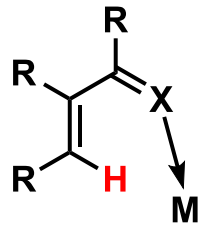
C-H activation using Metal-Organic Cooperative Catalysis

2016/2/27 B4 Hirano Ryo

Contents

1. Introduction

C-H activation using intramolecular Directing-Group(DG)

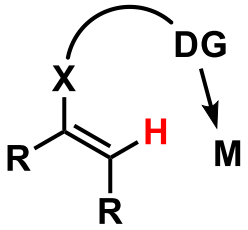


2. Metal-Organic Cooperative Catalysis (MOCC)

Examples

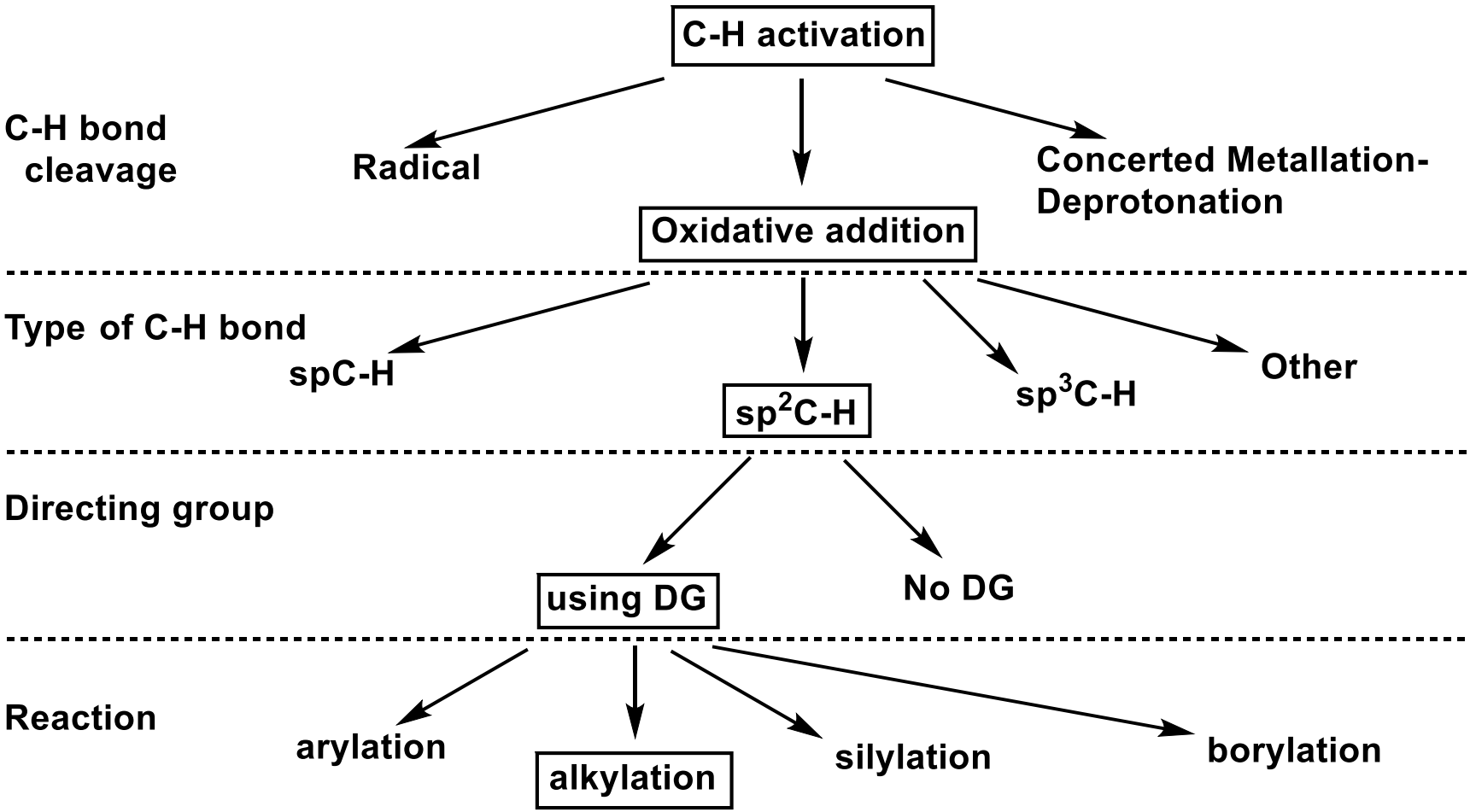
Ketone-α-H activation by MOCC

Mechanism



3. Summary

Contents

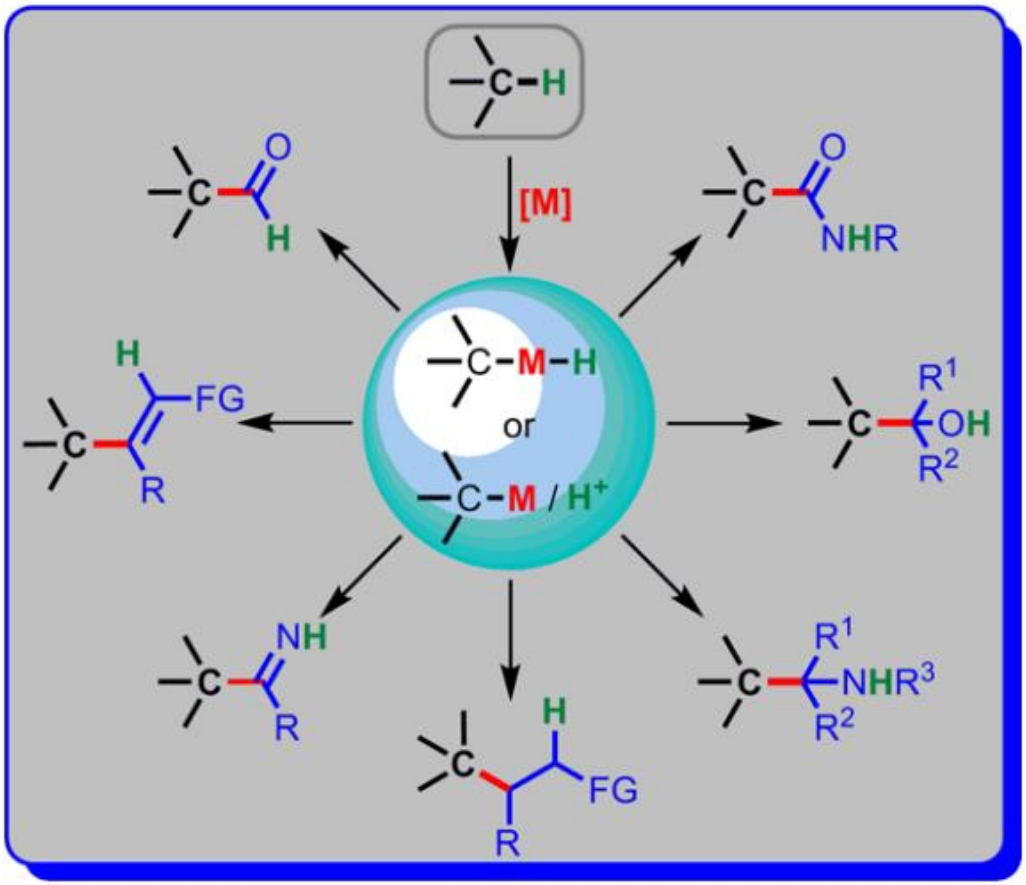

C-H activation
C-H bond cleavage
Radical
Oxidative addition
Concerted Metallation-Deprotonation
Type of C-H bond
spC-H
sp2C-H
sp3C-H
Other
Directing group
using DG
No DG
Reaction
arylation
alkylation
silylation
borylation

1. Introduction

C-H activation

Very strong synthetic method

- **Short-step**
- **Atom economical**



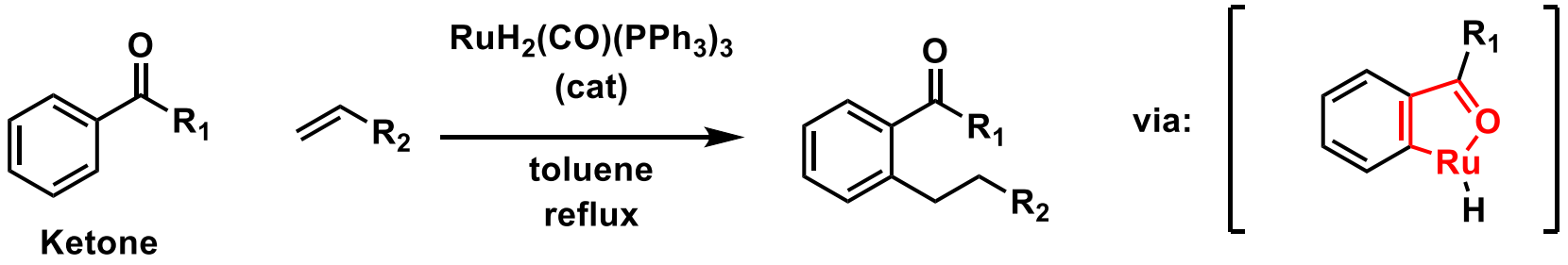
But

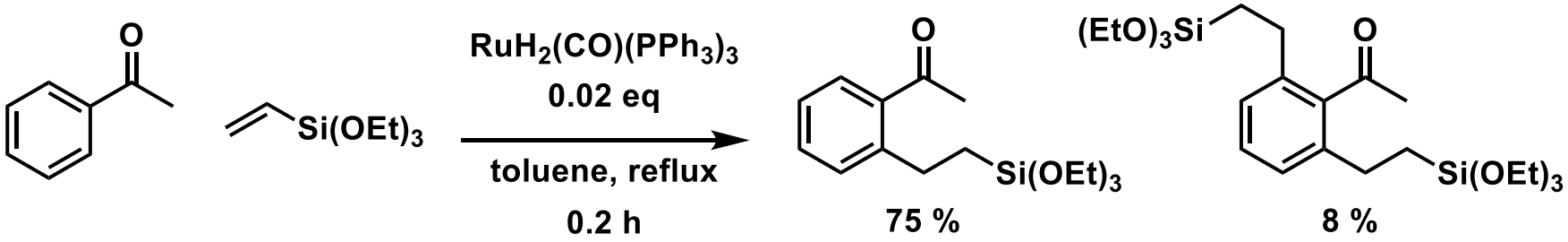
- **Difficult to proceed**
- **Difficult to distinguish C-H bonds**

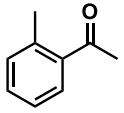
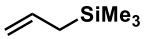
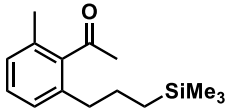
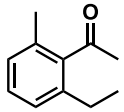
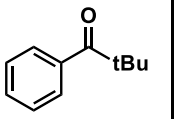
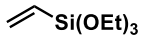
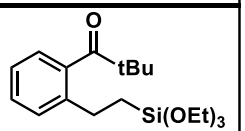
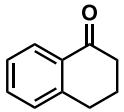
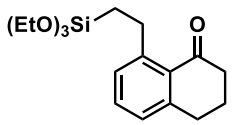
Chem. Rev., **2015**, *115* , 3468–3517

Directing group is effective.

First synthetically useful C-H activation



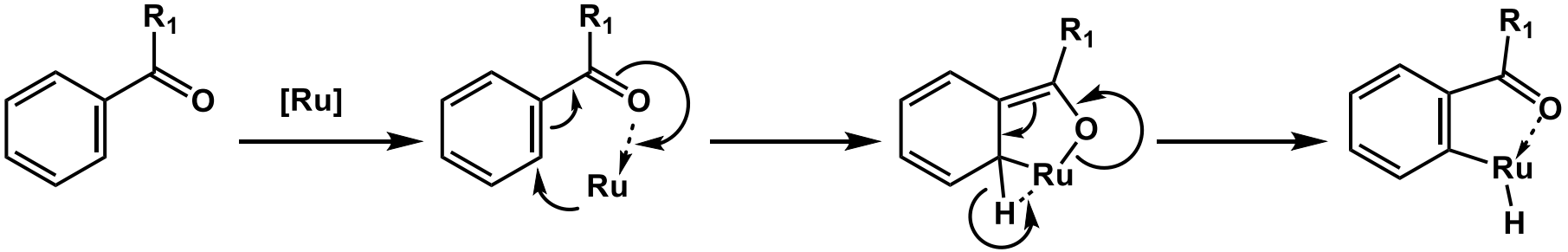


Ketone (A)	Olefin (B)	A:B:cat	Time (h)	Yield (%)	Product
		1:5:0.06	4	100 %	
		1:6:0.02	2	100 %	
		1:1:0.02	0.5	100 %	
		1:1:0.02	0.5	100 %	

Murai *et. al*. *Nature* **1993**, *366*, 529-531.

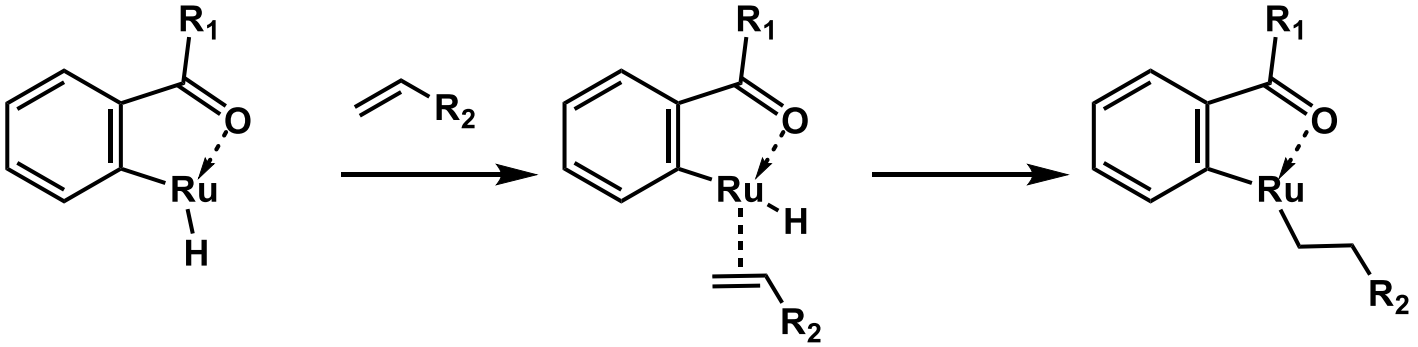
C-H activation –mechanism

Oxidative addition

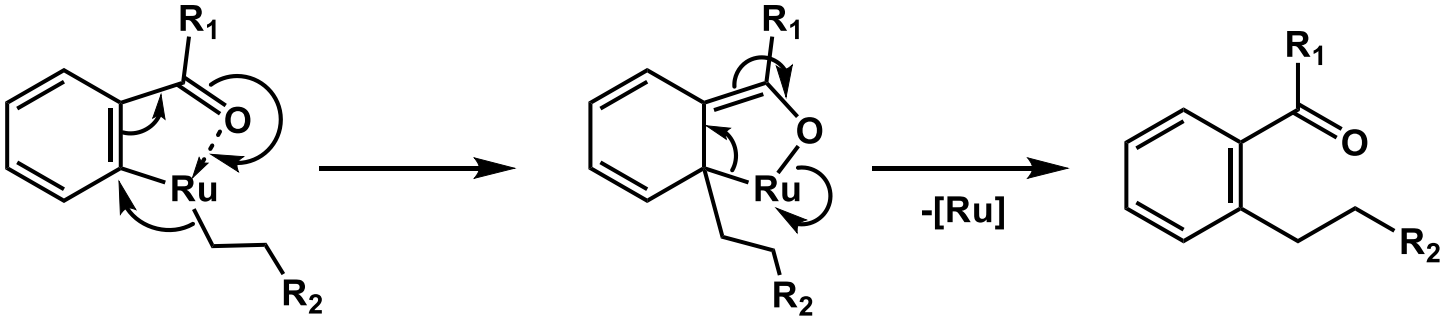


Olefin insertion

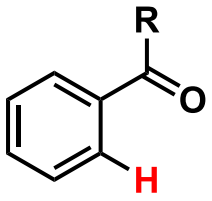
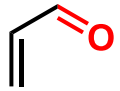
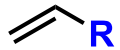
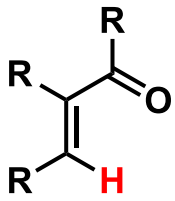
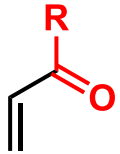
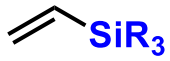
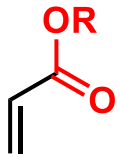
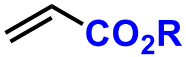
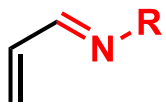
Morokuma *et. al. J. Am. Chem. Soc.* **1998,** *120*, 12692-12693.



Reductive elimination



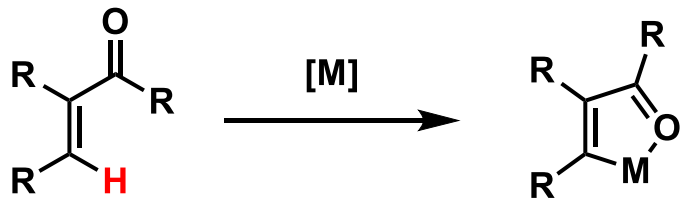
C-H activation –Ex

C-H	substrate	olefin	metal	ligand
 aromatic	 aldehyde		Ru	CO
 olefinic	 ketone		Rh	PR_3
	 ester		Ir	NHC
	 imine			

2. Metal-Organic Cooperative Catalysis (MOCC)

Outer directing group (1)

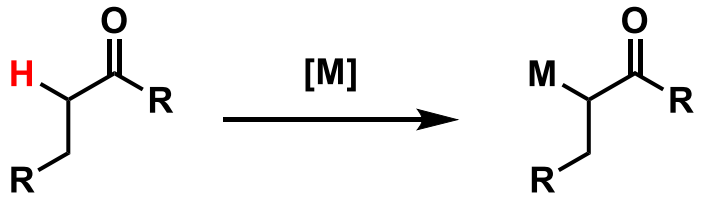
β-H



Possible!

Chelation-assisted

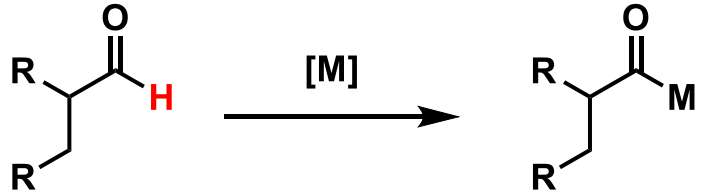
α-H



Possible?

