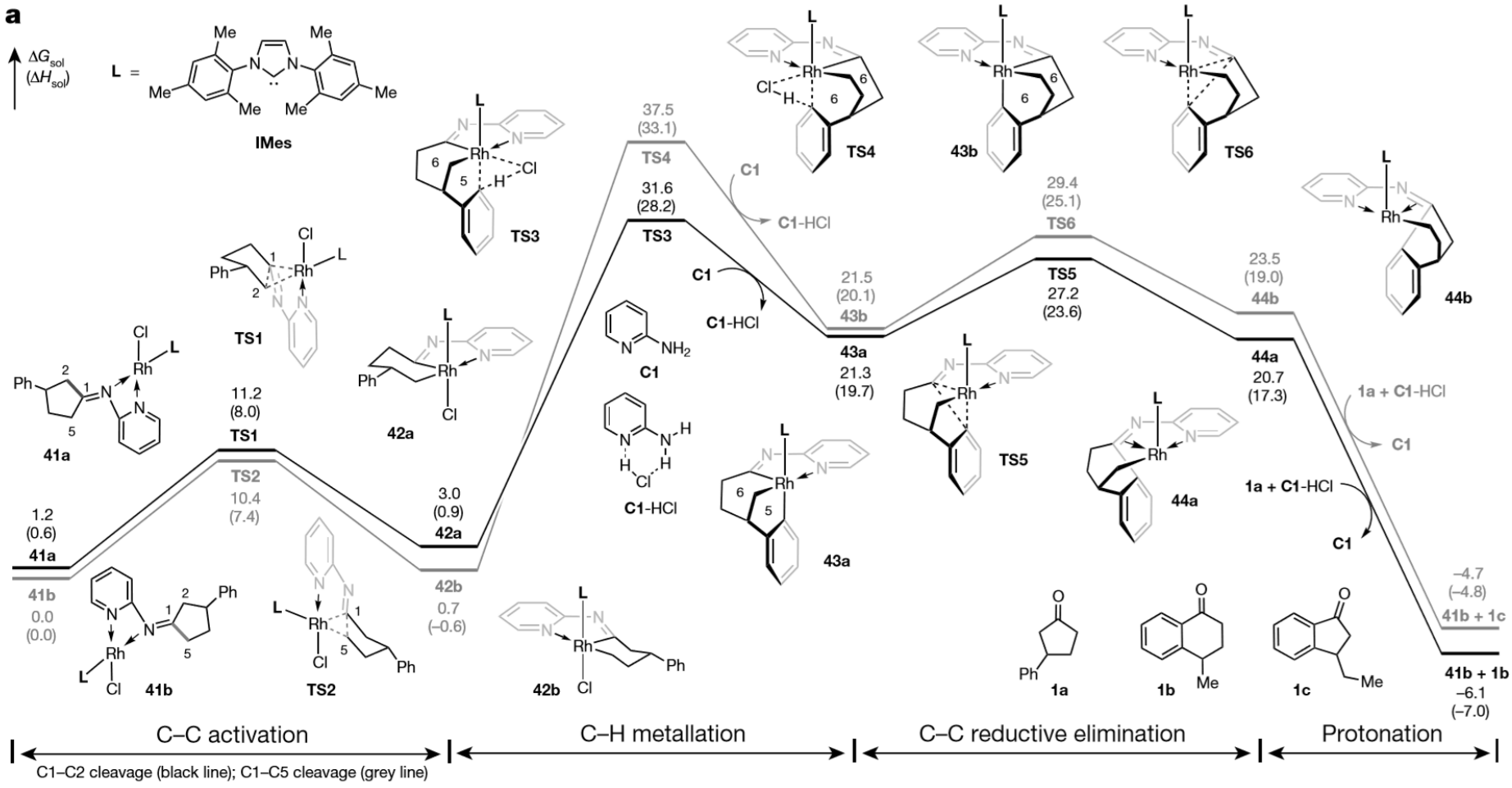
Dong, G. *et al*. *Nature* **2016**, *539*, 546.

Selectivity of C-C activation



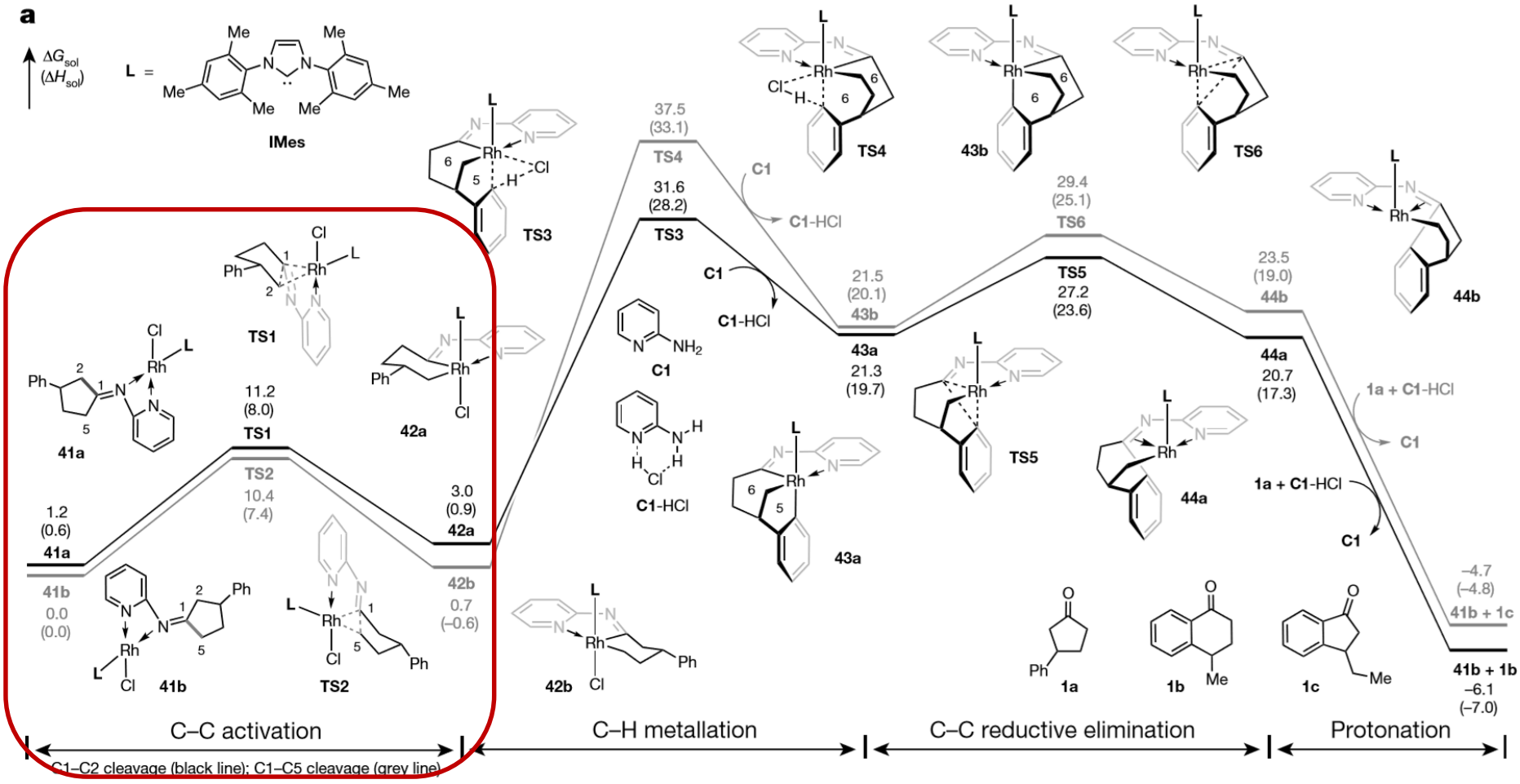
Why cleavage is occurred at hindered position?

Calculation study



Dong, G. *et al*. *Nature* **2016**, *539*, 546.