No chelation

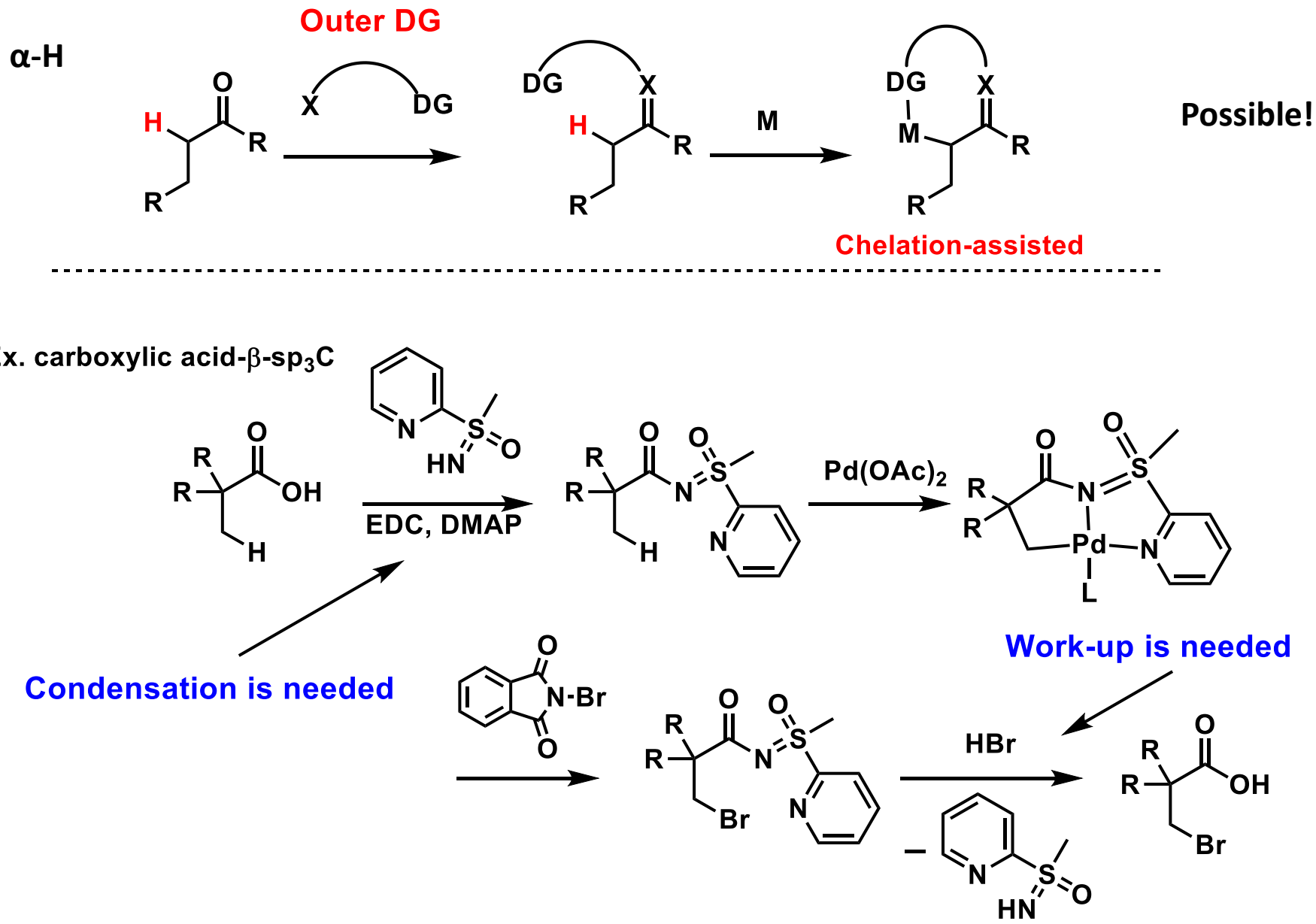
aldehyde-H



Possible?

No chelation

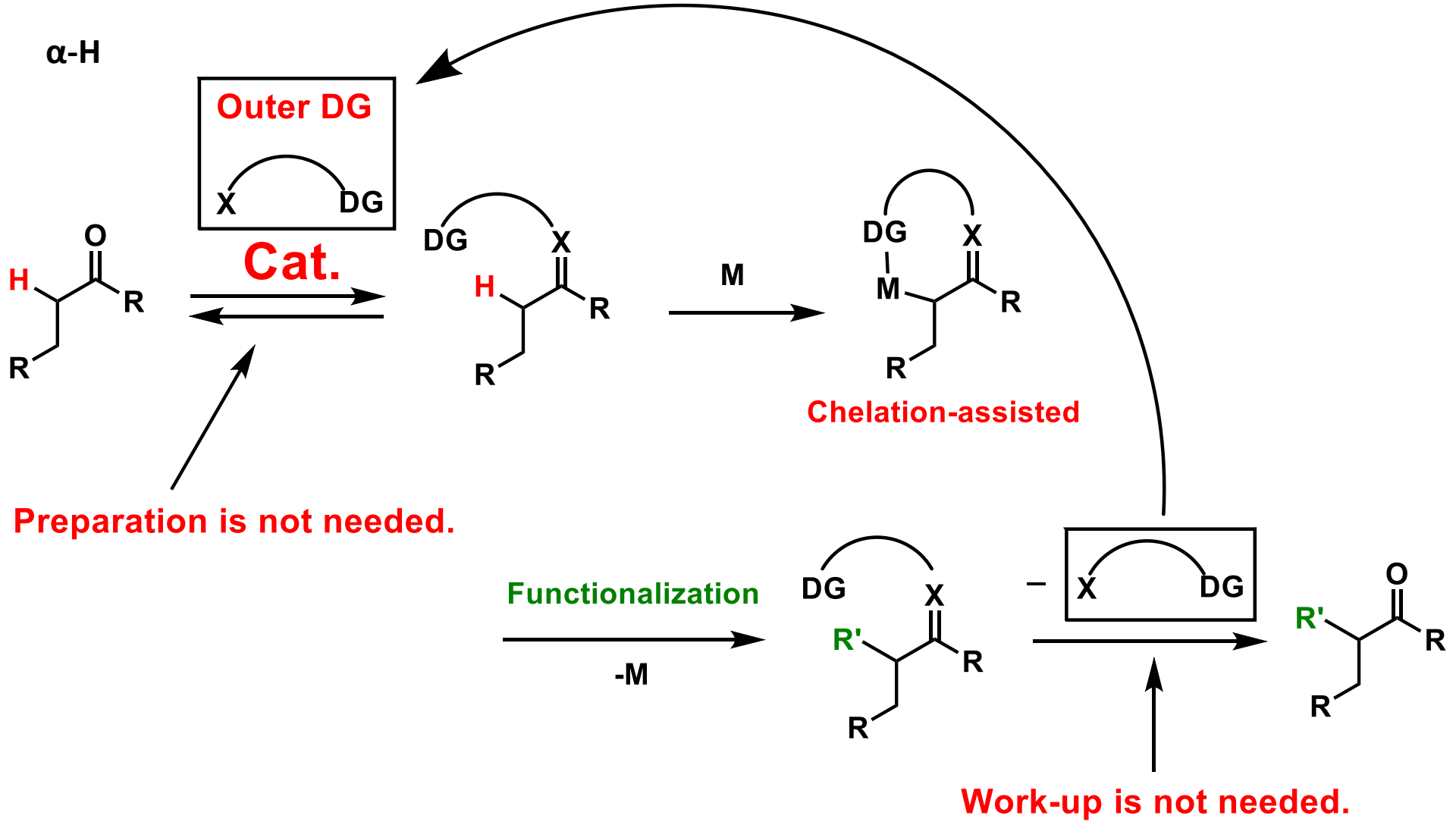
Outer directing group (2)



Sahoo *et al. Org. Lett.*, **2014**, *16* , 5258–5261.

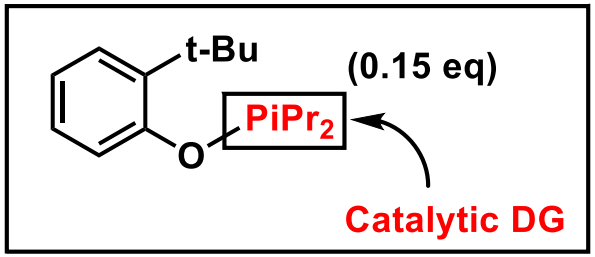
Concept of MOCC

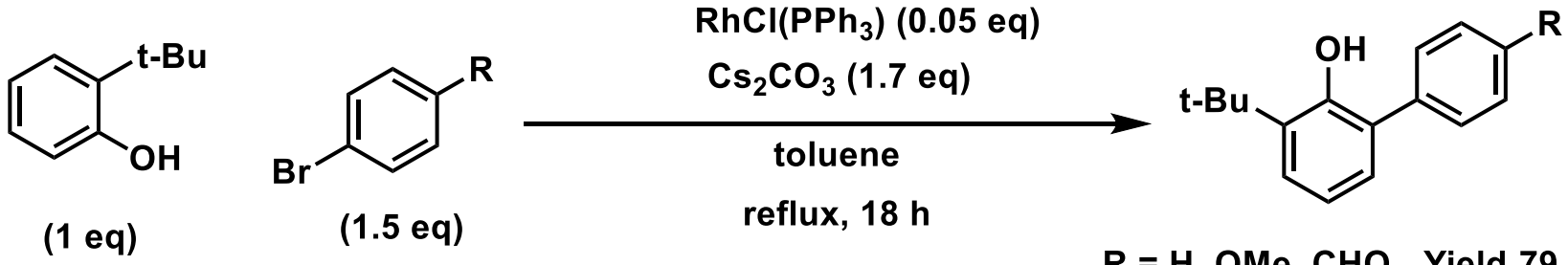
C-H activation using catalytic outer DG



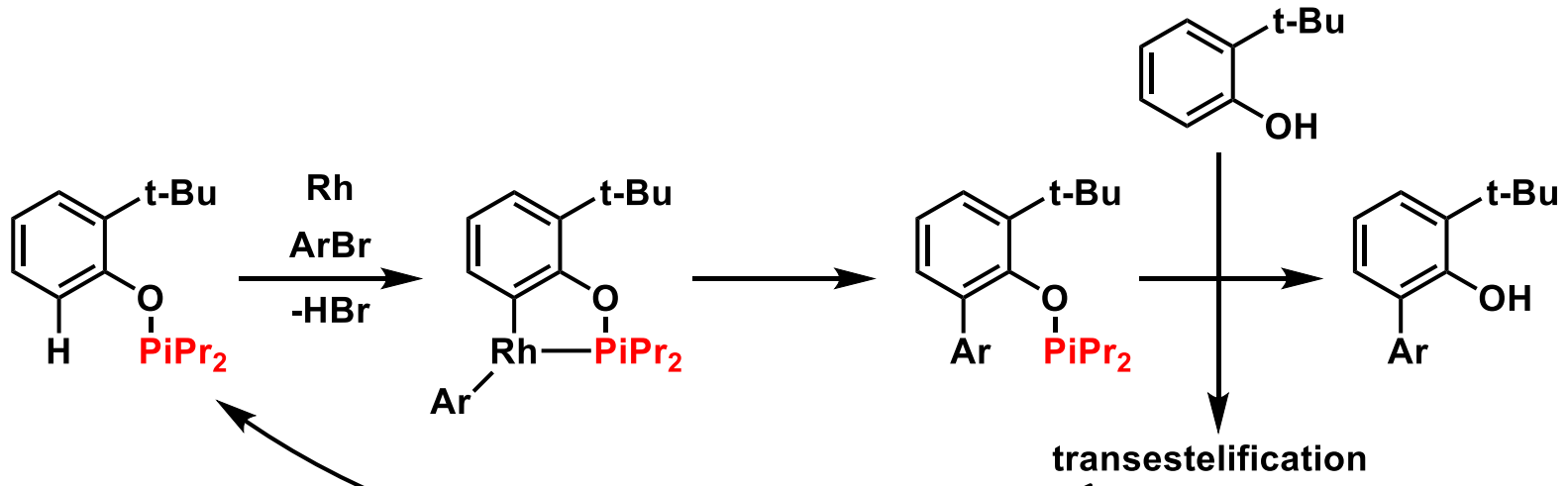
MOCC ex1

Aromatic C-H





R = H, OMe, CHO Yield 79 ~ 96 %



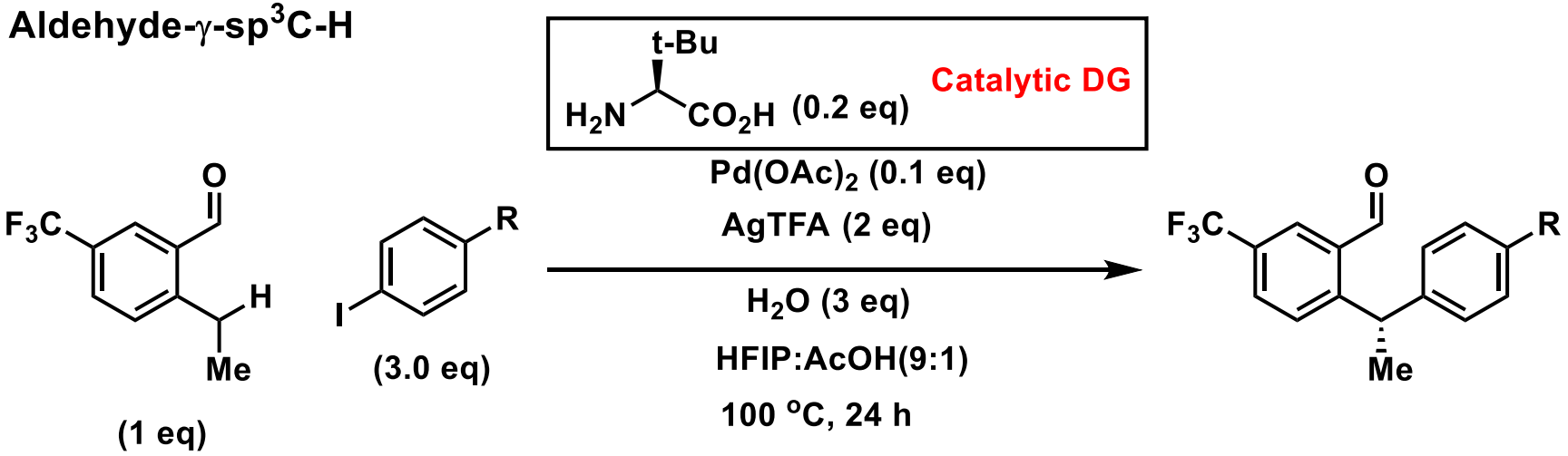
DG is catalytic.

Work-up is not needed.

Bedford *et al. Angew. Chem. Int. Ed*. **2003**, *42*, 112-114.

MOCC ex2

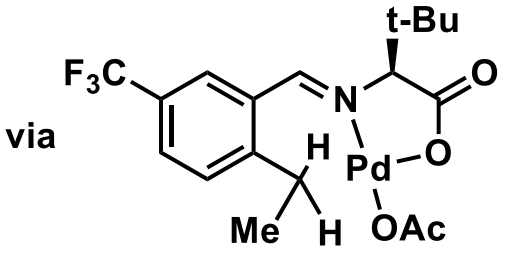
Aldehyde-γ-sp^{3}C-H



R = Me, F, Cl, Br, CO_2Me **Yield 62 ~ 80 %** **er - over 97:3**

---

via



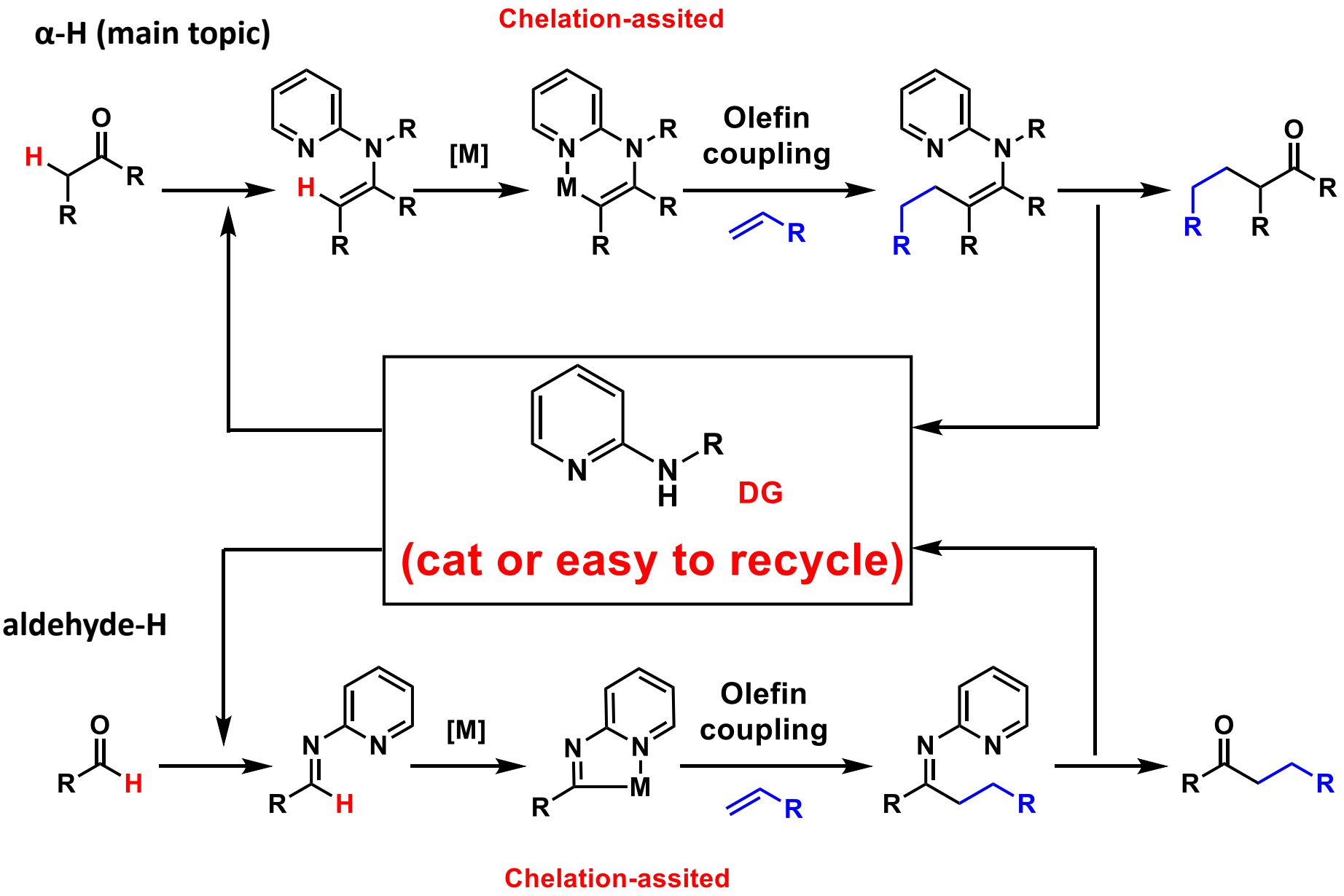
stereoselective.

DG is catalytic.

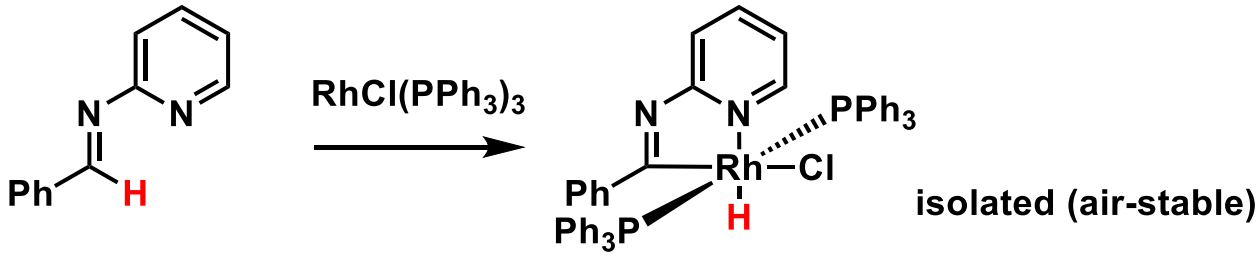
Preparation/work-up is not needed.

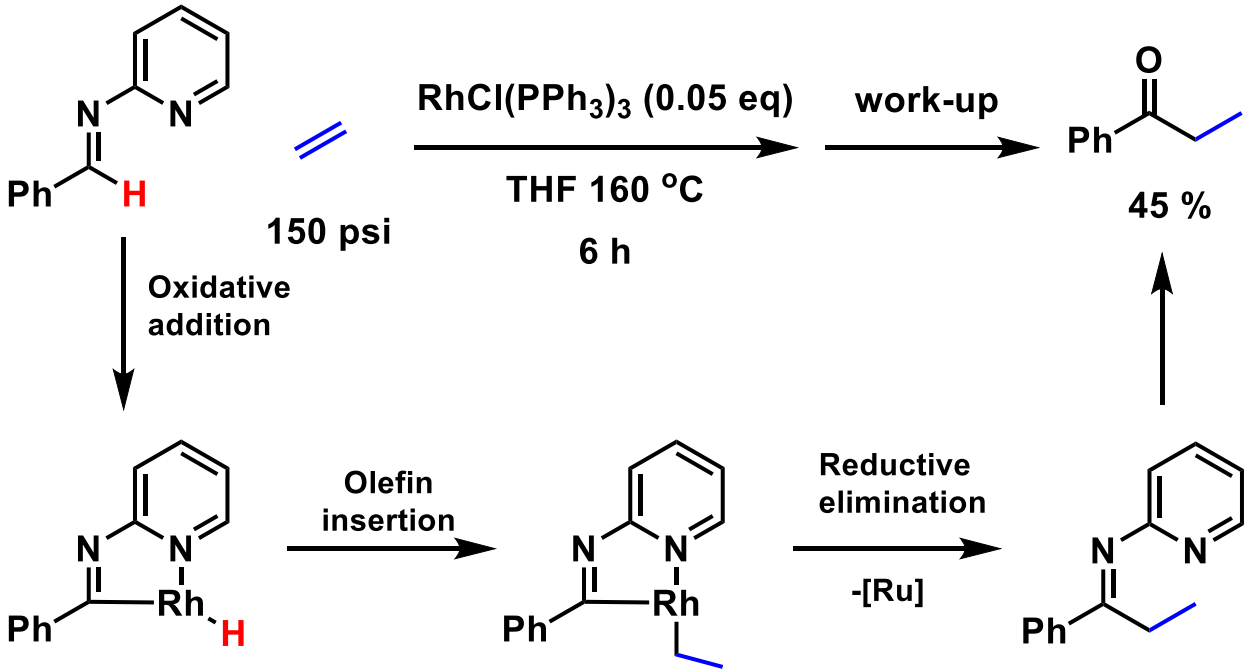
Jin. Q. Yu *et al*. *Science* **2016**, *351*, 252-256.

MOCC -today's topic



MOCC aldehyde-H ex1





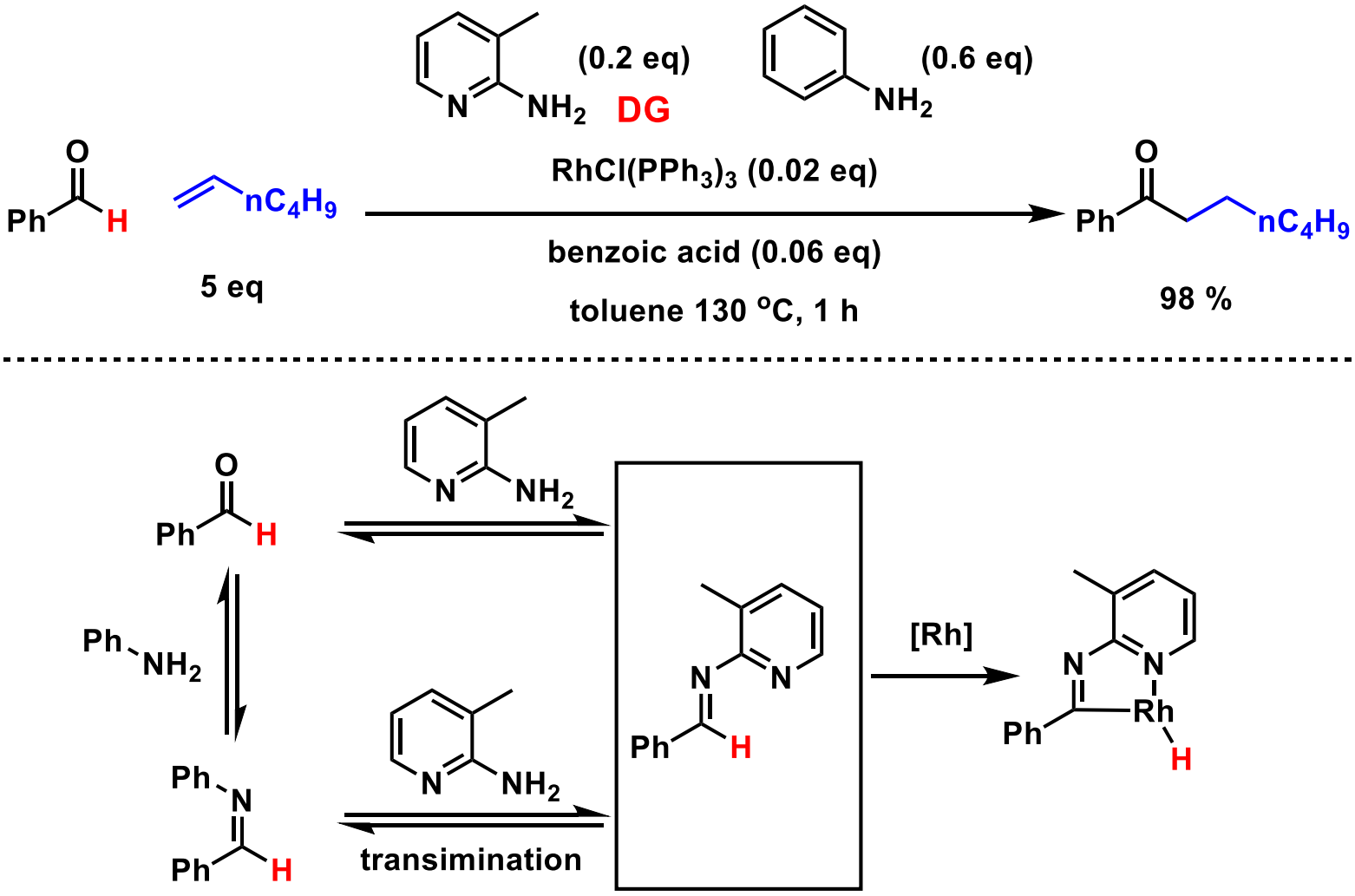
DG is not catalytic.

Imine formation is needed in advance.

Yield is bad.

Suggs *et al. J. Am. Chem. Soc.* **1979**, *101*, 489.

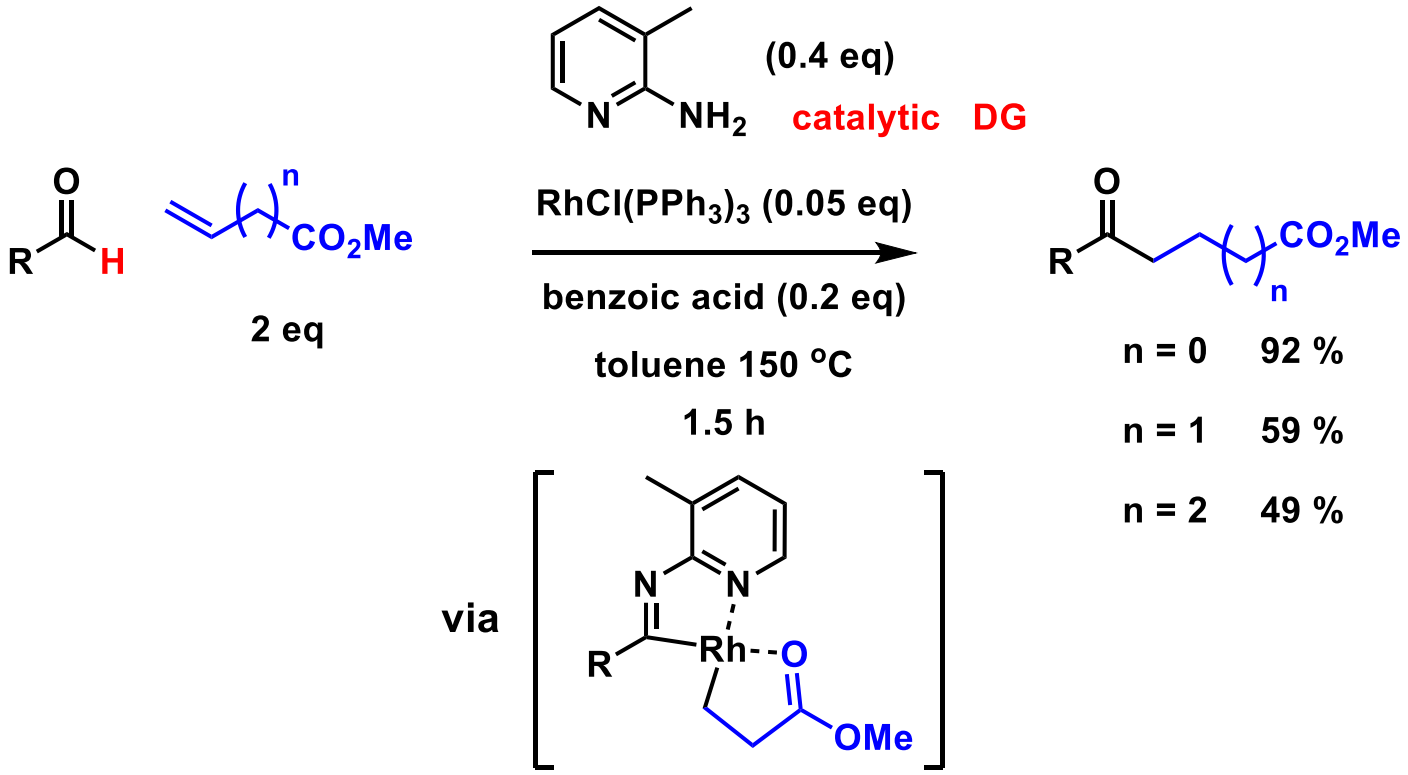
MOCC aldehyde-H ex2



Stoichiometric amount of amine is needed.

Jun *et al*. *Angew. Chem. Int. Ed*. **2000**, *39*, 3070-3072.

MOCC aldehyde-H ex3

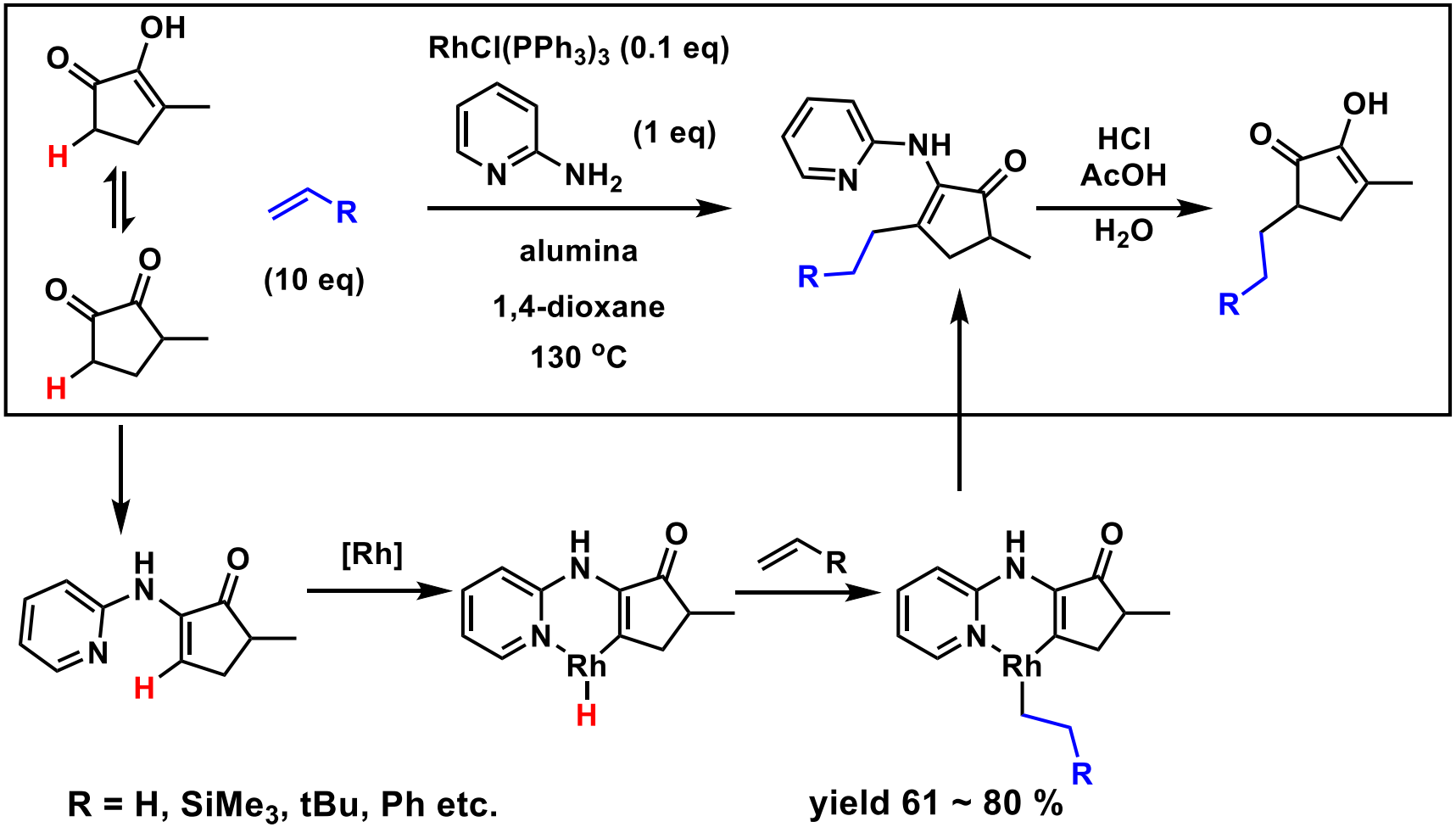


DG is catalytic.

Preparation/work-up is not needed.

Jun *et al. Eur. J. Org. Chem*. **2006**, 2504–2507.

MOCC ketone α-H ex1

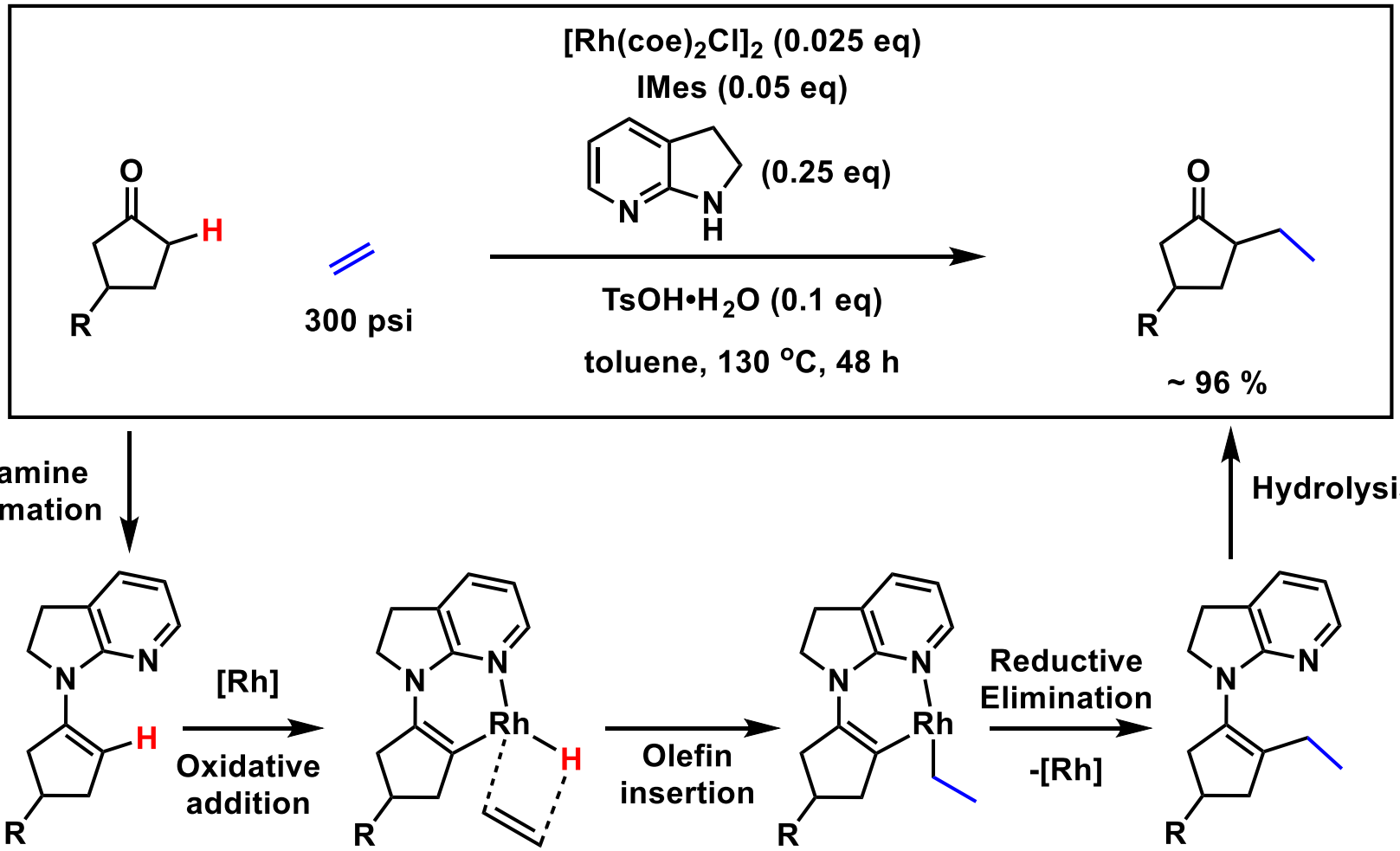


Substrate is limited.