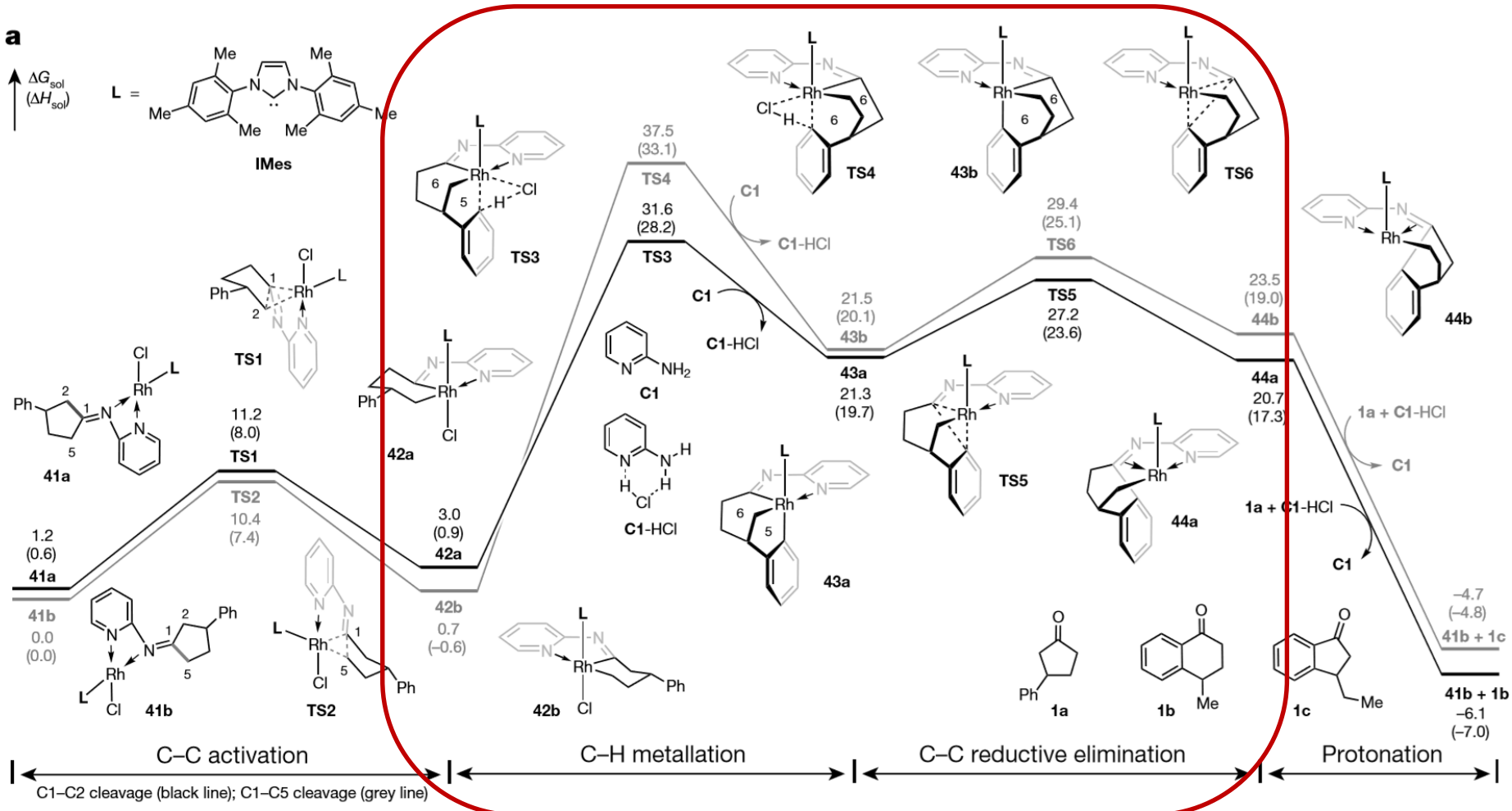
Calculation study



relatively low barrier = reversible

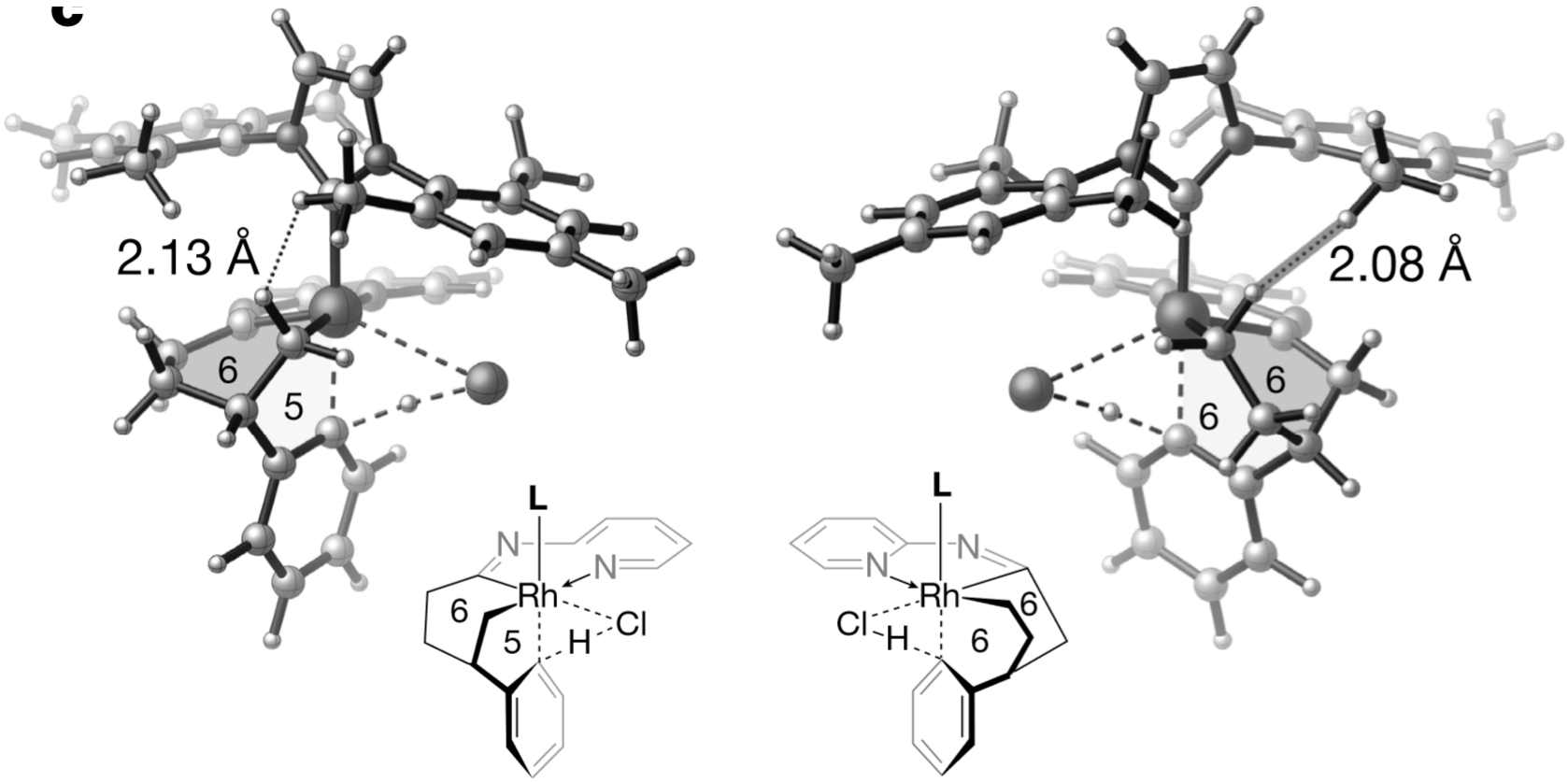
Dong, G. *et al*. *Nature* **2016**, *539*, 546.

Calculation study



determine selectivity.

Calculation study



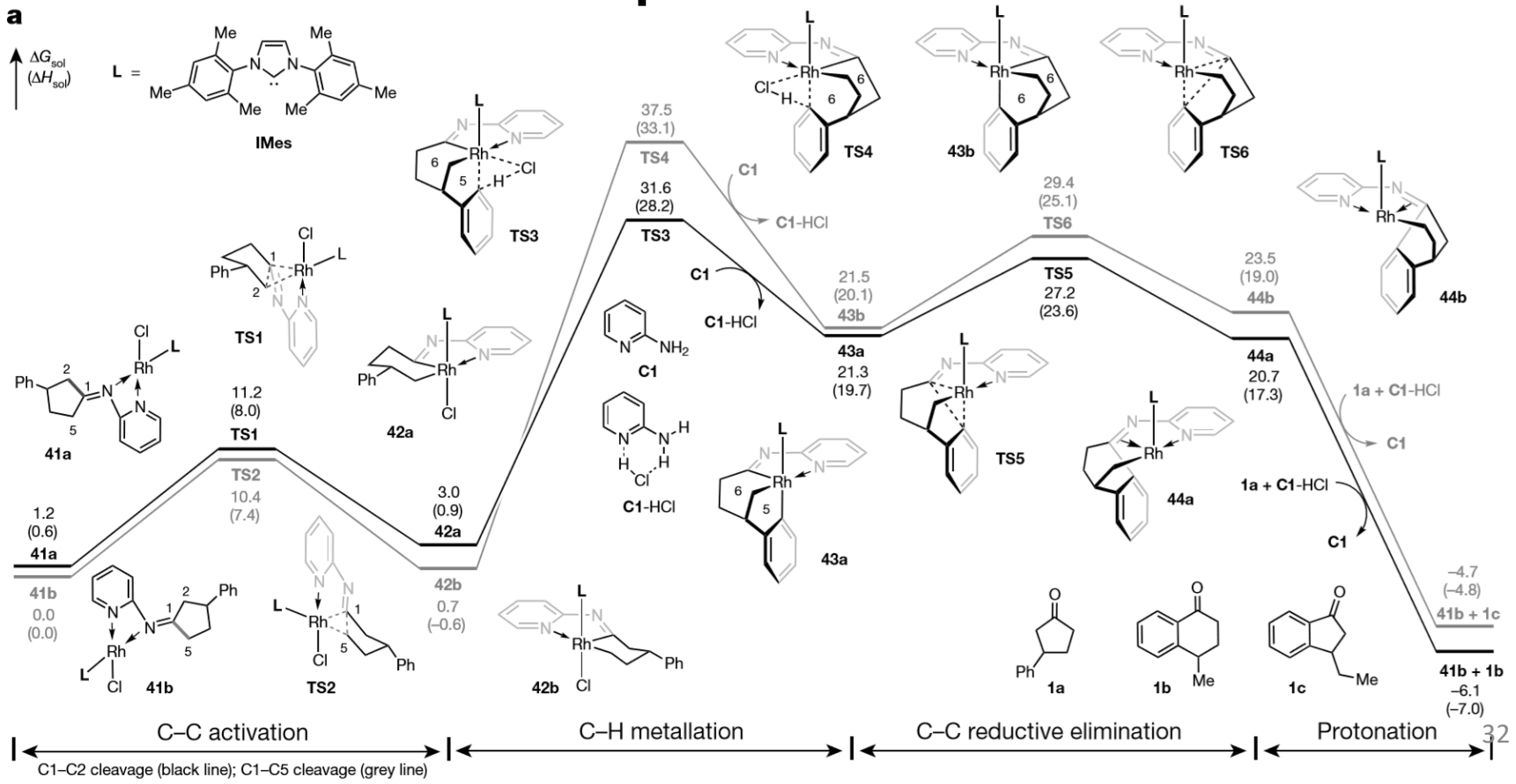
TS3 (favoured)
$\Delta G^{\ddagger}$ = 31.6 kcal mol^{-1}