Stoichiometric amount of amine is needed.

Dong *et al. J. Am. Chem. Soc*. **2012**, *134*, 13954-13957.

MOCC ketone α-H ex2(main topic)



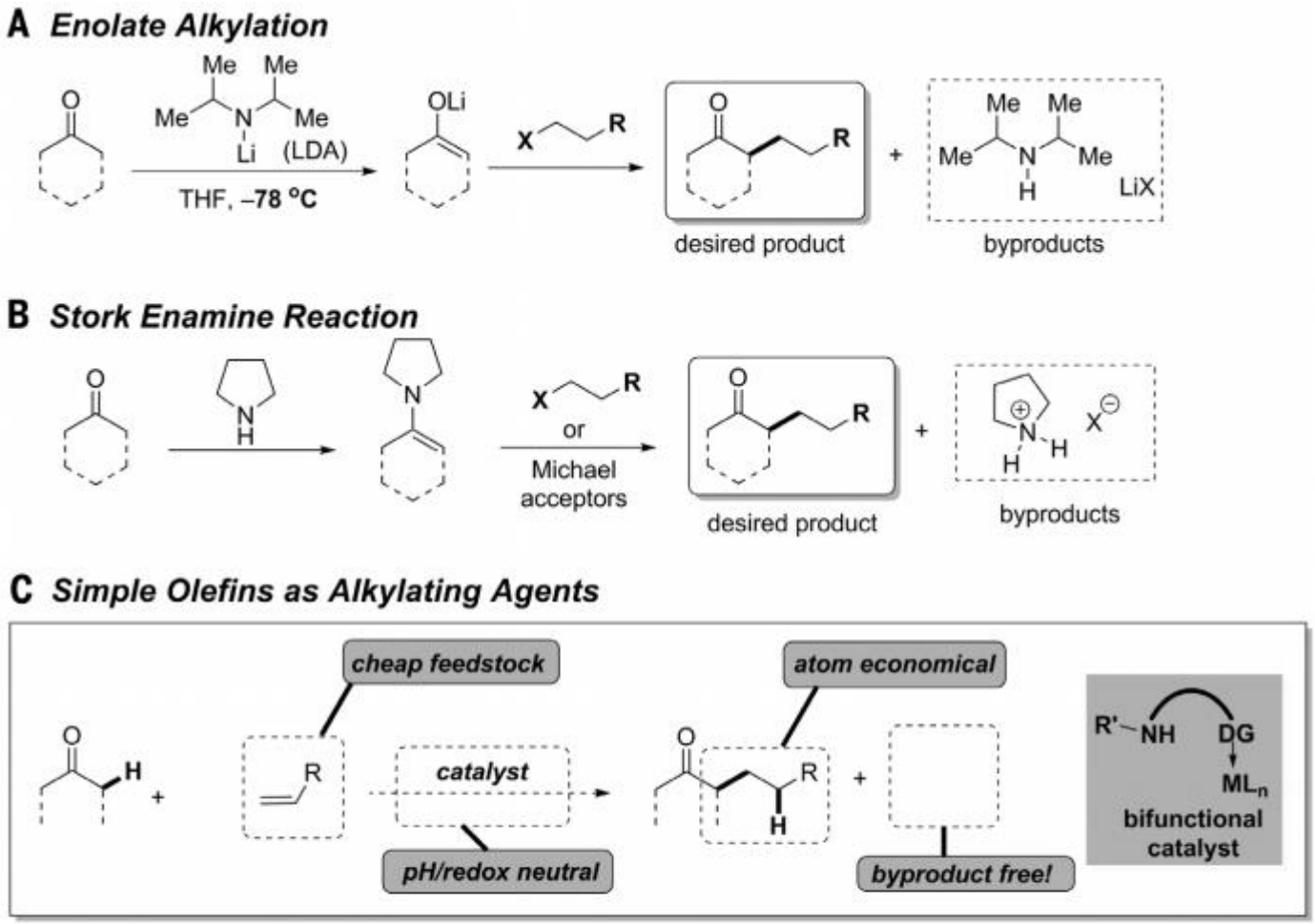
Regioselective.

DG is catalytic.

Preparation/work-up is not needed.

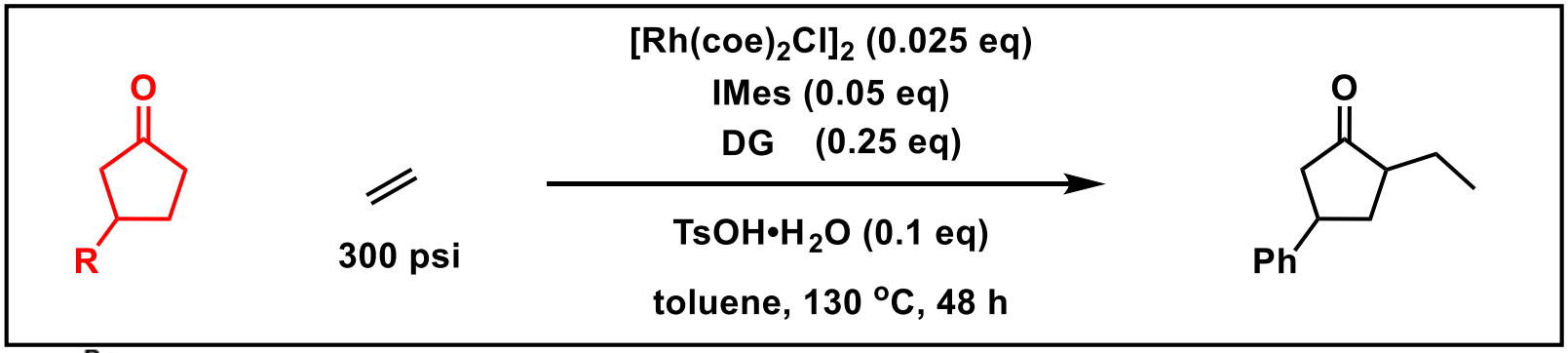
Dong *et al*. *Science* **2014**, 68-72.

Usefulness of MOCC –vs. aldol-

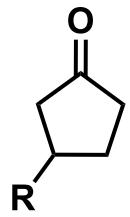


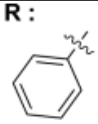
	$H_2C=CH_2$		ICH_2CH_3	$BrCH_2CH_3$
estimated cost:	$1/kg (ICIS market price)	**VS**	$280/kg (Aldrich)	$55/kg (Aldrich)
	$0.028/mol		$43.7/mol	$6.0/mol
molecular weight:	**28**		**156**	**109**

α-H MOCC -Ketone substrate

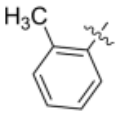


R :

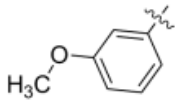




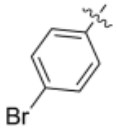
3a, 82%
1.7:1 dr



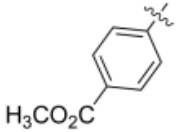
3b, 67%
1.6:1 dr



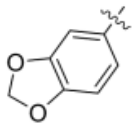
3c, 78%
1.8:1 dr



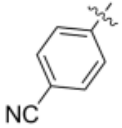
3d, 71%
2.0:1 dr



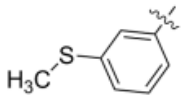
3e, 71%
2.0:1 dr



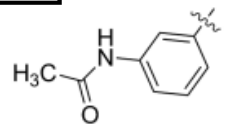
3f, 74%
1.8:1 dr



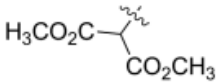
3g, 75%
2.3:1 dr



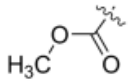
3h, 60%
1.8:1 dr



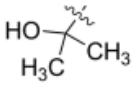
3i, 84%
1.9:1 dr



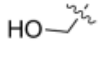
3j, 87%
1.6:1 dr



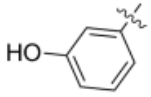
3k, 96%*
1.3:1 dr
2 mmol scale



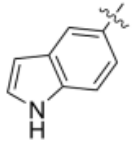
3l, 88%
2.1:1 dr



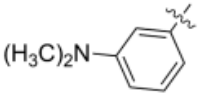
3m, 95%
1.6:1 dr



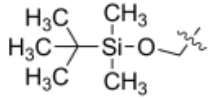
3n, 65%
2:1 dr



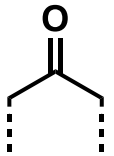
3o, 52%
2:1 dr



3p, 62%
1.3:1 dr



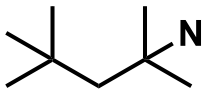
3q, 62%
1:1 dr



1 mL

= 8.5~11 mmol

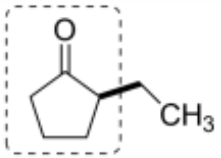
300 psi



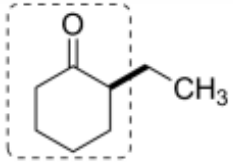
2,4,4-trimethylpentan-2-amine (0.1mmol)

[Rh(coe)2Cl]2 (0.005 mmol)
IMes (0.01 mmol)
DG (0.2 mmol)

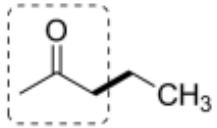
TsOH•H2O (0.02 mmol)
neat, 130 °C, 48 h



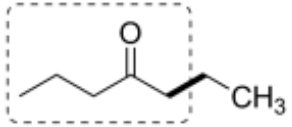
3u
TON 110§



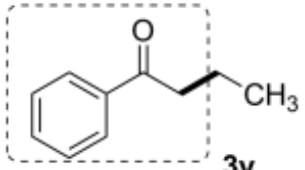
3v
TON 15‖



3w
TON 16‖

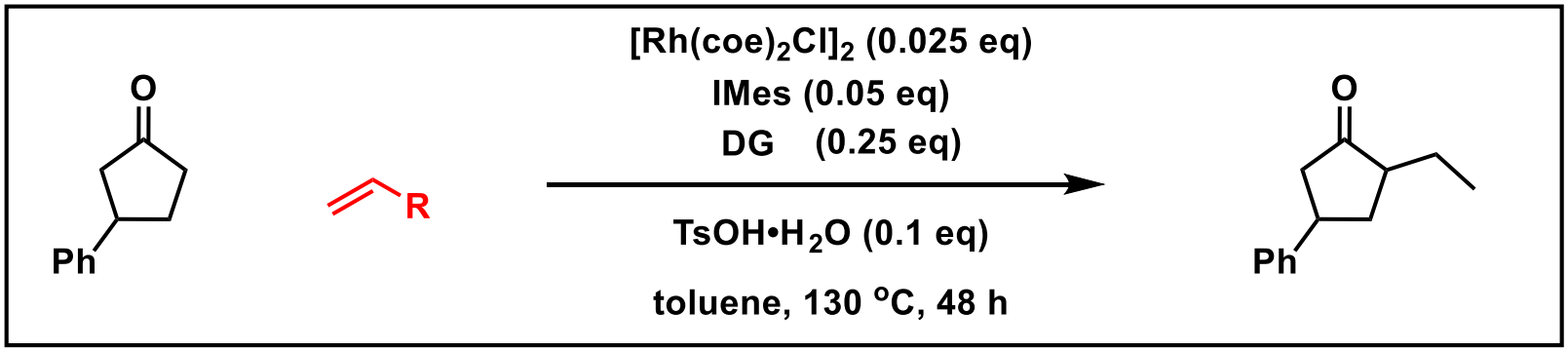


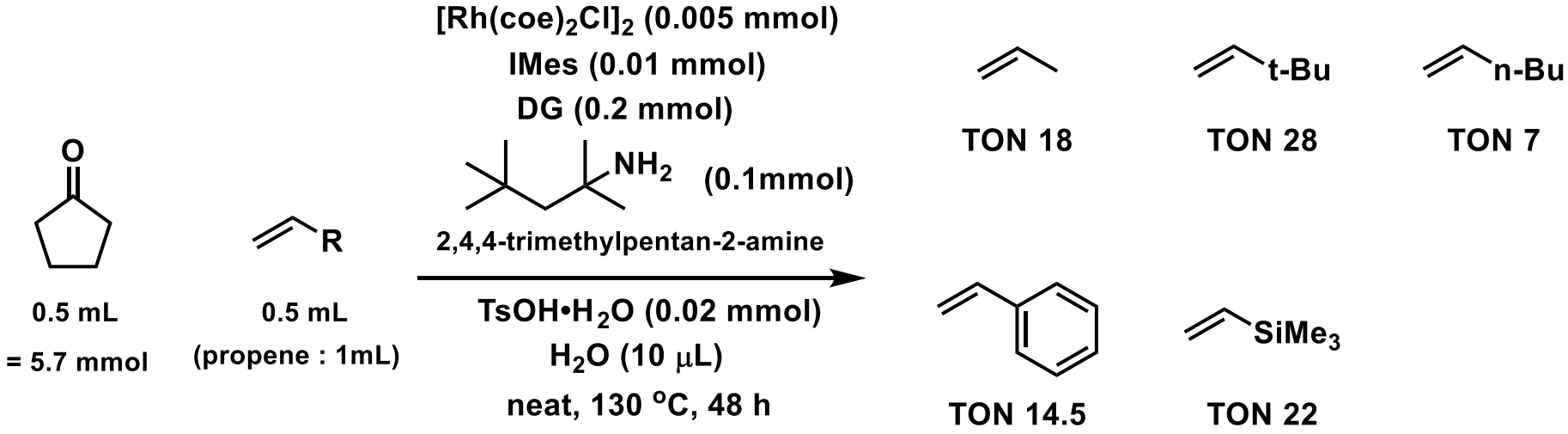
3x
TON 20‖



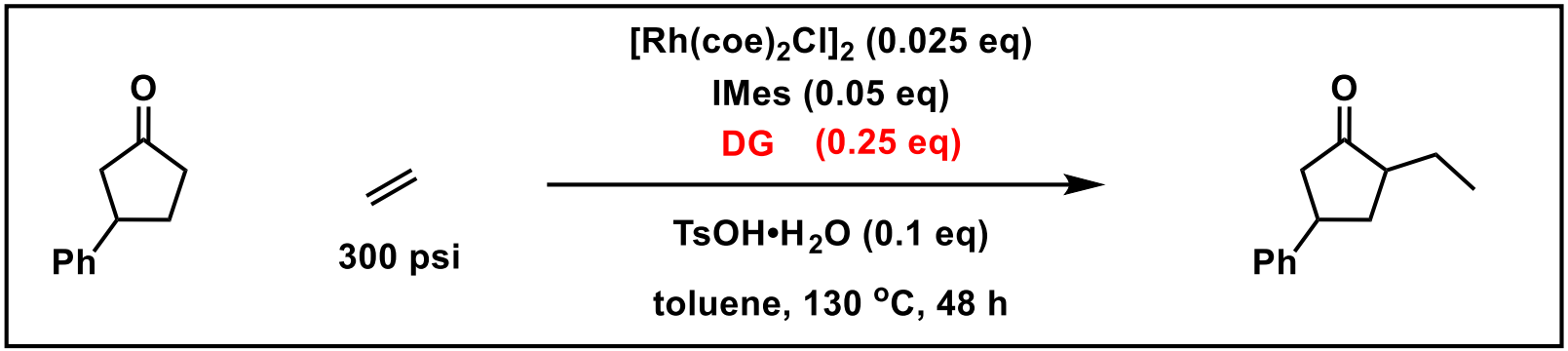
3y
TON 37‖

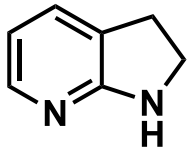
α-H MOCC -Olefin



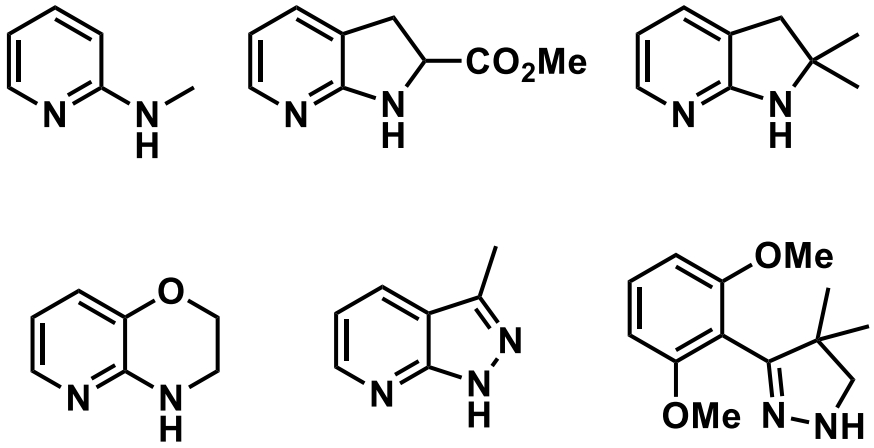


α-H MOCC –Direction group



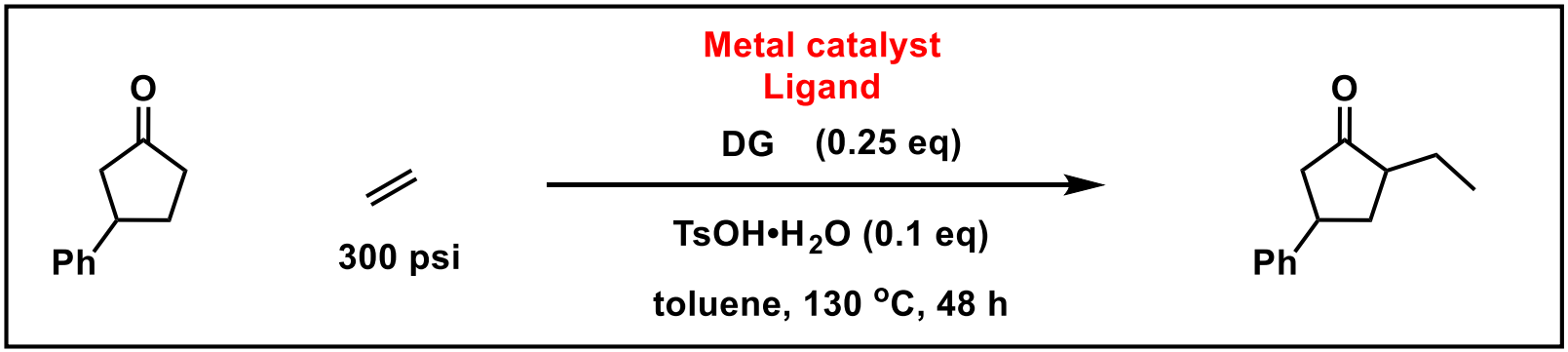


82 %

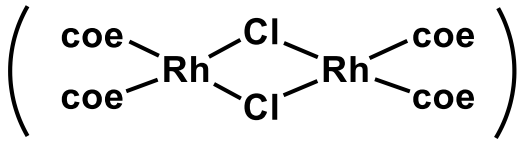


0 %

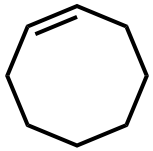
α-H MOCC -Ligand



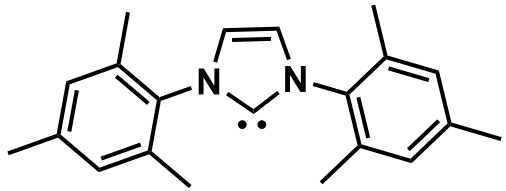
$[Rh(coe)_2Cl]_2$ (0.025 eq) IMes (0.05 eq)	82 %
$RhCl(PPh_3)$ (0.05 eq)	37 %