TS4 (disfavoured)
$\Delta G^{\ddagger}$ = 37.5 kcal mol^{-1}

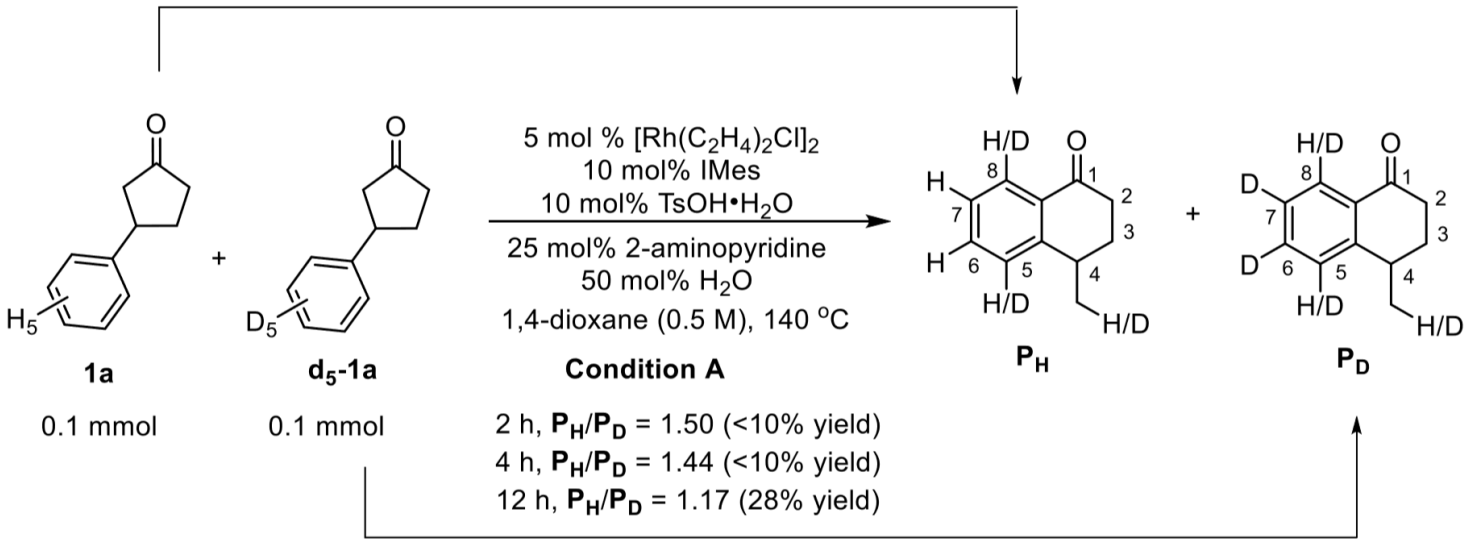
Steric repulsion between ligand and C5 methylene group, due to six-membered rhodacycle.

Where is TLS (turnover limiting step) ?

- **According to calculation study, C-H metalation requires large energy.**
- **Is C-H metalation step TLS?**



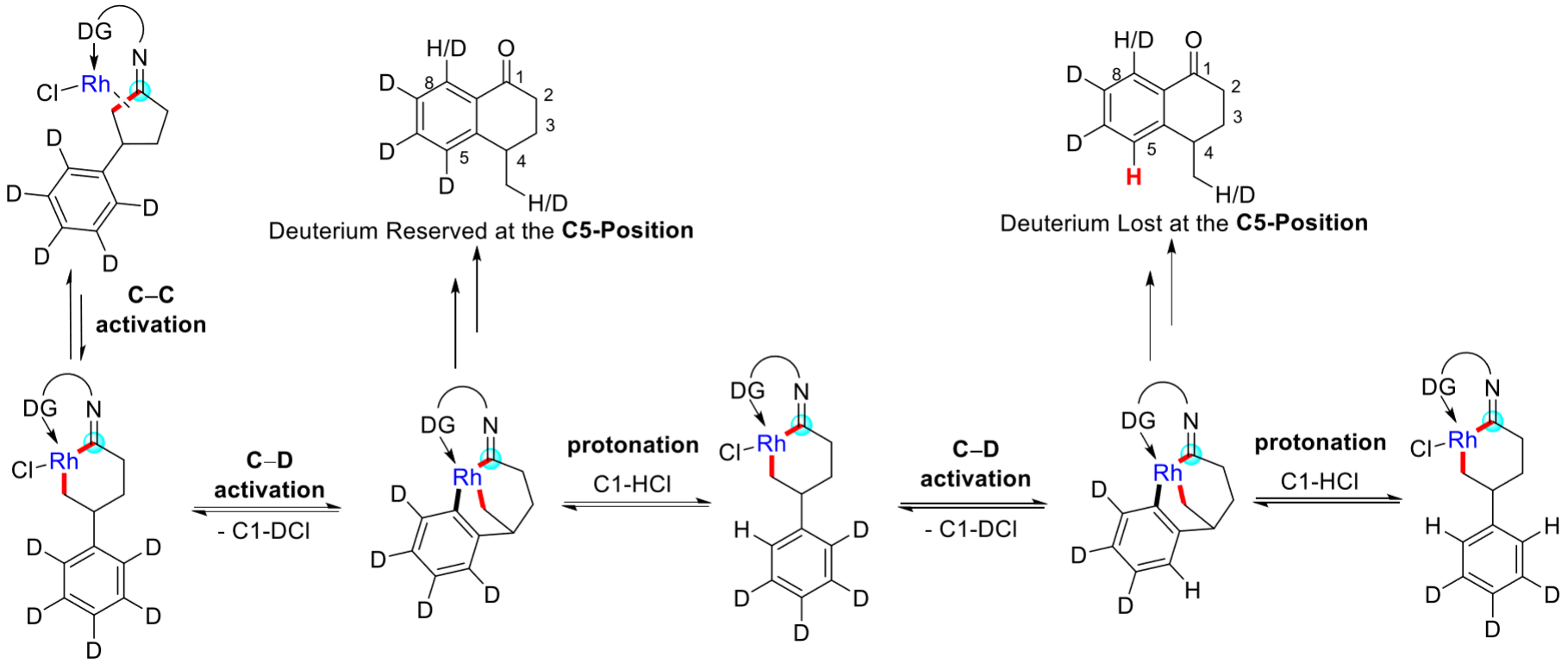
KIE experiment



- **According to calculation study, If C-H metalation is a sole turnover limiting step, KIE≃4.3.**
- **This result indicated *slow and reversible C-H metalation step (*C5 scrambling*).***
- **Both C-H metalation and reductive elimination are TLS?**

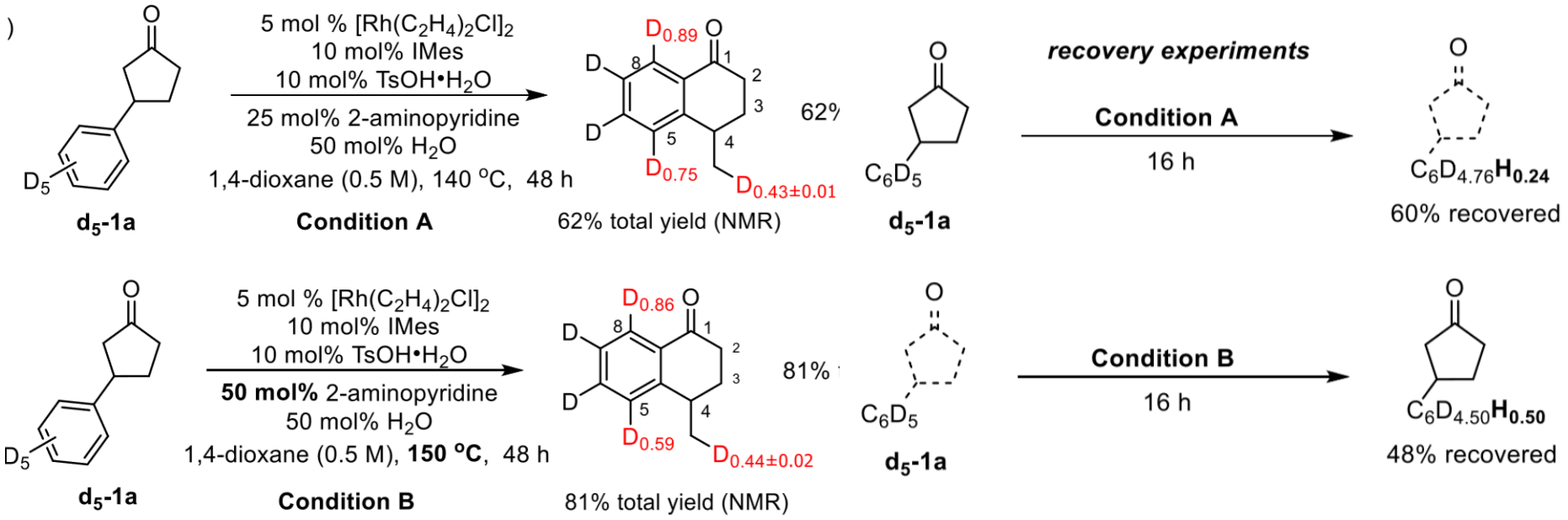
Dong, G. *et al*. *Nature* **2016**, *539*, 546.

Reversible C-H metalation step



Dong, G. *et al*. *Nature* **2016**, *539*, 546.