coe =

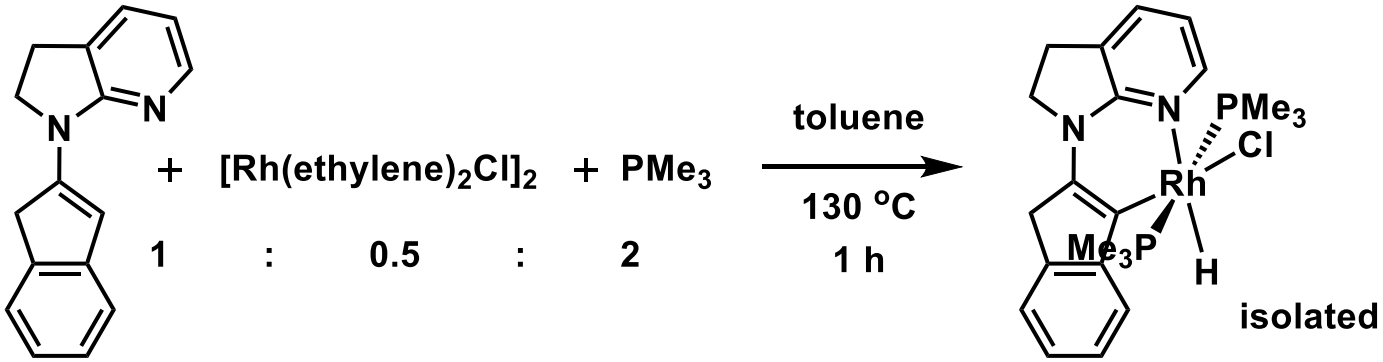


IMes =

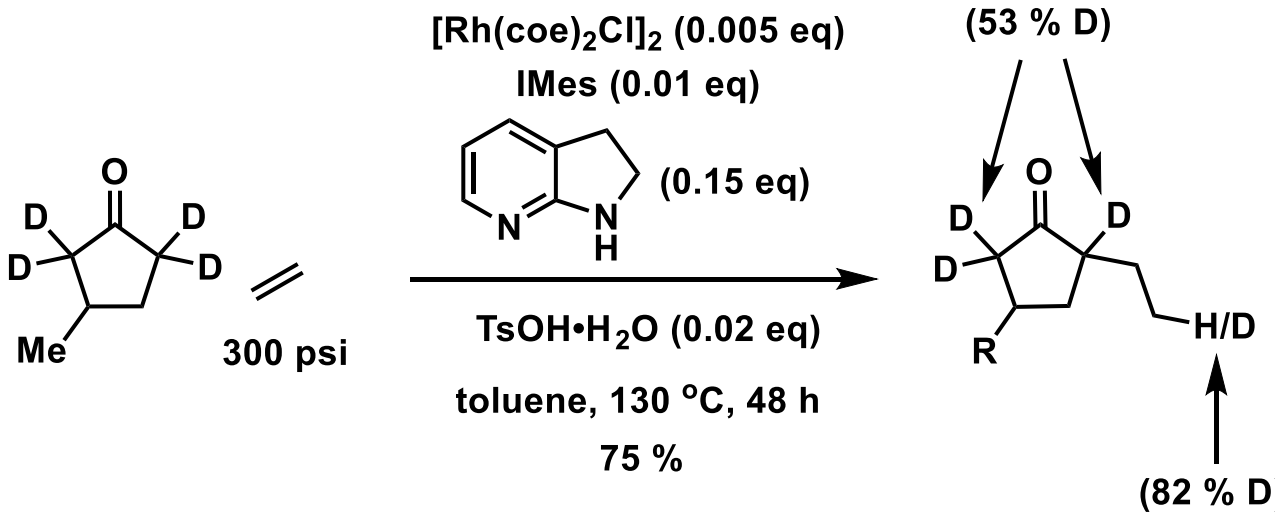


1,3-dimesityl-1*H*-imidazol-3-ium-2-ide

α-H MOCC -Mechanistic insight

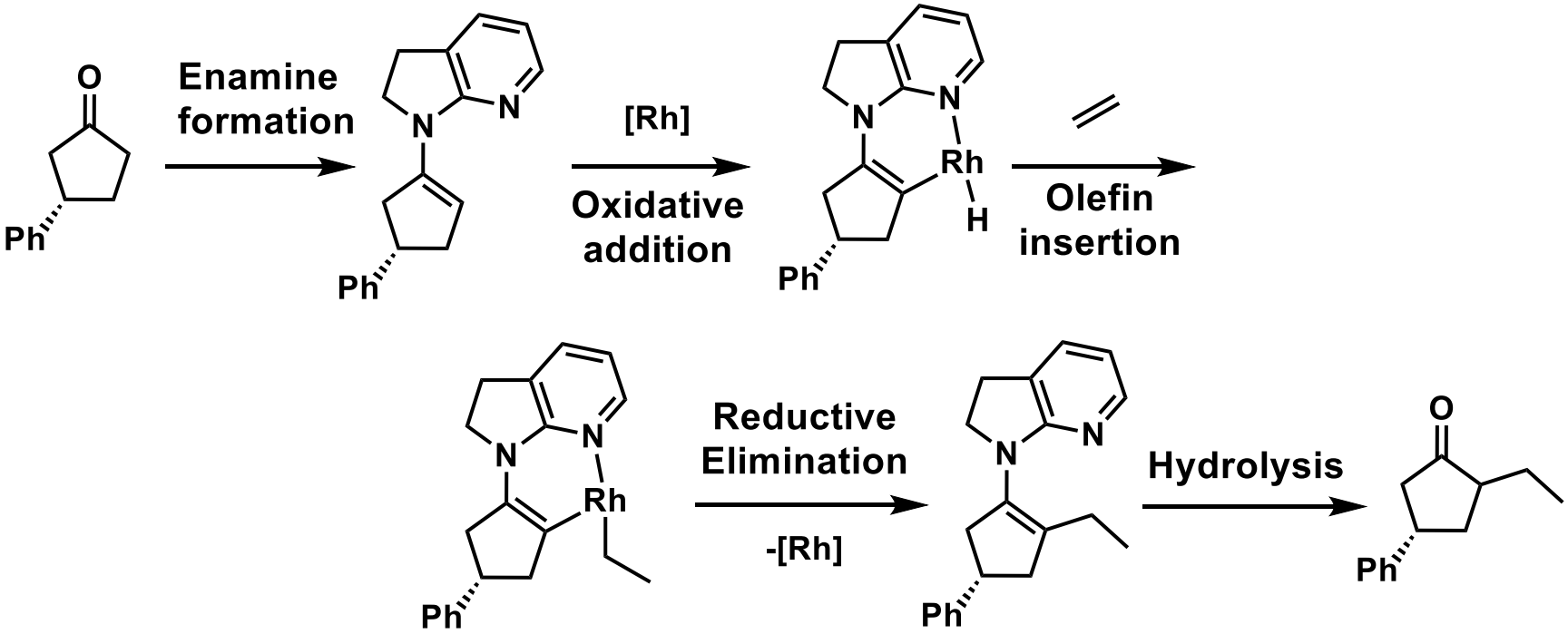


Oxidative addition occurs.



Olefin insertion occurs as expected.

α-H MOCC -Mechanism

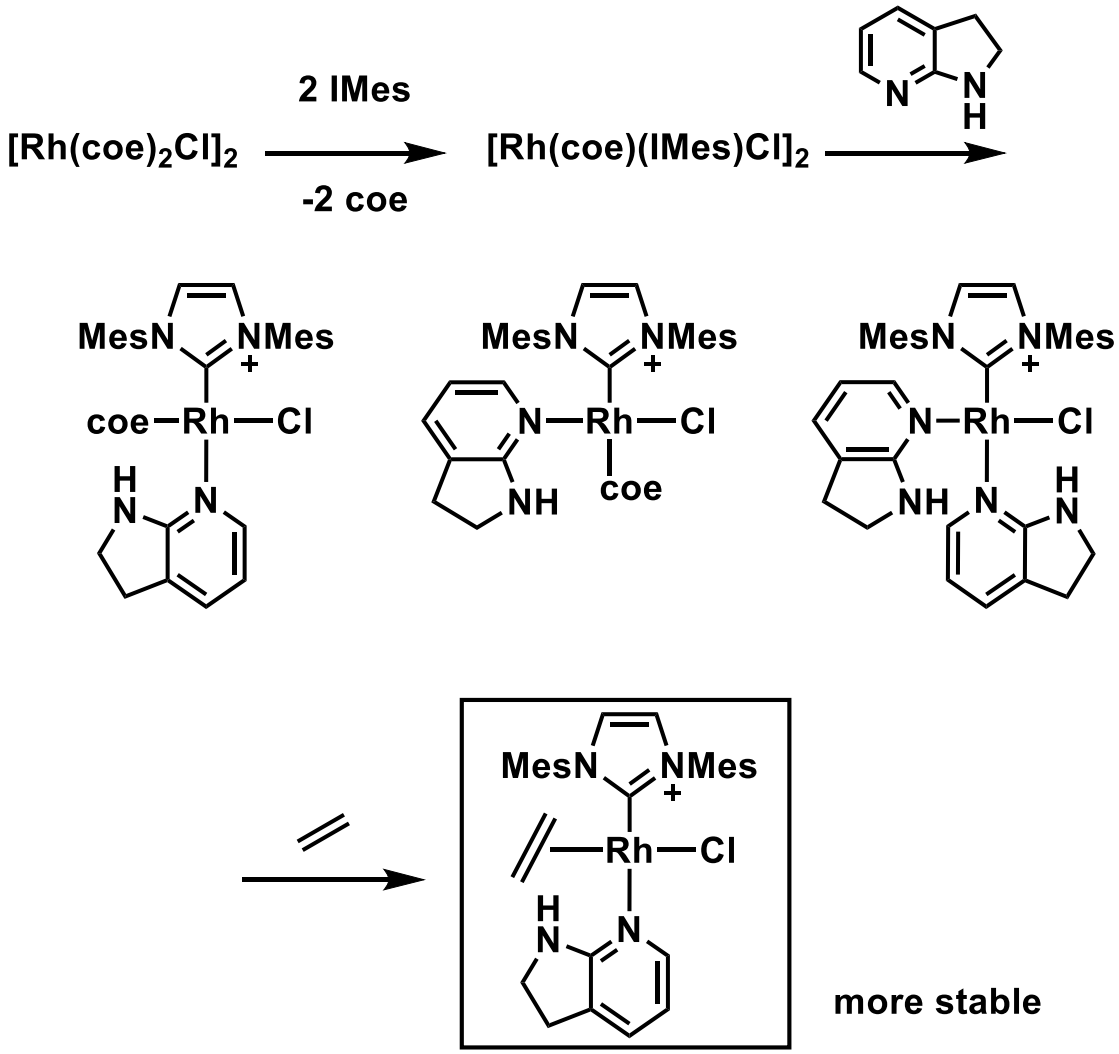


How does reaction proceeds?

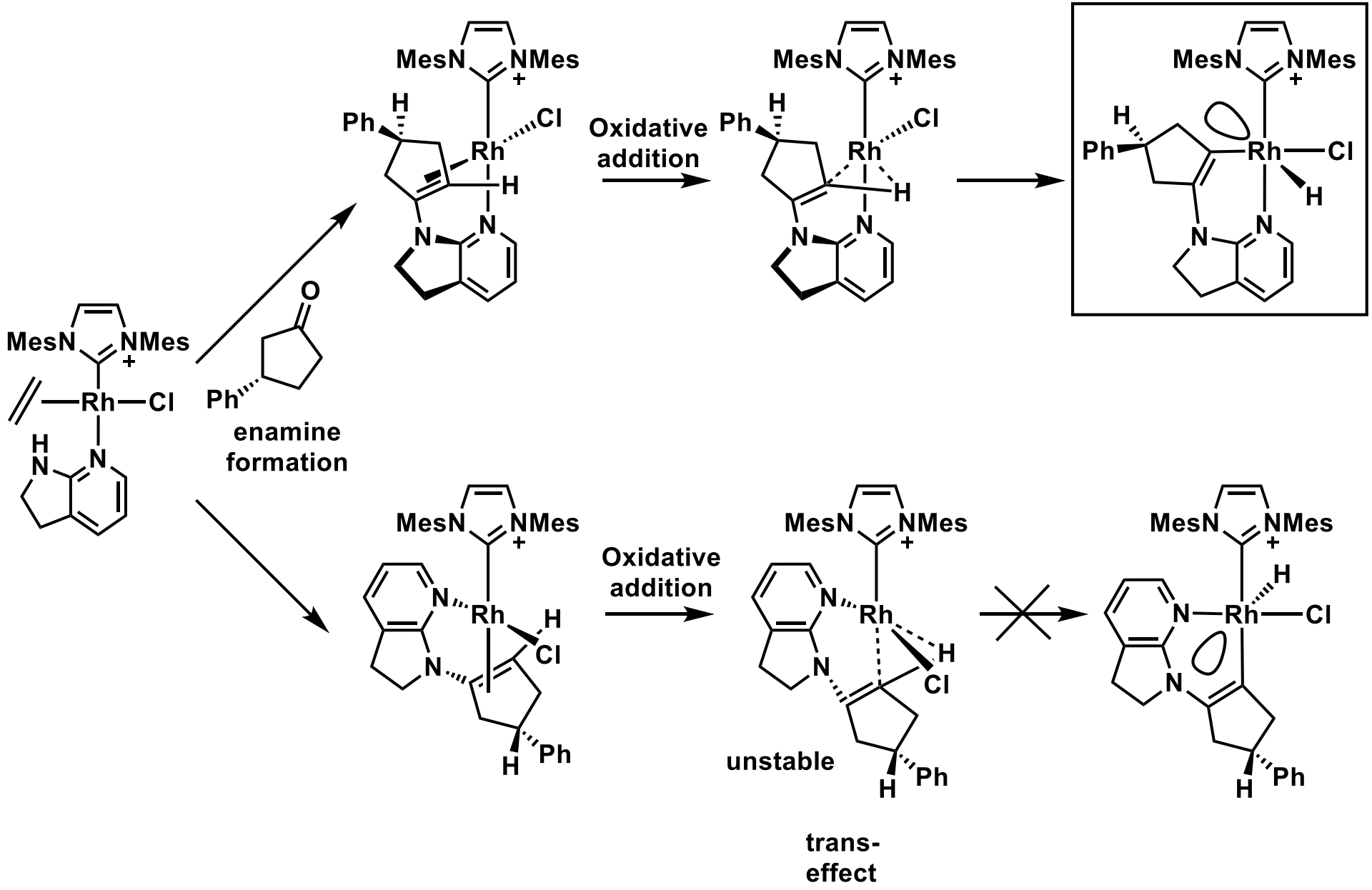
Wang *et al. J. Am. Chem. Soc*. **2015**, *137*, 6279-6291.

Reaction mechanism was investigated by DFT computations.