Deuterium labeling experiments

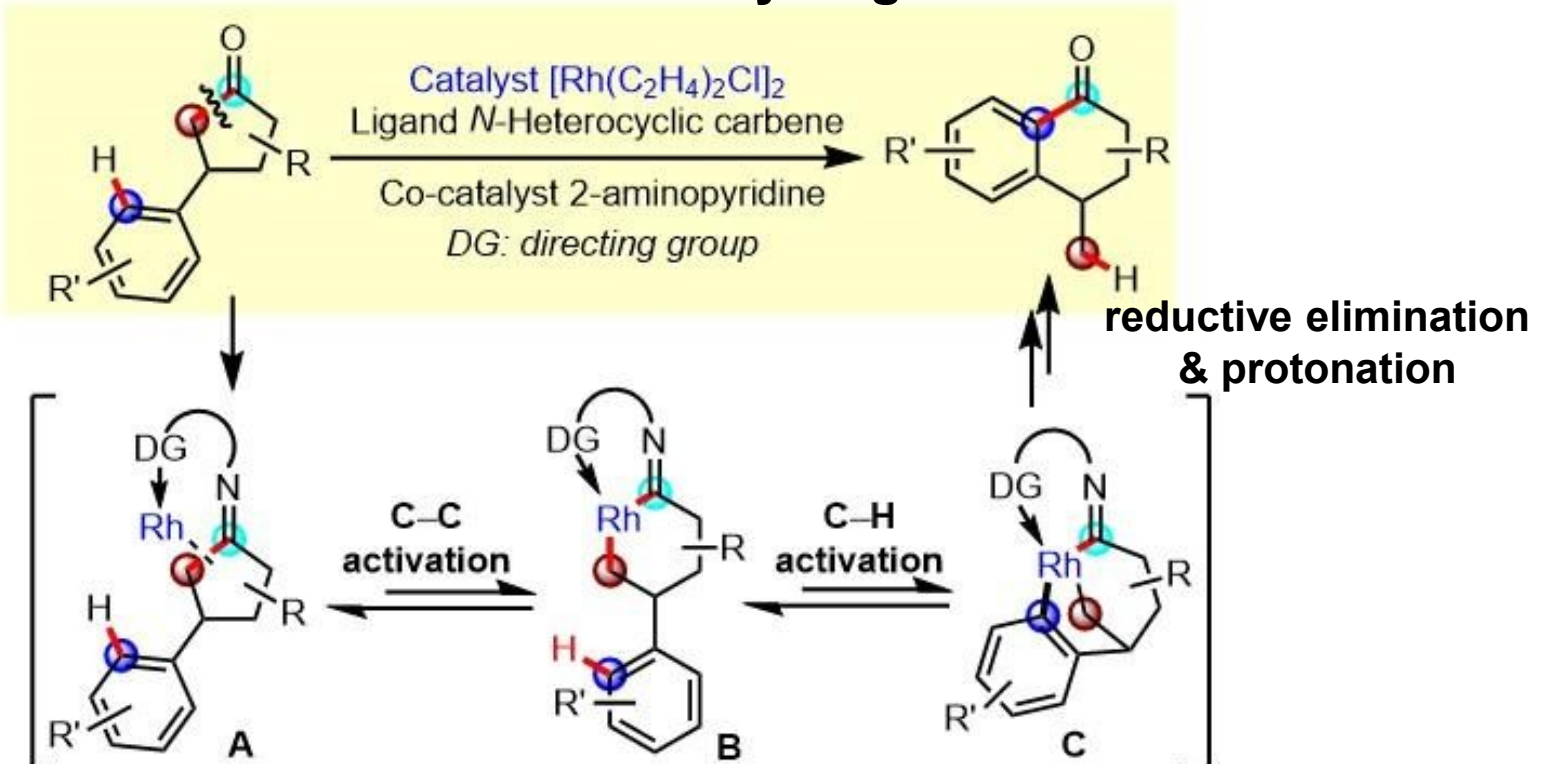


- **C5 scrambling is consist with reversible C-H step.**
- **Unreacted reactants showed deuterium lost at phenyl group.**

Dong, G. *et al*. *Nature* **2016**, *539*, 546.

C-H activation type reaction

- **Carbon-carbon bond and carbon-hydrogen bond activation**



- **Due to reaction design, driving force is obtained.**

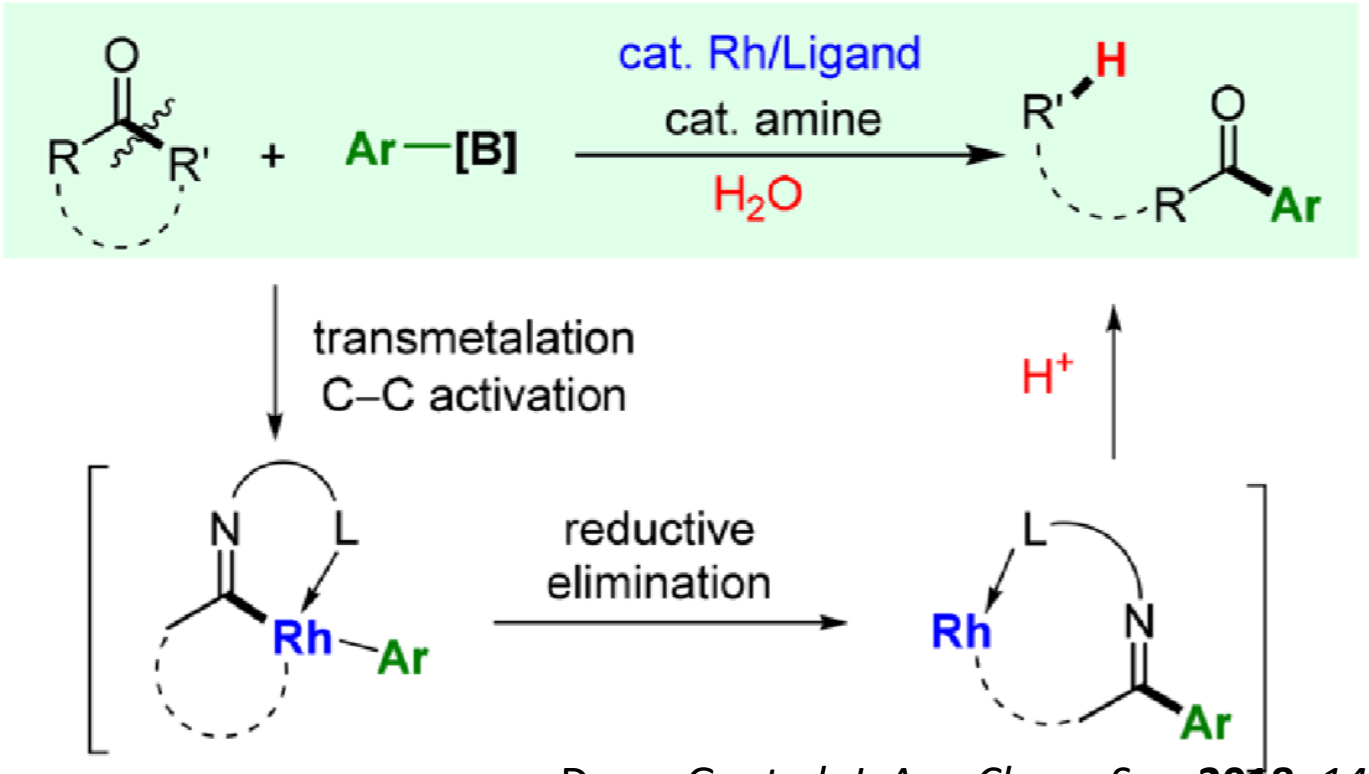
Dong, G. *et al*. *Nature* **2016**, *539*, 546.

Today's Content

1. *Overview of C-C activation*
2. *C-H activation*
3. ***SMC (Suzuki-Miyaura coupling)***

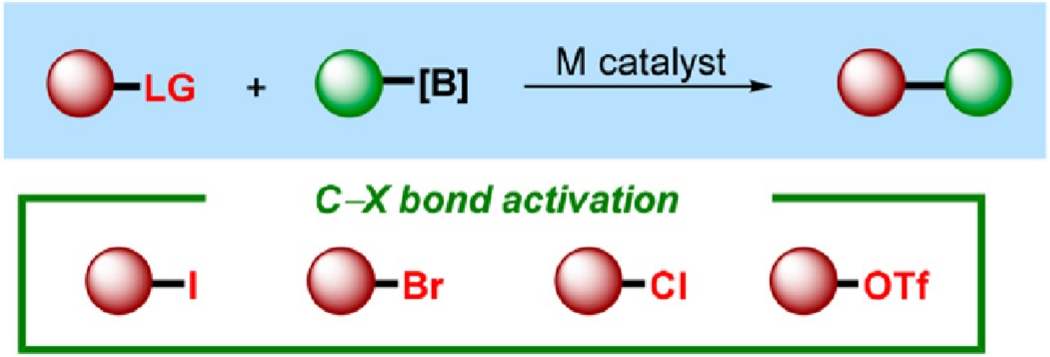
Suzuki-Miyaura coupling type reaction

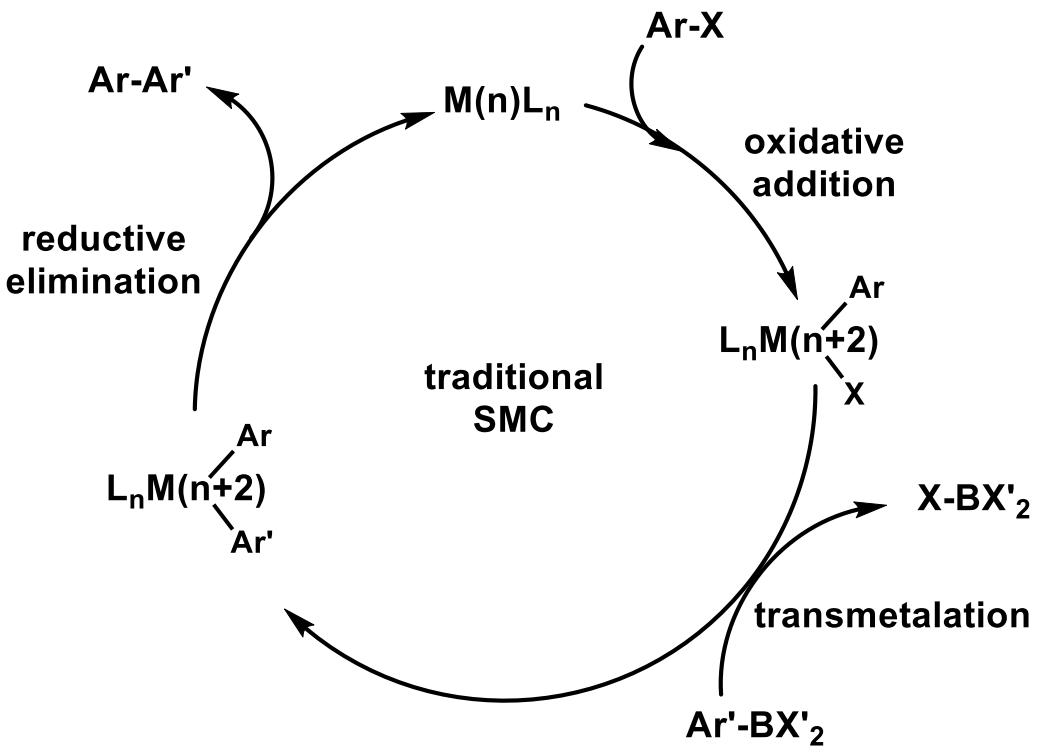
- **Carbon-carbon bond activation Suzuki-Miyaura crosscoupling**



Dong, G. *et al. J. Am. Chem. Soc.* **2018**, *140*, 5347.

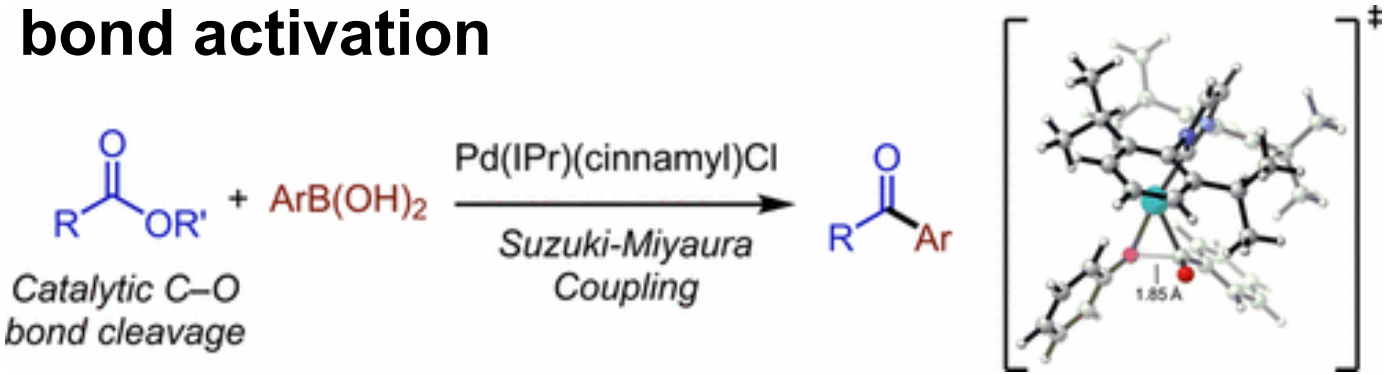
SMC (Suzuki-Miyaura coupling)





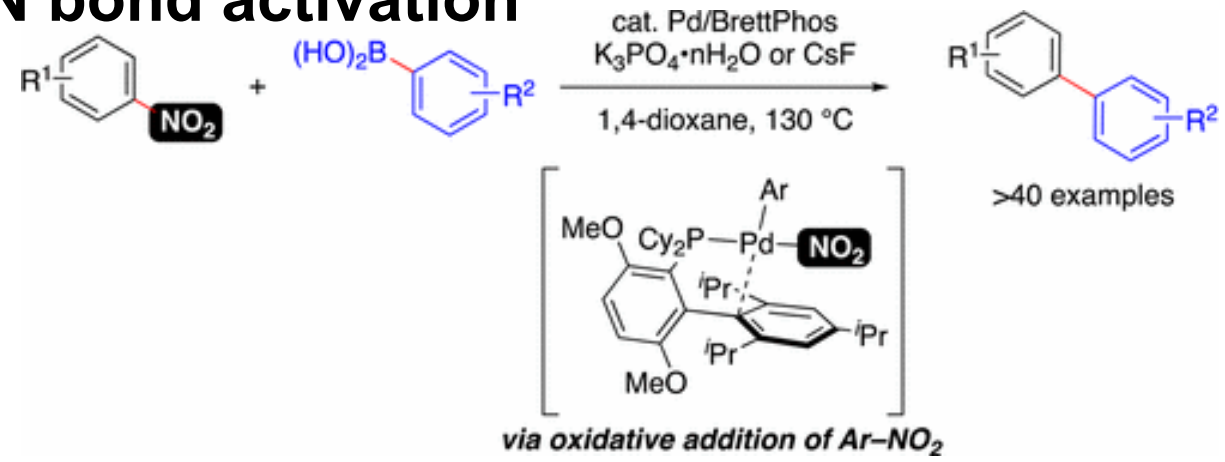
C-O or C-N bond activation

- **C-O bond activation**



Houk, K. N.; Newman, S. G. *et al. J. Am. Chem. Soc.* **2017**, *139*, 1311.

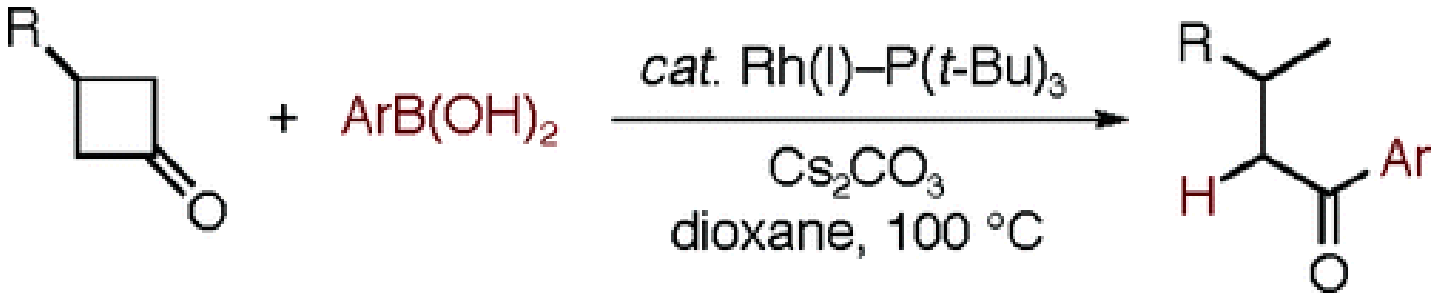
- **C-N bond activation**



Sasaki, S.; Nakao, Y. *et al. J. Am. Chem. Soc.* **2017**, *139*, 9423.

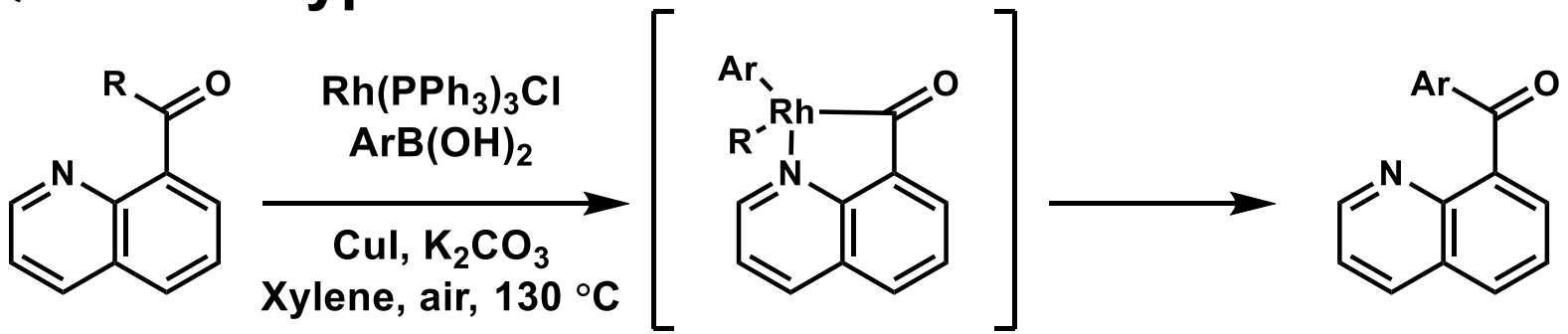
C-C bond activation

- **Strained molecules**



Murakami, M. *et al*. *Org. Lett.* **2004**, *6*, 1257.