α-H MOCC –Mechanism : SM of catalytic cycle

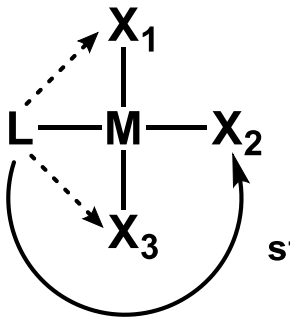


α-H MOCC –Mechanism : oxidative addition



α-H MOCC –Mechanism : oxidative addition : trans-effect

trans-effect : Stability of metal-ligand bond is influenced by its trans-ligand

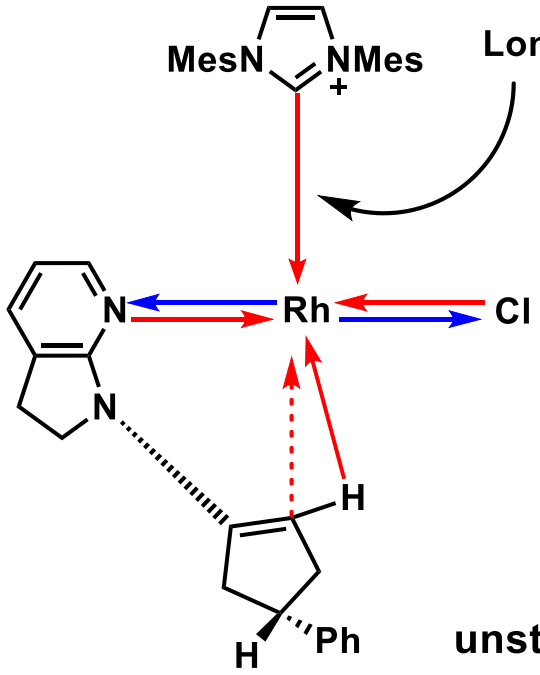


strong influence

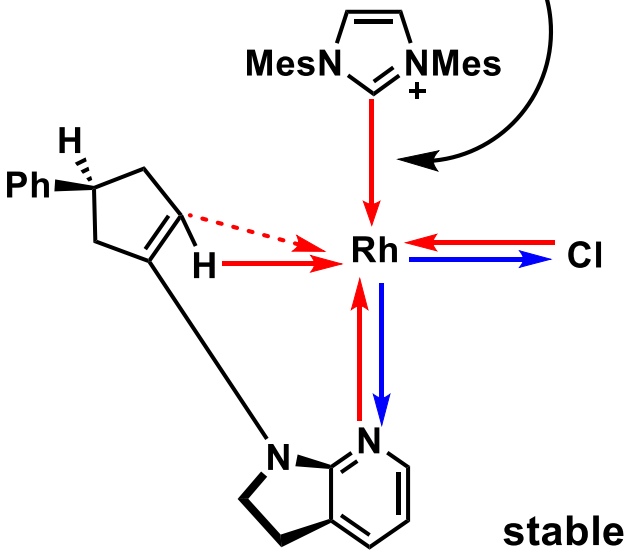
Oxidative addition

σ-donation

π-back donation

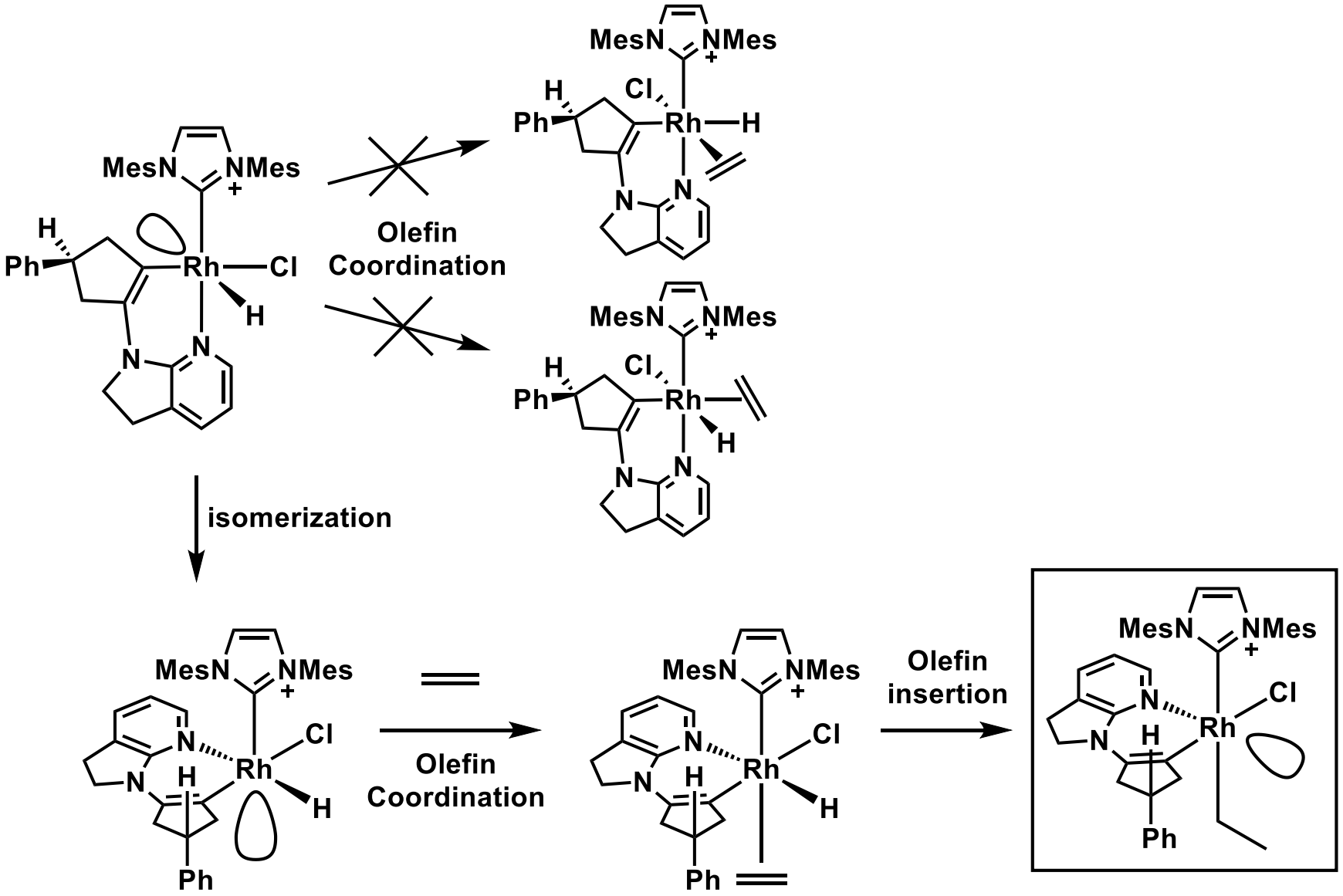


unstable

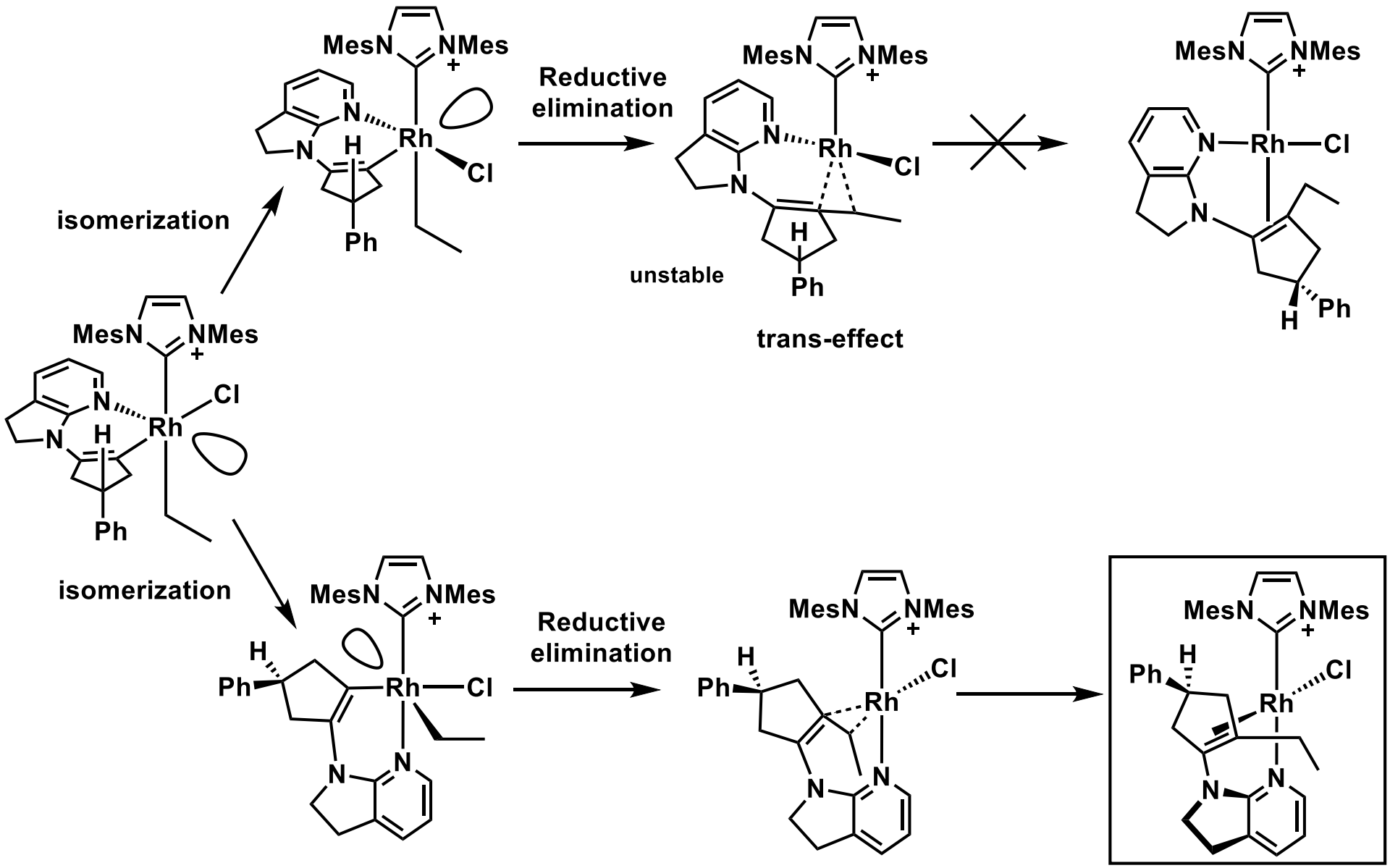


stable

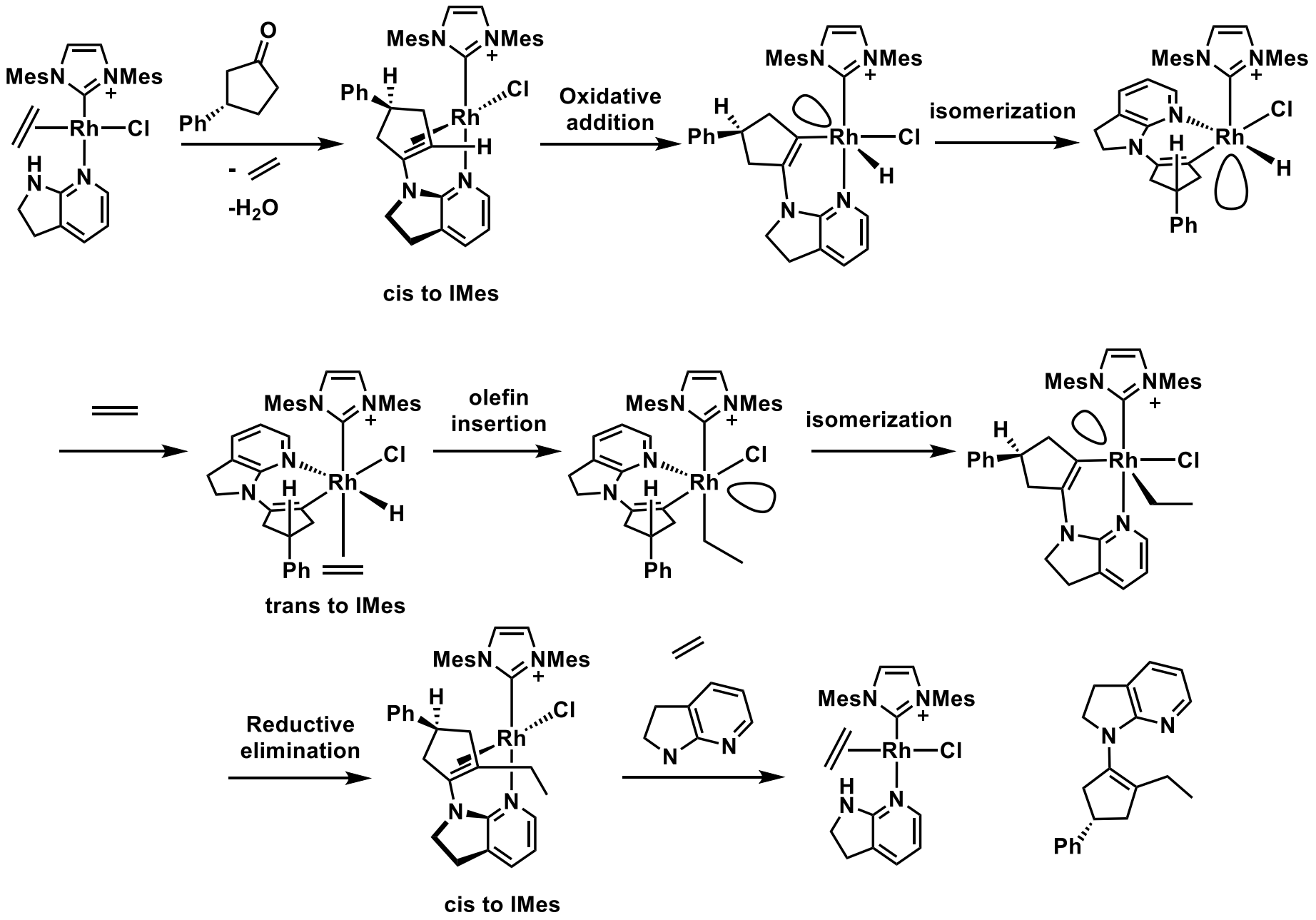
α-H MOCC –Mechanism : insertion of olefin



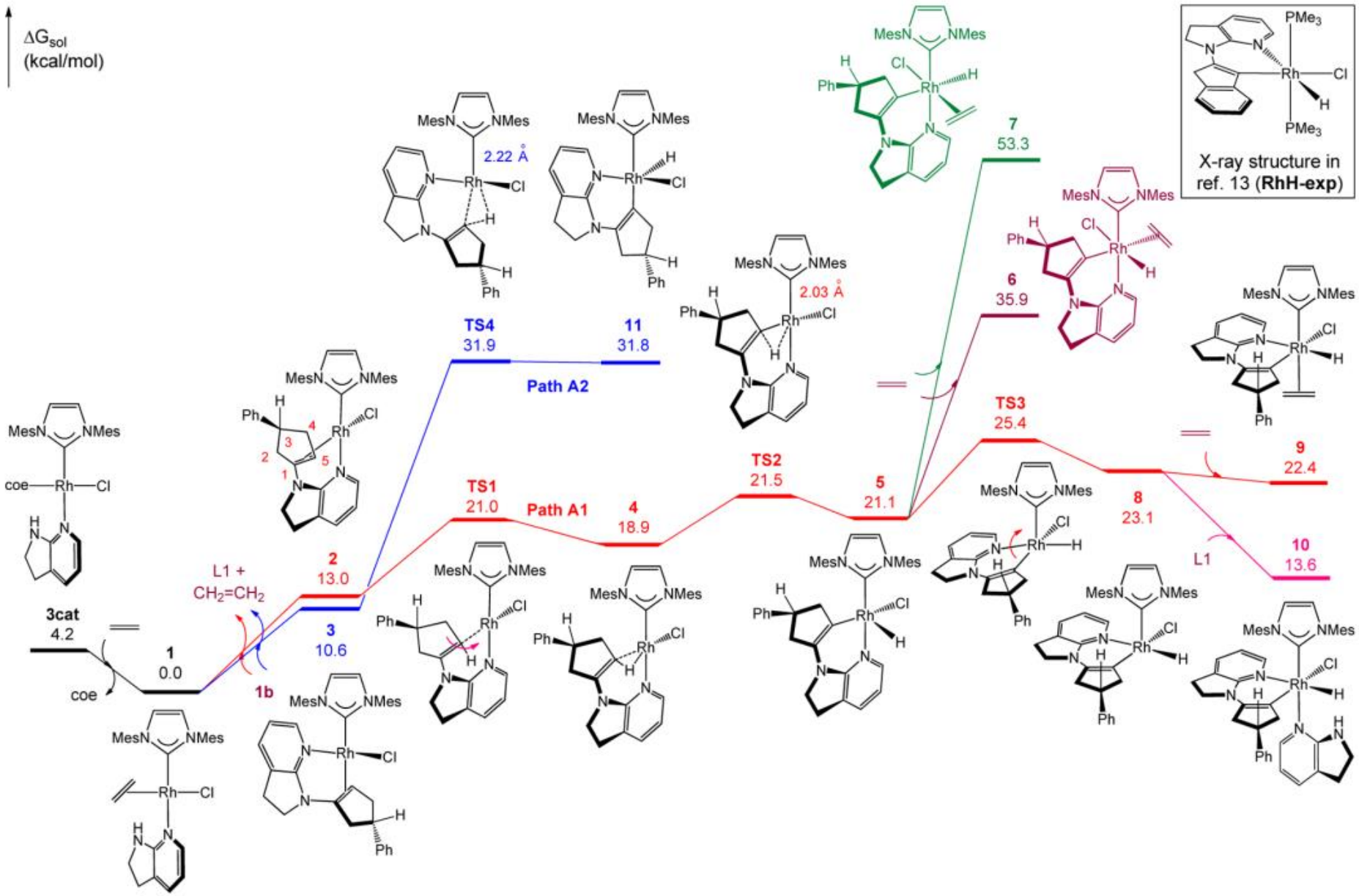
α-H MOCC –Mechanism : reductive elimination



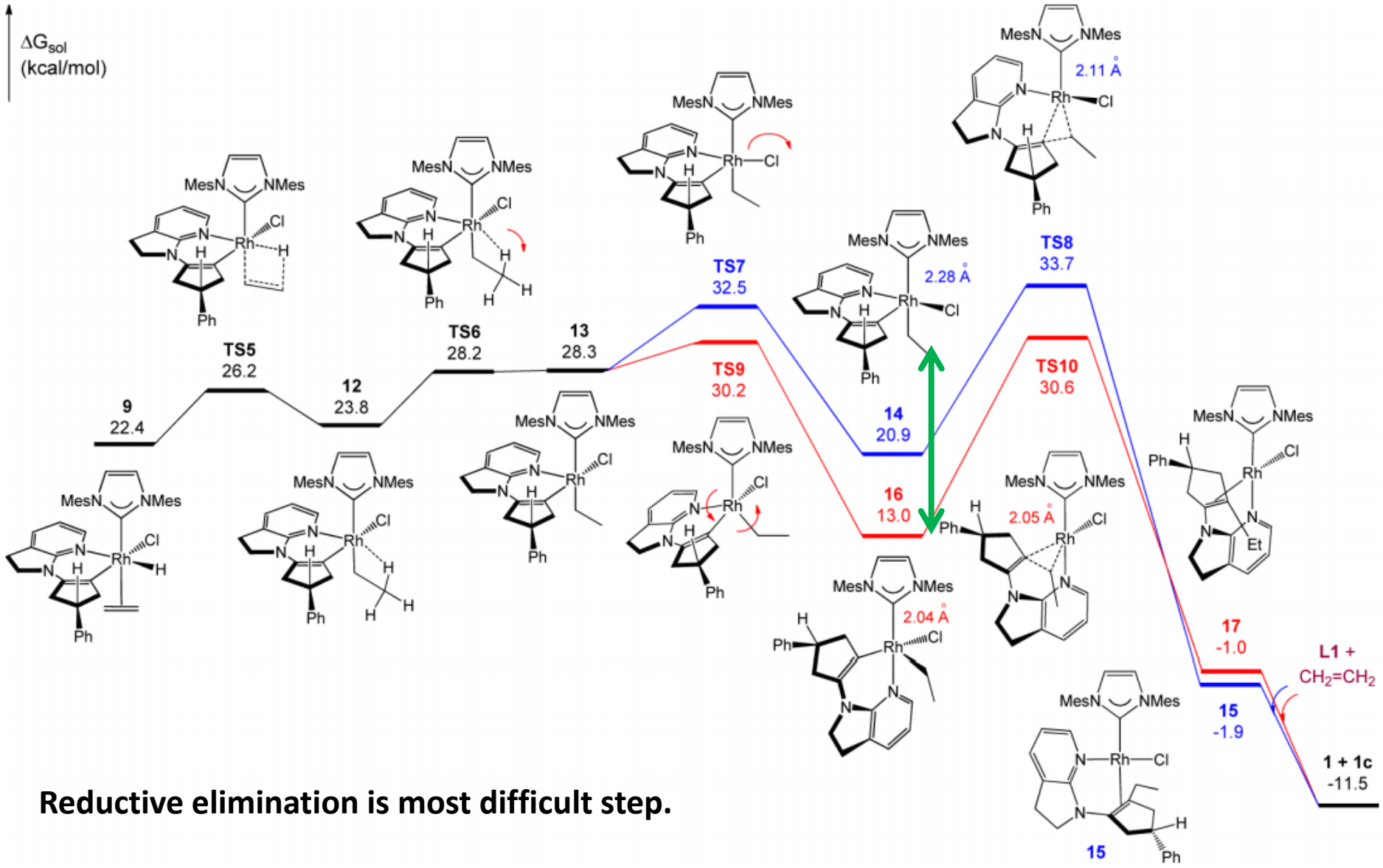
α-H MOCC –Mechanism : total steps



α-H MOCC –Mechanism : energy profiles (1)