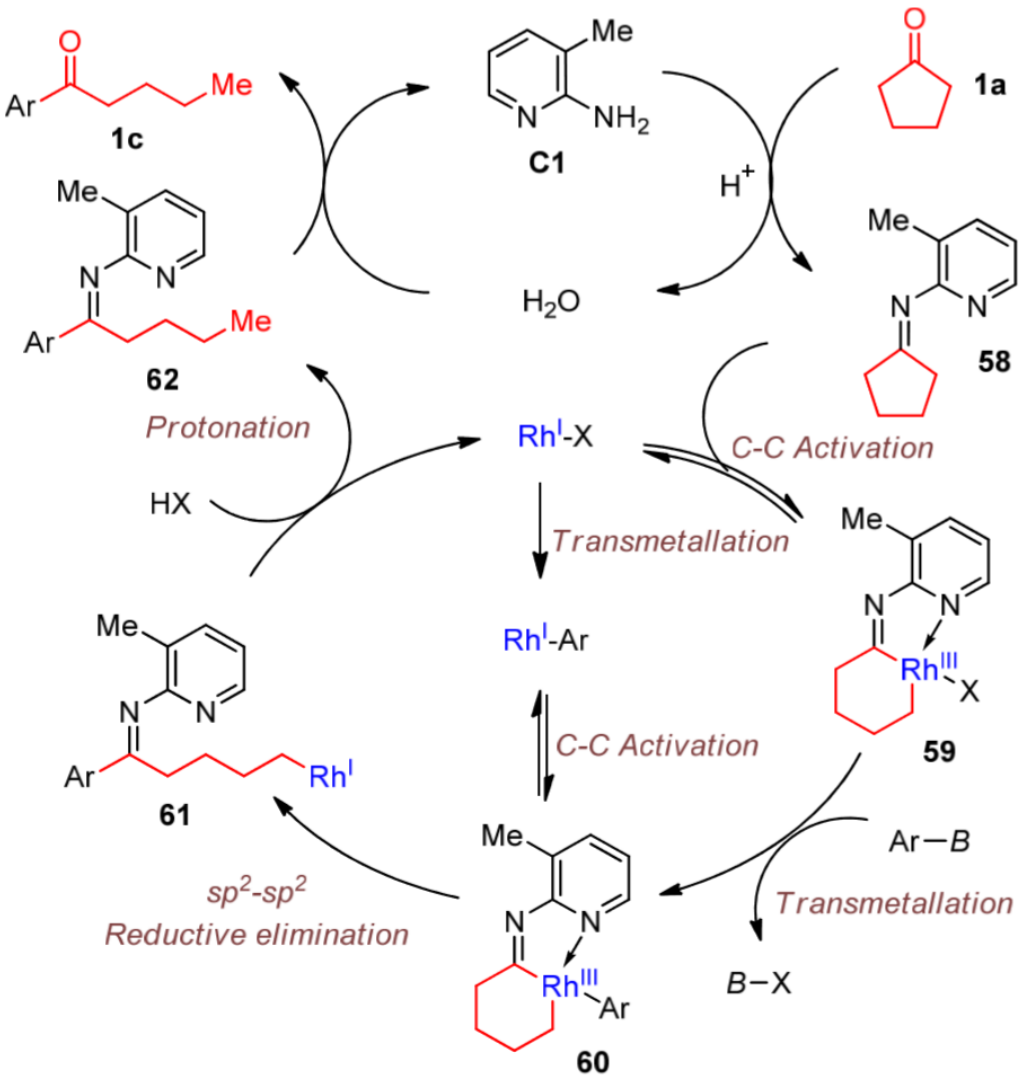
- **Quinoline type**



Wang, J. *et al. Angew. Chem., Int. Ed.* **2012**, *51*, 12334.

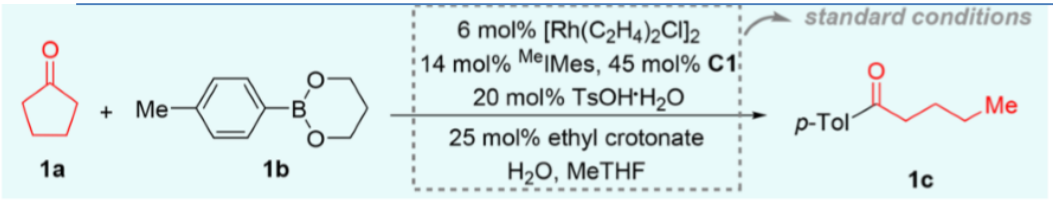
C-C bond activation SMC is developed not so much.

Catalytic cycle

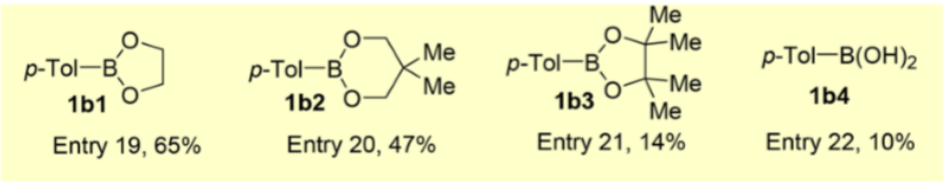


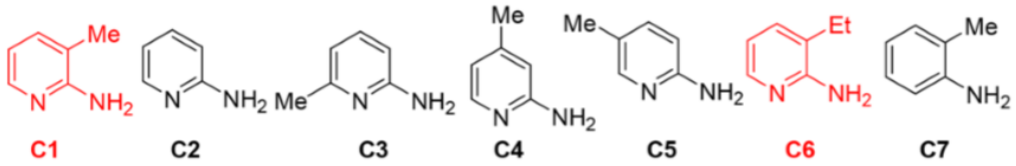
Dong, G. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 5347.

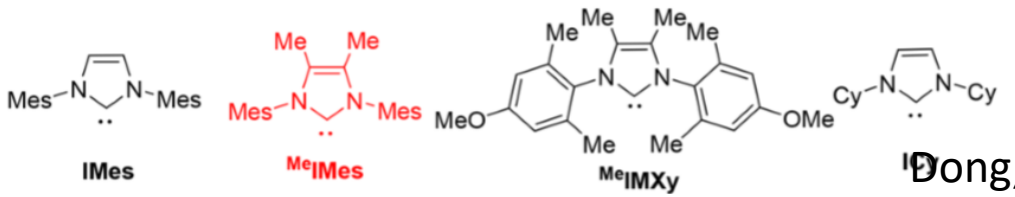
Optimization study



Entry	Variation	Yield (%)[b]	Entry	Variation	Yield (%)[b]
1	None	68 (67)[c]	10	**C4** instead of **C1**	19
2	w/o $[Rh(C_2H_4)_2Cl]_2$	0	11	**C5** instead of **C1**	11
3	w/o **C1**	0	12	**C6** instead of **C1**	67
4	w/o $TsOH·H_2O$	2	13	**C7** instead of **C1**	0
5	w/o ^{Me}IMes	7	14	IMes instead of ^{Me}IMes	58
6	w/o H_2O	20	15	ICy instead of ^{Me}IMes	41
7	w/o ethyl crotonate	59	16	IMxy instead of ^{Me}IMes	61
8	**C2** instead of **C1**	19	17	130 °C	46
9	**C3** instead of **C1**	<1	18	1.5 equiv. **1b**	56

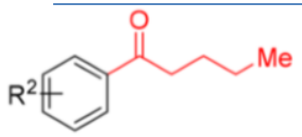




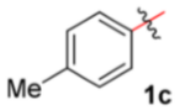


Dong, G. *et al. J. Am. Chem. Soc.* **2018**, *140*, 5347.

Scope of Arylborates

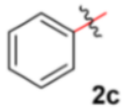


1c-29c



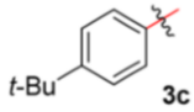
1c

Entry 1, 67%



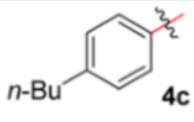
2c

Entry 2, 65%



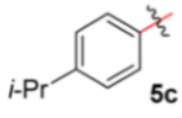
3c

Entry 3, 3c, 58%



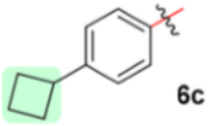
4c

Entry 4, 64%



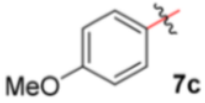
5c

Entry 5, 64%



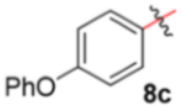
6c

Entry 6, 60%



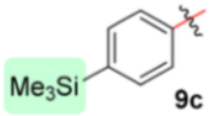
7c

Entry 7, 55%



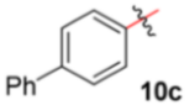
8c

Entry 8, 47%



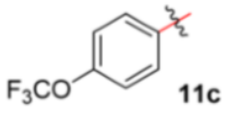
9c

Entry 9, 45%



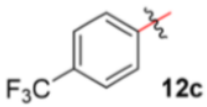
10c

Entry 10, 51%



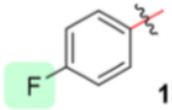
11c

Entry 11, 43%



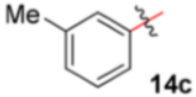
12c

Entry 12, 35%



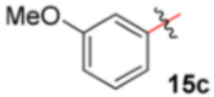
13c

Entry 13, 56%



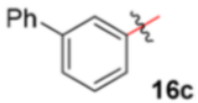
14c

Entry 14, 64%



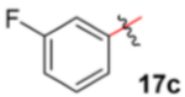
15c

Entry 15, 61%



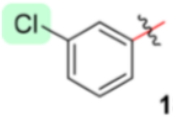
16c

Entry 16, 45%



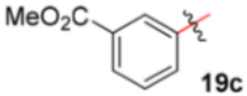
17c

Entry 17, 43%



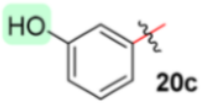
18c

Entry 18, 32%[b]



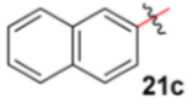
19c

Entry 19, 29%



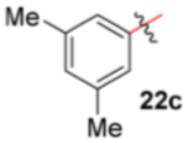
20c

Entry 20, 31%



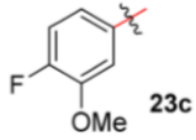
21c

Entry 21, 53%



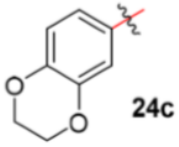
22c

Entry 22, 60%



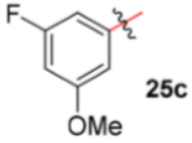
23c

Entry 23, 53%



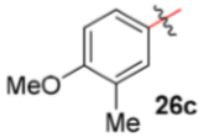
24c

Entry 24, 52%



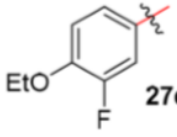
25c

Entry 25, 42%



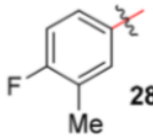
26c

Entry 26, 47%



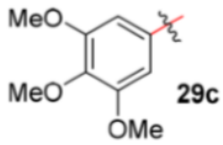
27c

Entry 27, 52%



28c

Entry 28, 56%



29c

Entry 29, 46%

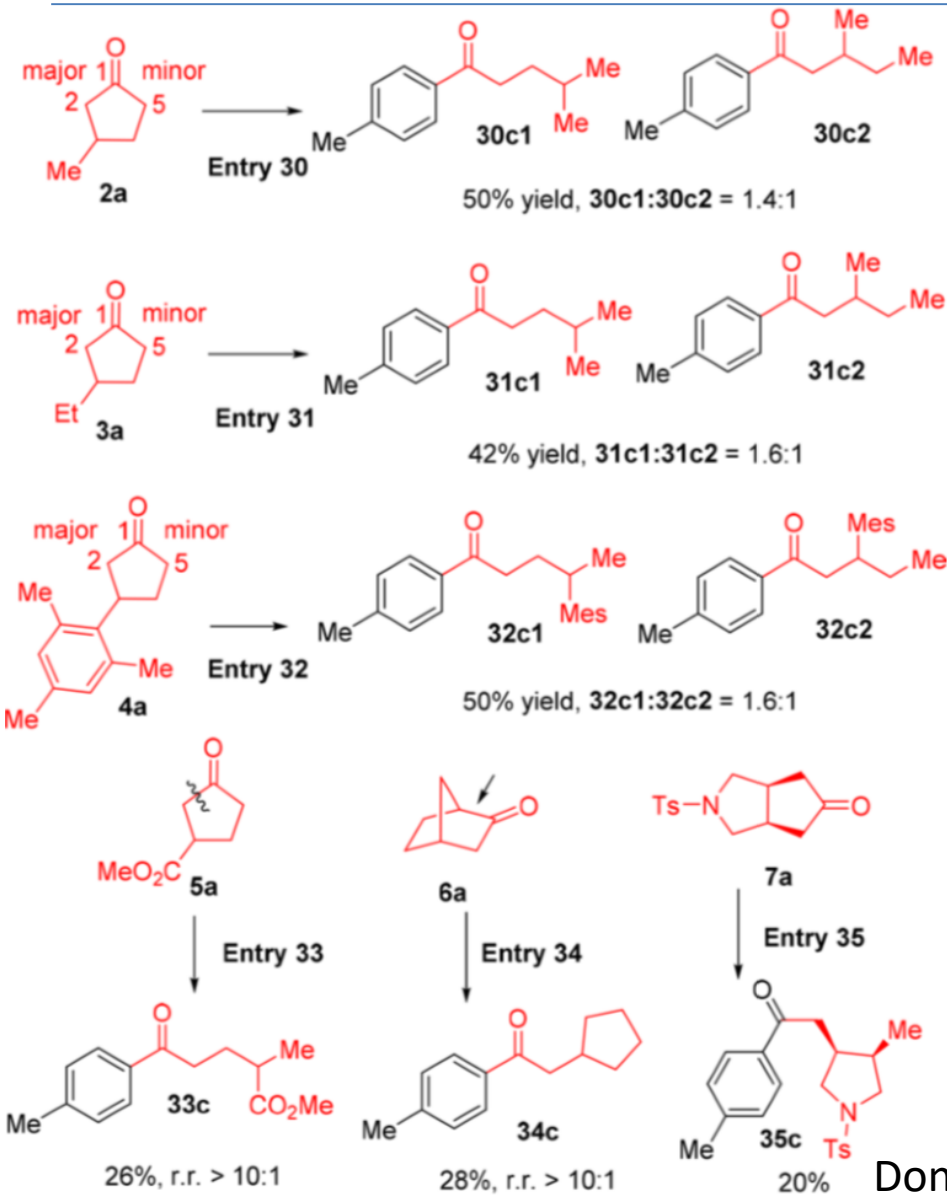
Strain cyclobutane ring is remained. (Entry 6)

Various functional groups which are useful in cross-coupling are tolerated (Entry 9, 13, 18, 20)

***Ortho*-substituted substrates are difficult.**

Dong, G. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 5347.

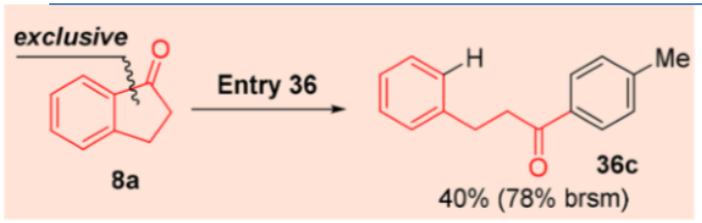
Scope of substituted cyclopentanones

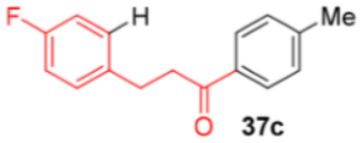


The site-selectivity slightly favored the more sterically hindered side.

Dong, G. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 5347.

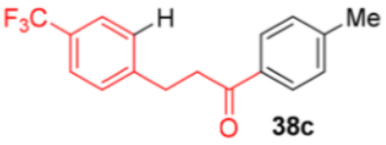
Scope of 1-indanones



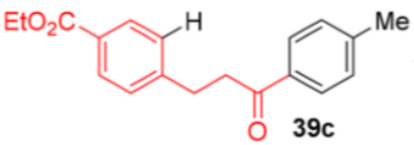


Entry 37, 61% (88% brsm)

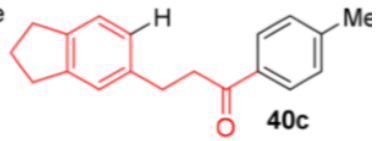
First example of C–C activation of 1-indanone is achieved.



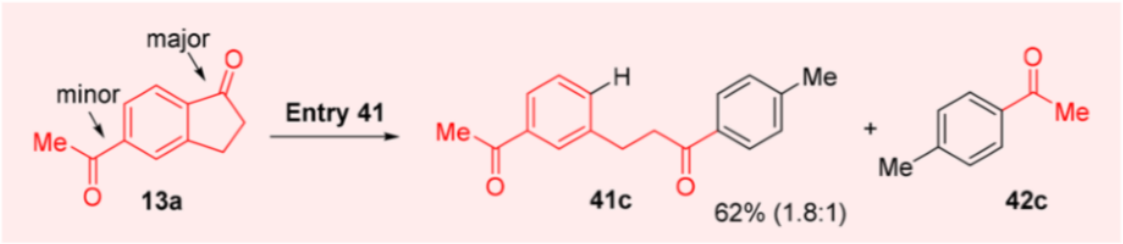
Entry 38, 64% (79% brsm)

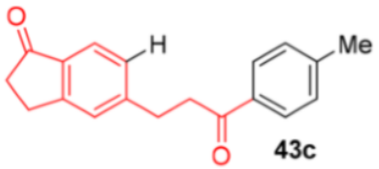


Entry 39, 41% (76% brsm)

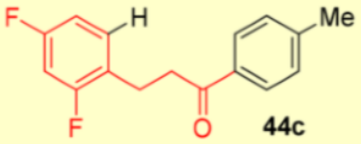


Entry 40, 24% (73% brsm)

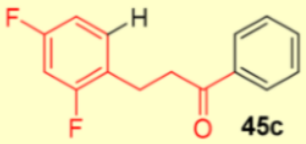




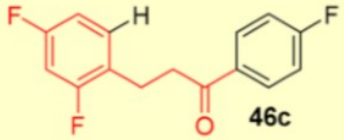
Entry 42, 47% (51% brsm)



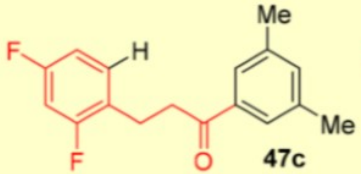
Entry 43, 75% (86% brsm)



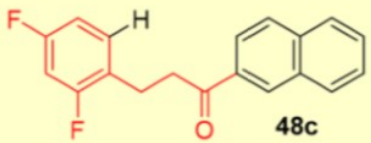
Entry 44, 72% (86% brsm)



Entry 45, 66% (86% brsm)



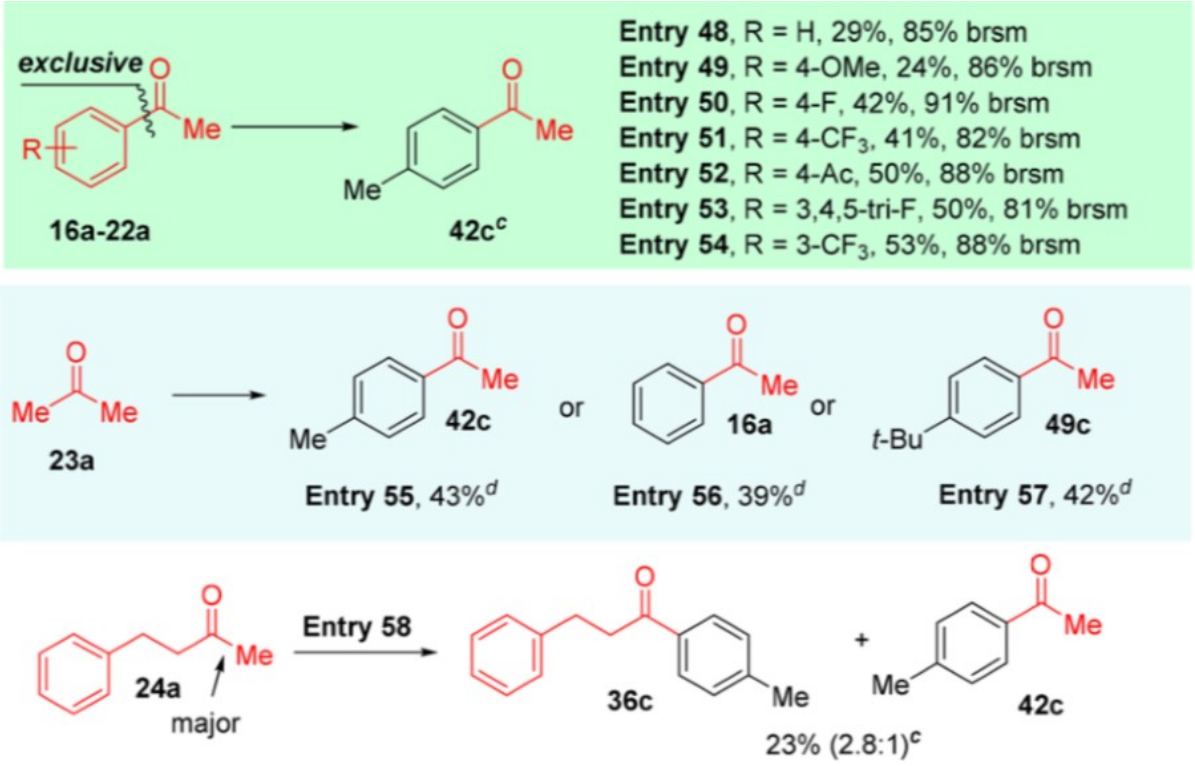
Entry 46, 70% (83% brsm)



Entry 47, 74% (86% brsm)

Dong, G. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 5347.