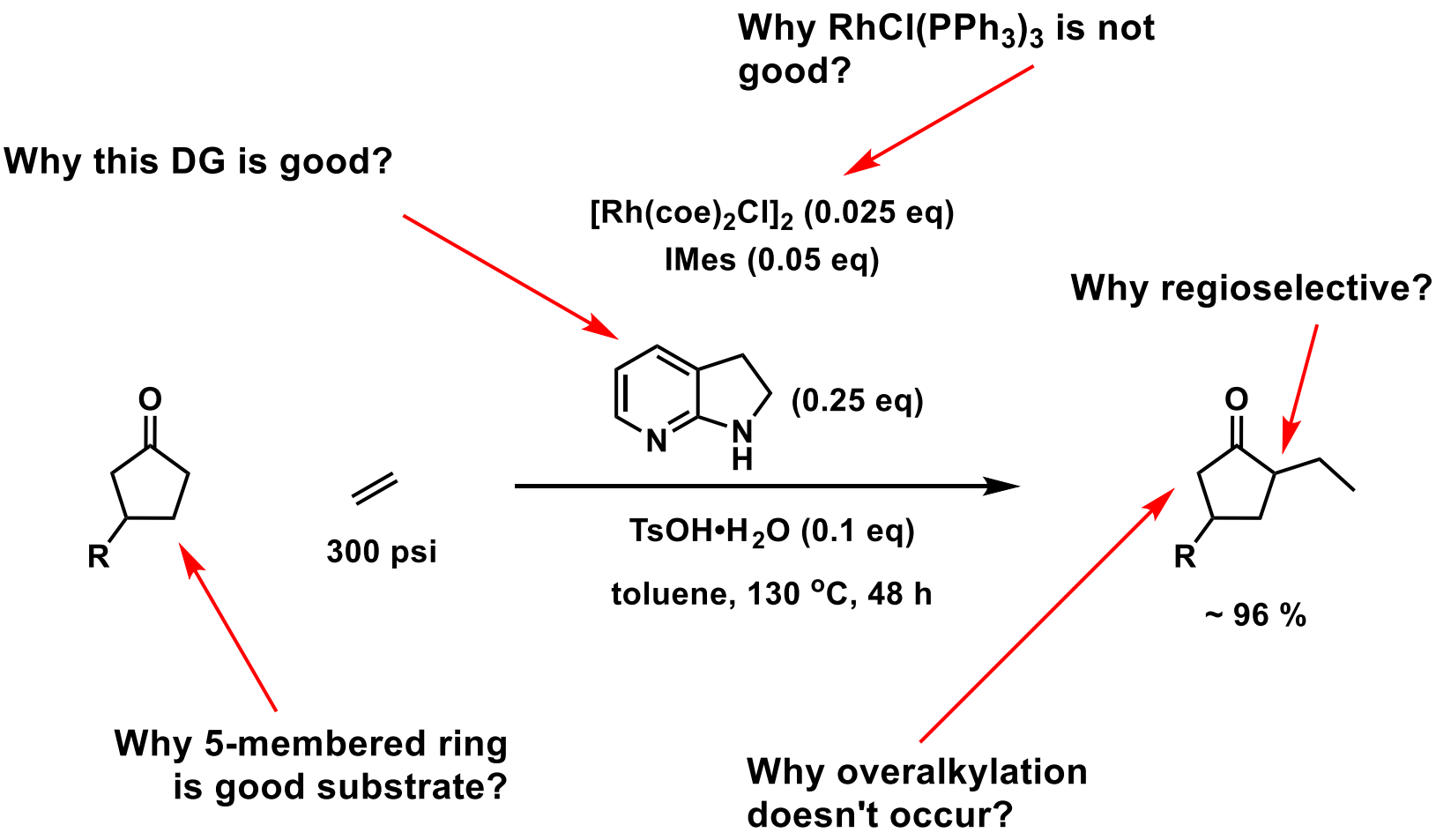


α-H MOCC –Mechanism : energy profiles (2)

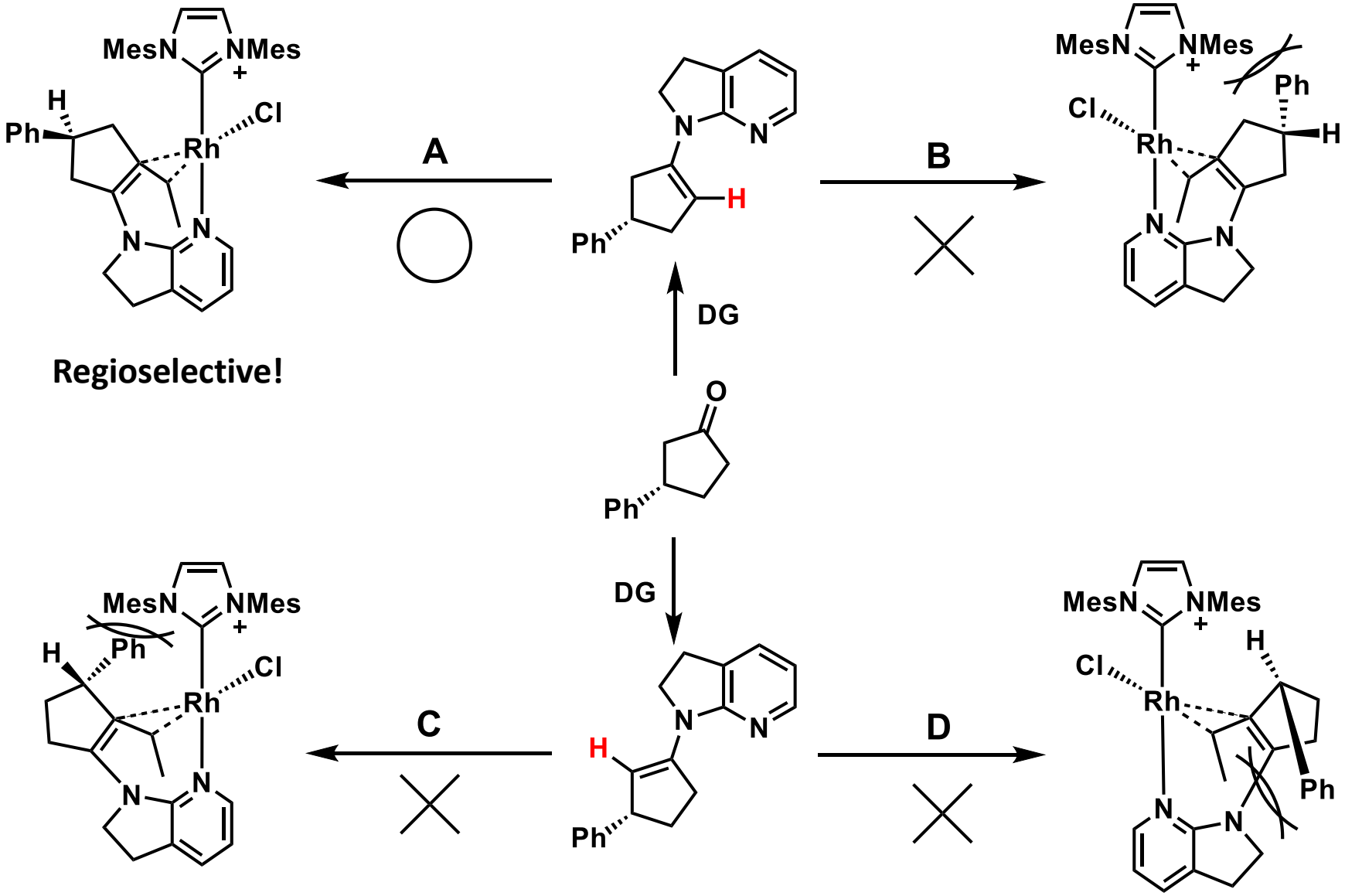


Reductive elimination is most difficult step.

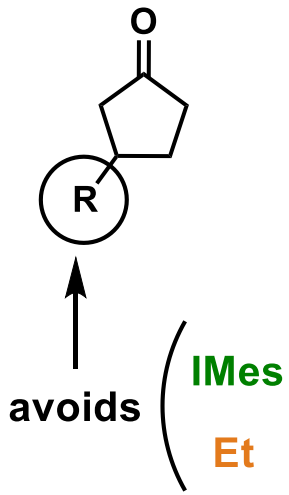
α-H MOCC -reactivity

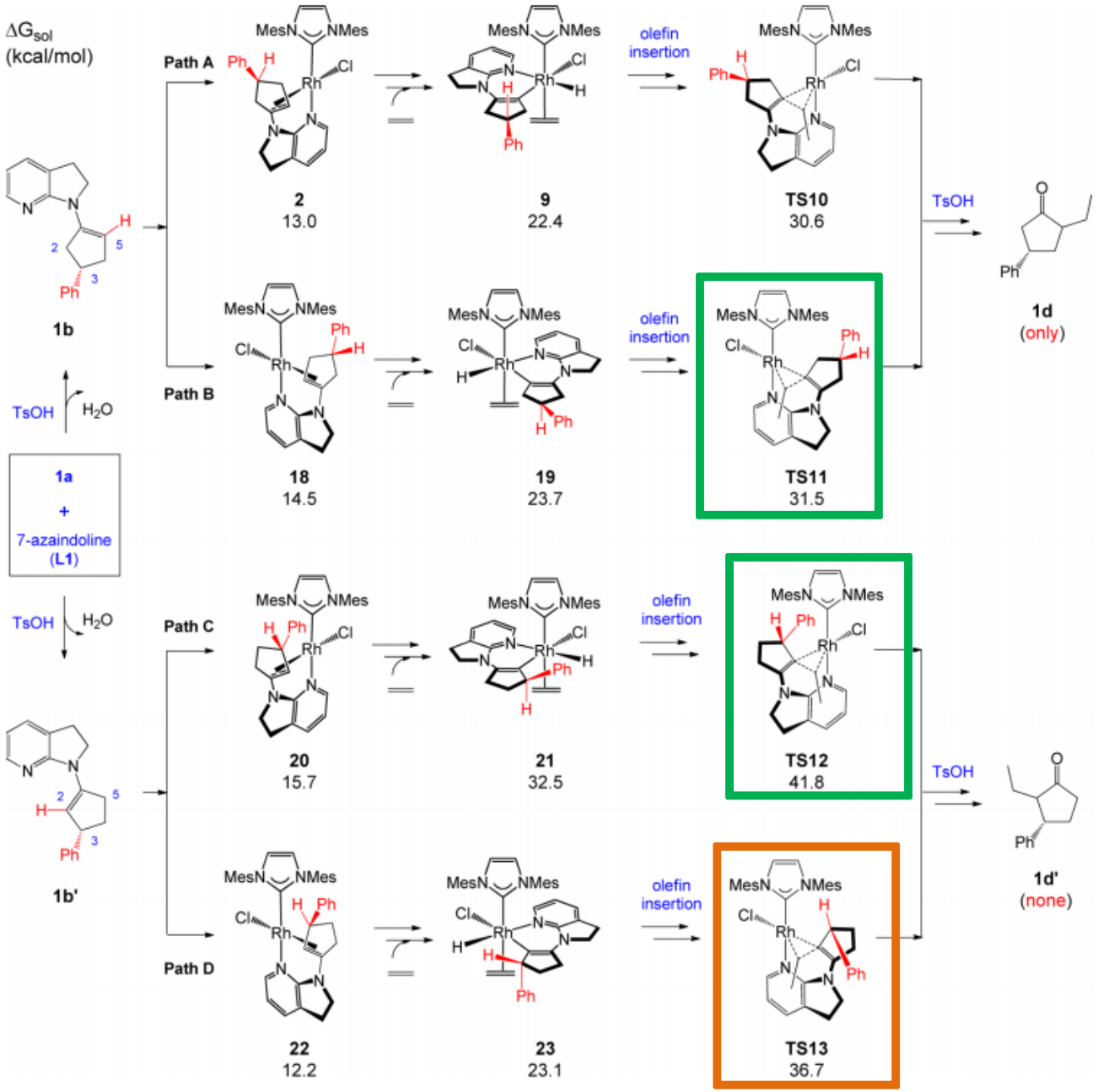


α-H MOCC –reactivity : regioselectivity



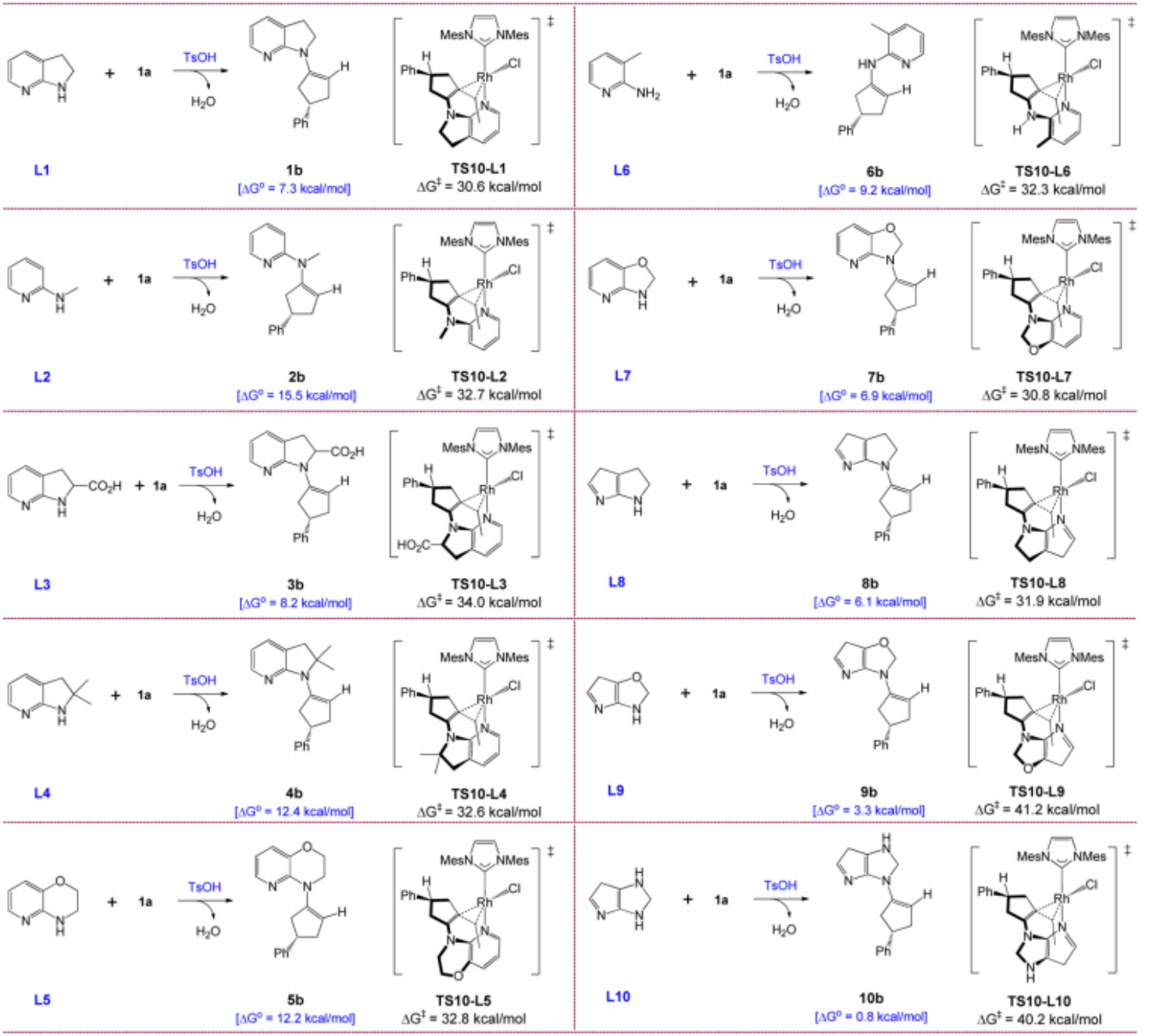
α-H MOCC –reactivity : regioselectivity





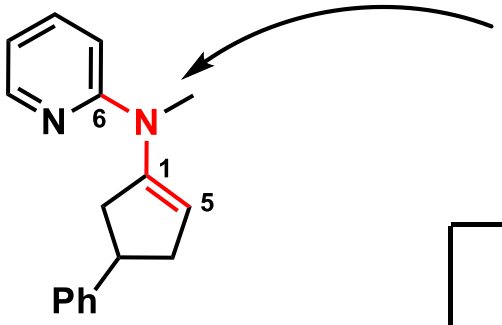
α-H MOCC –reactivity : structure of DG

Difficulty of enamine formation and reductive elimination changes due to the structure of DG

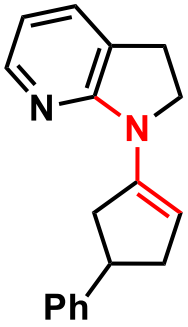
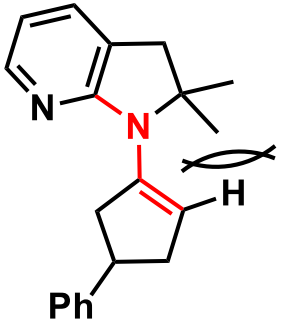
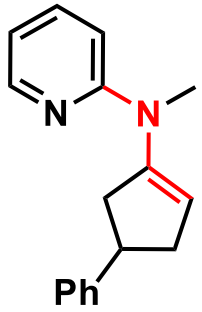