Scope of acyclic ketones

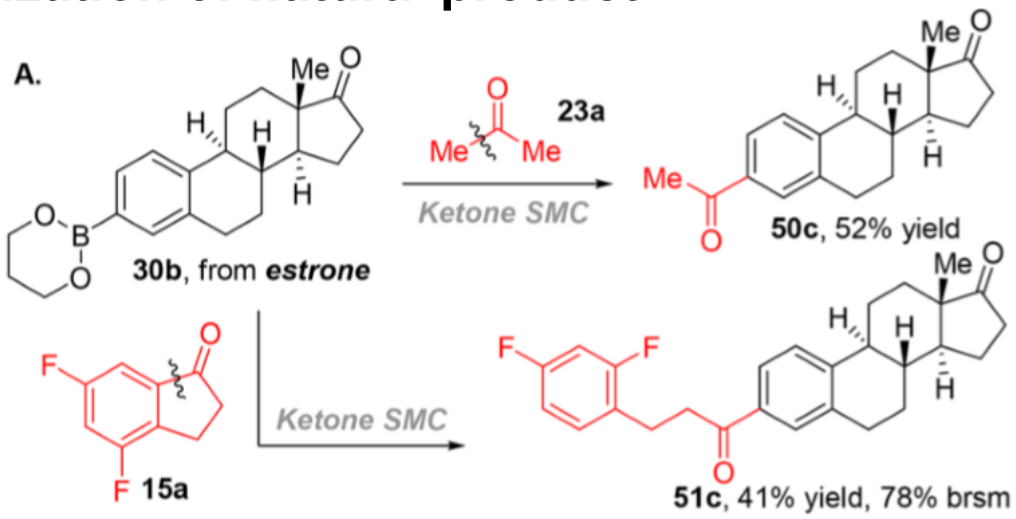


Even acyclic bond can be activated.

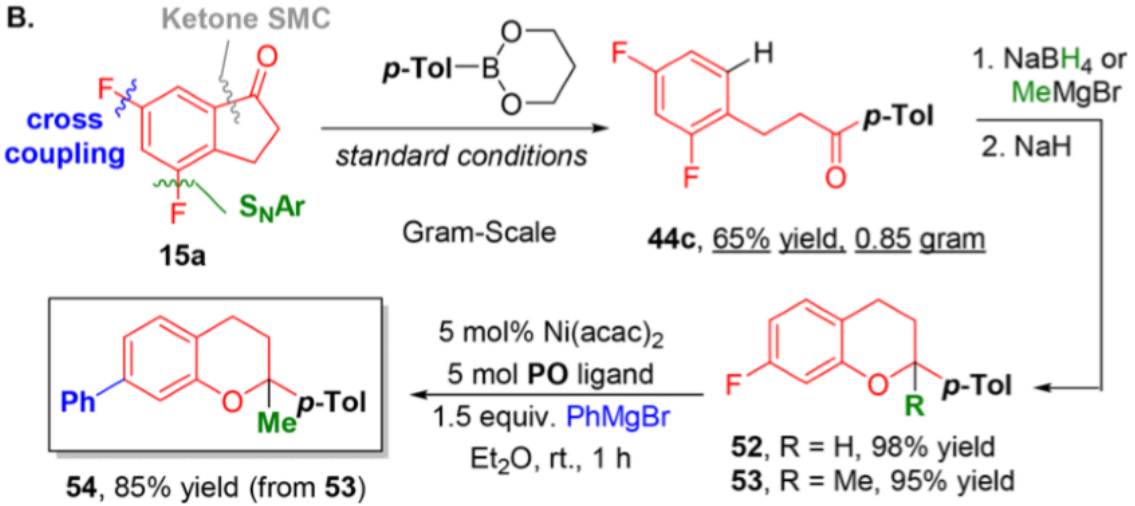
Dong, G. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 5347.

Synthetic utility

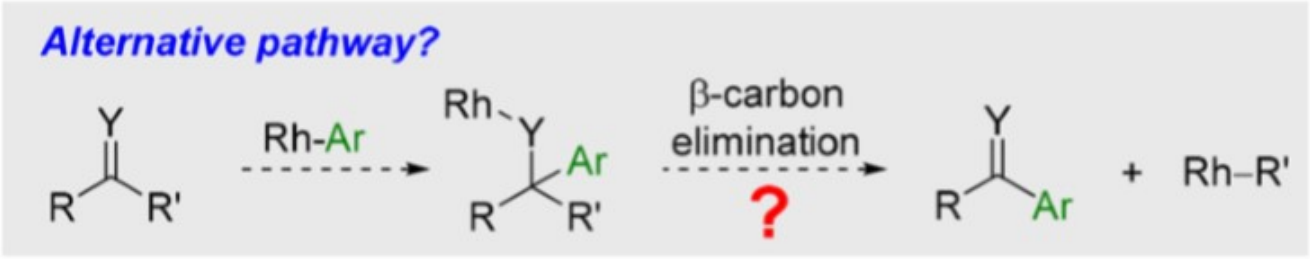
- **Deriatization of natural product**



- **Scalability and chromane synthesis**



Mechanistic insight

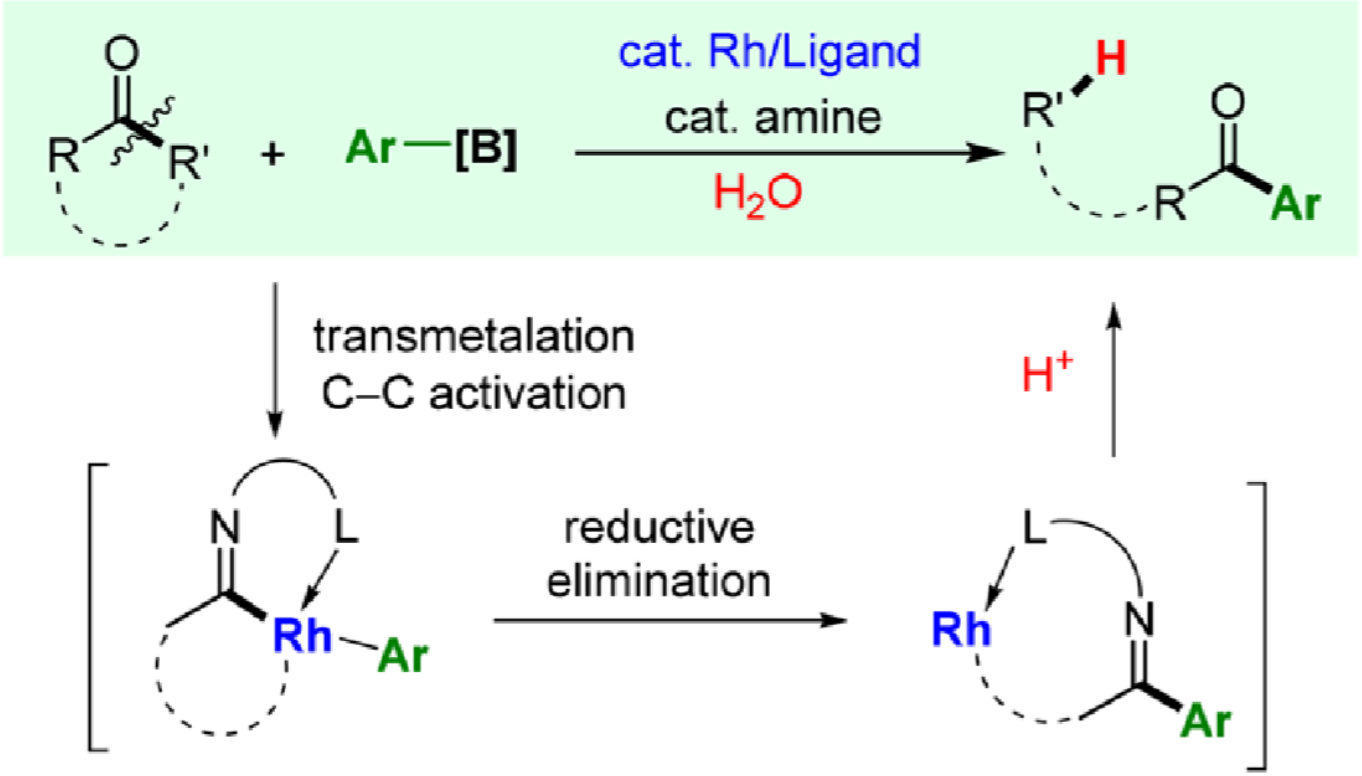


cf. Murakami, M. *et al*. *Org. Lett.* **2004**, *6*, 1257.

- ***β*-carbon elimination pathway is denied.**

Dong, G. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 5347.

Suzuki-Miyaura coupling type reaction



- **Even 5 or 6-membered ring and acyclic bond can be activated.**

Dong, G. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 5347.

Summary

- **Achievement**
  - **Unstrained (5, 6-membered ring or acyclic) C-C bond can be cleaved.**
  - **C-H activation and SMC**

- **Future perspective**
  - **Harsh conditions (Application to complex molecules is difficult.)**
  - **Mainly for ketone substrates**