α-H MOCC –reactivity : structure of DG

1) Difficulty of condensation is imprtant

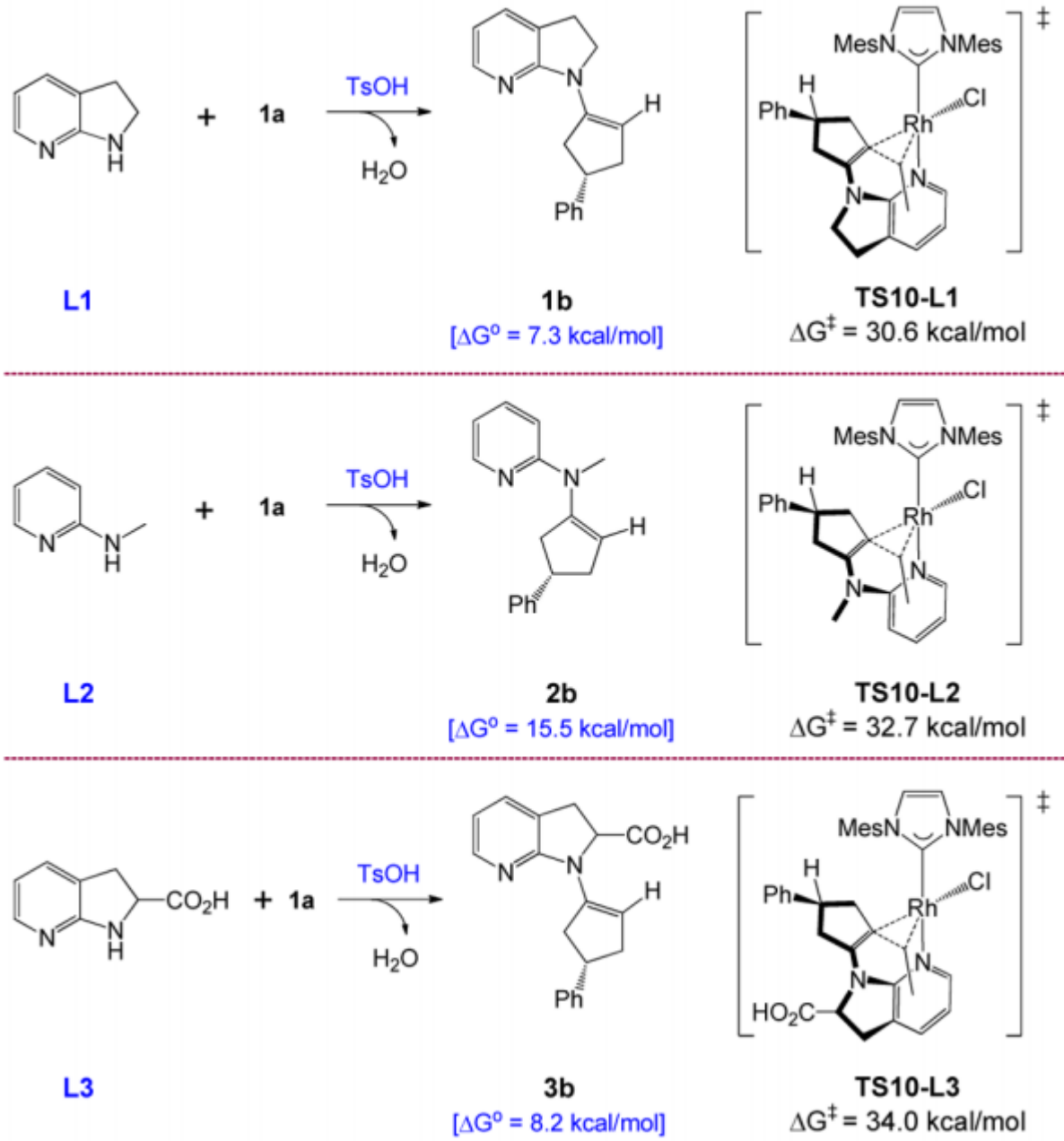


The angle of these bonds defines stabilization by π(Py)-p(N)-π(C=C) conjugation

			
∠C⁶-N-C¹-C⁵	170.5°	160.5°	152.2°
planarity	High ←		→ Low
ΔG°	7.3 kcal/mol	12.4 kcal/mol	15.5 kcal/mol

2) Difficulty of reductive elimination depends on the structure of DG

α-H MOCC –reactivity : structure of DG



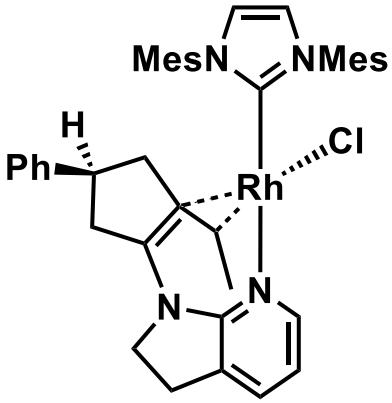
L1 → **1b** [ΔG° = 7.3 kcal/mol] → **TS10-L1** ΔG‡ = 30.6 kcal/mol

L2 → **2b** [ΔG° = 15.5 kcal/mol] → **TS10-L2** ΔG‡ = 32.7 kcal/mol

L3 → **3b** [ΔG° = 8.2 kcal/mol] → **TS10-L3** ΔG‡ = 34.0 kcal/mol

α-H MOCC –reactivity : metal ligand

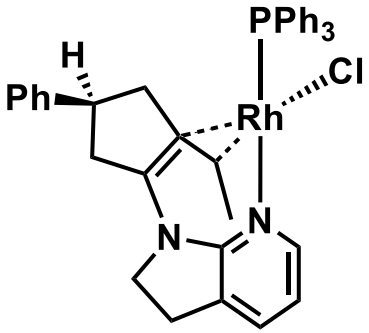
$[Rh(coe)_2Cl]_2$ + IMes VS. $RhCl(PPh_3)_3$



1) Reductive elimination is late-determining step.

→ To accelerate reductive elimination,
reducing electron density of metal is effective.

→weaker electron-donating ligand is effective.



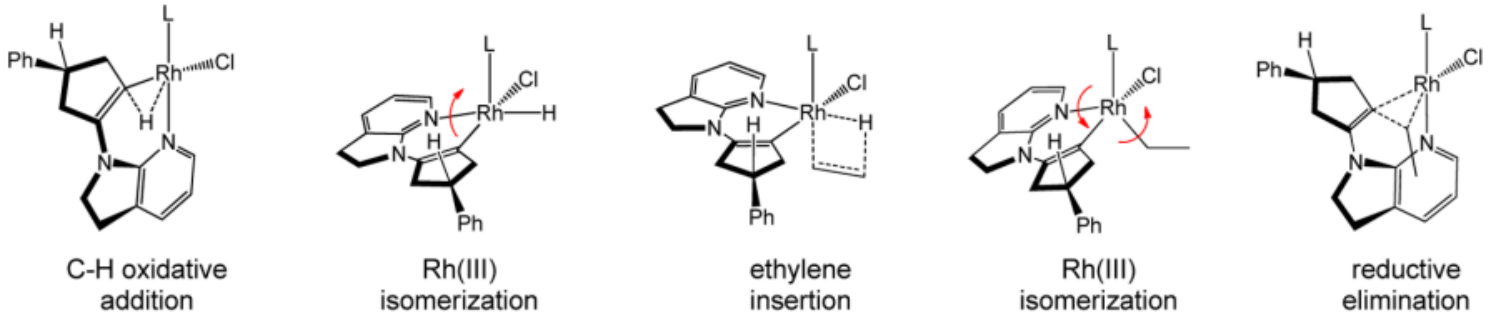
more favorable?

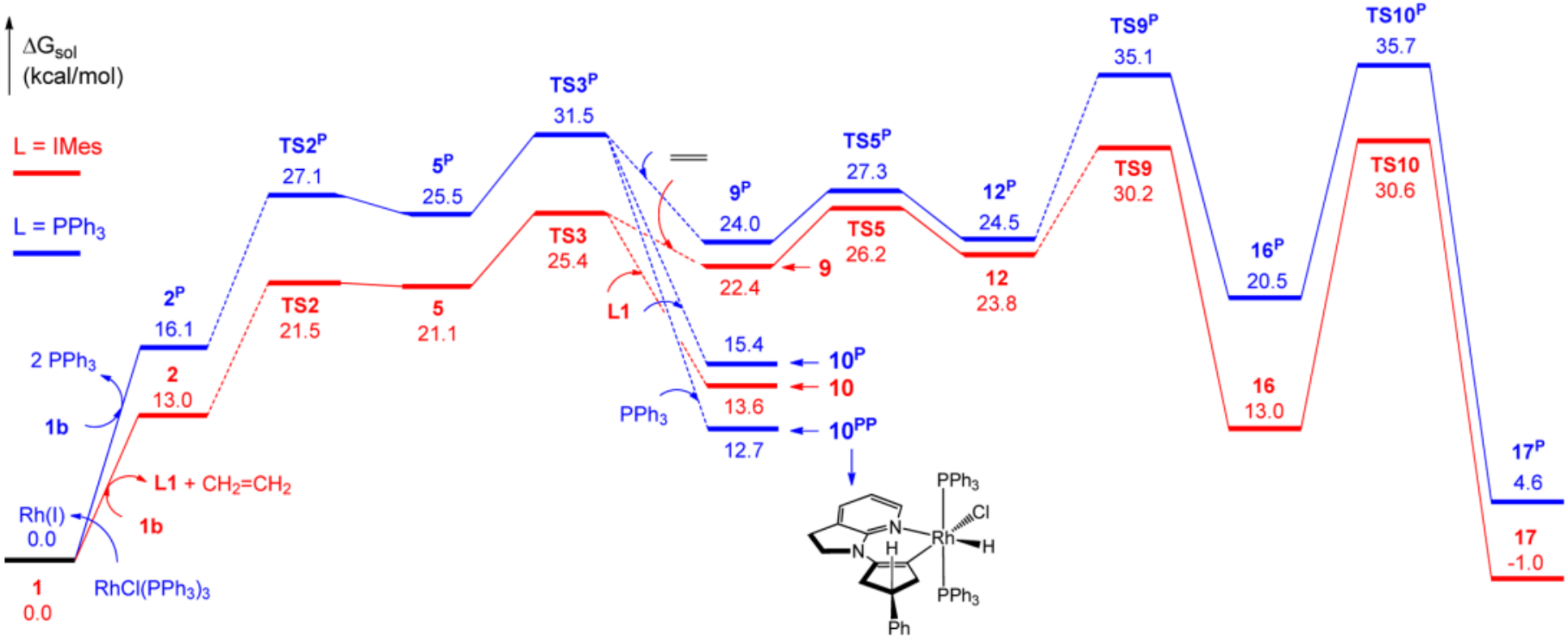
2) PPh_3 is weaker electron-donating ligand than IMes.

⟹ $RhCl(PPh_3)_3$ is more effetive?

⟹ No. Why?

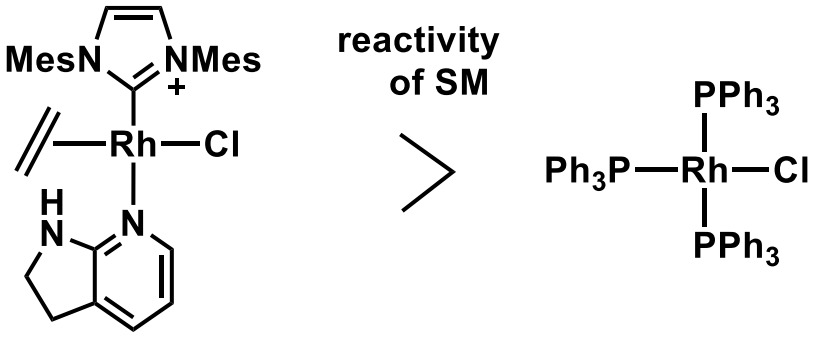
α-H MOCC –reactivity : metal ligand energy profiles





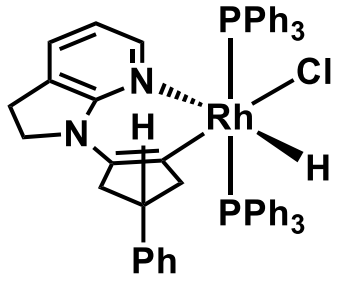
α-H MOCC –reactivity : metal ligand

1) Reactivity of catalyst



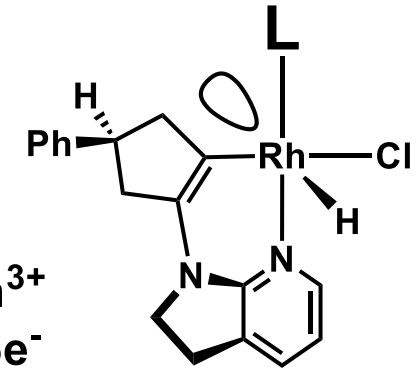
$RhCl(PPh_3)_3$ is stable. = Not effective.

2) Intermediate



PPh_3 constructs stable intermediate after oxidative addition
= ethylene insertion is difficult.

3) Electron donating



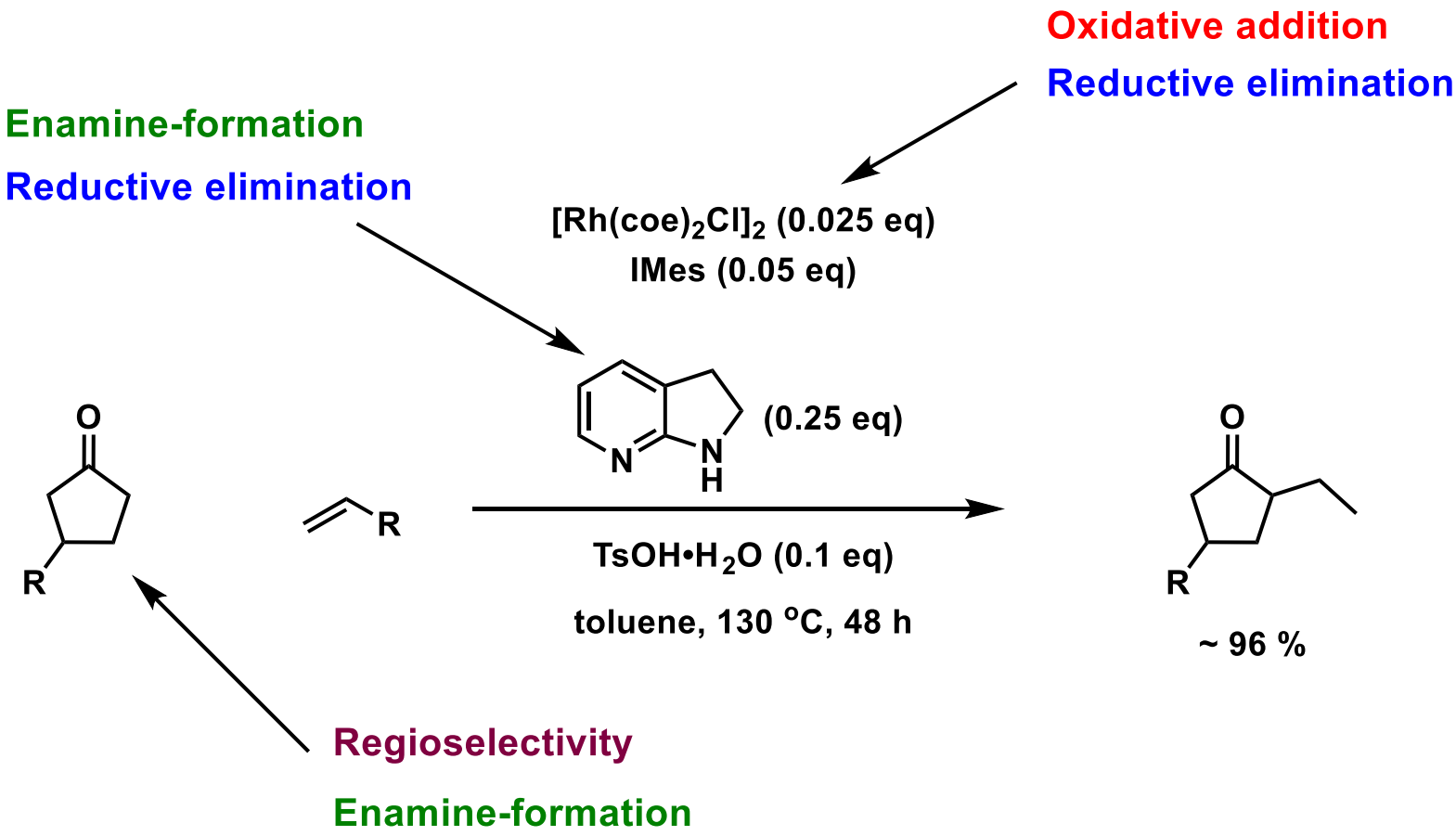
Rh^{3+}
$16e^-$

Electron-deficient ligand destabilizes the structures in high oxidation state.

= PPh_3 is inferior to IMes.

→ electron-rich ligand is preferable.

α-H MOCC summary



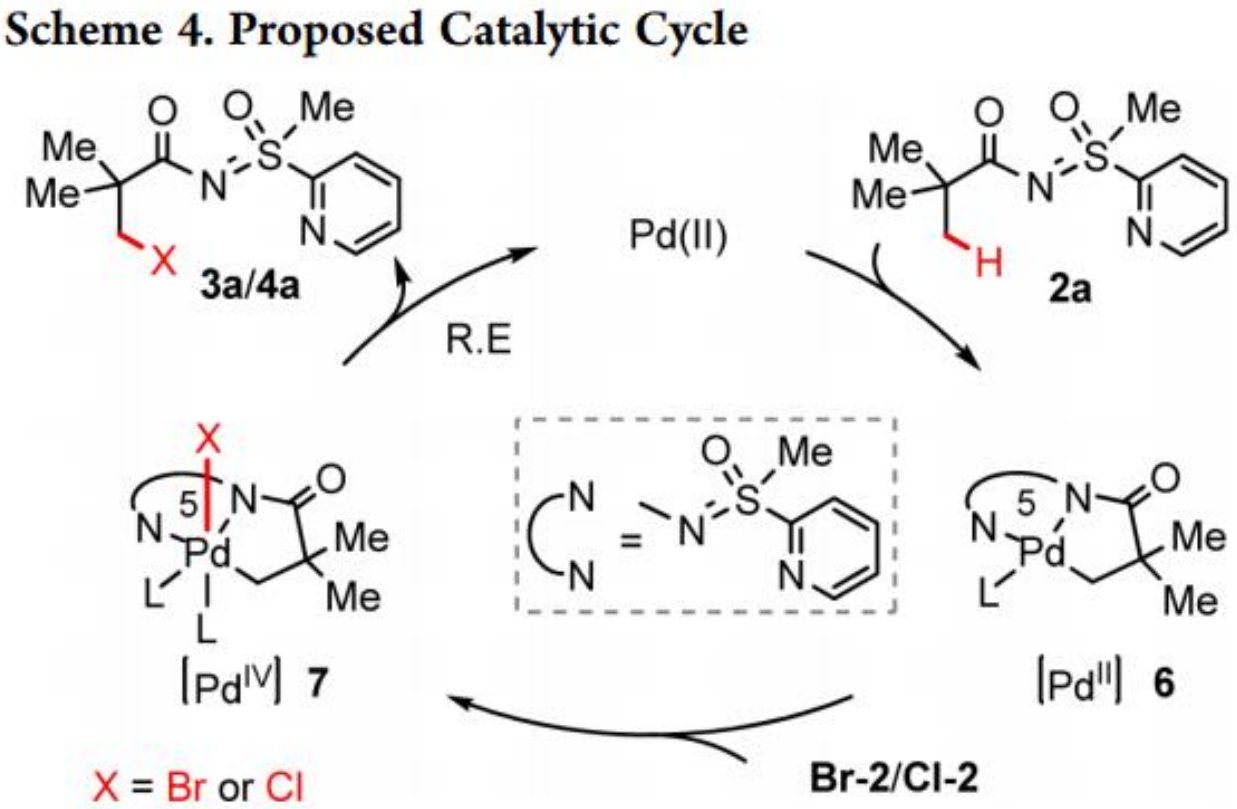
Each reactant influences several reaction steps.

Summary

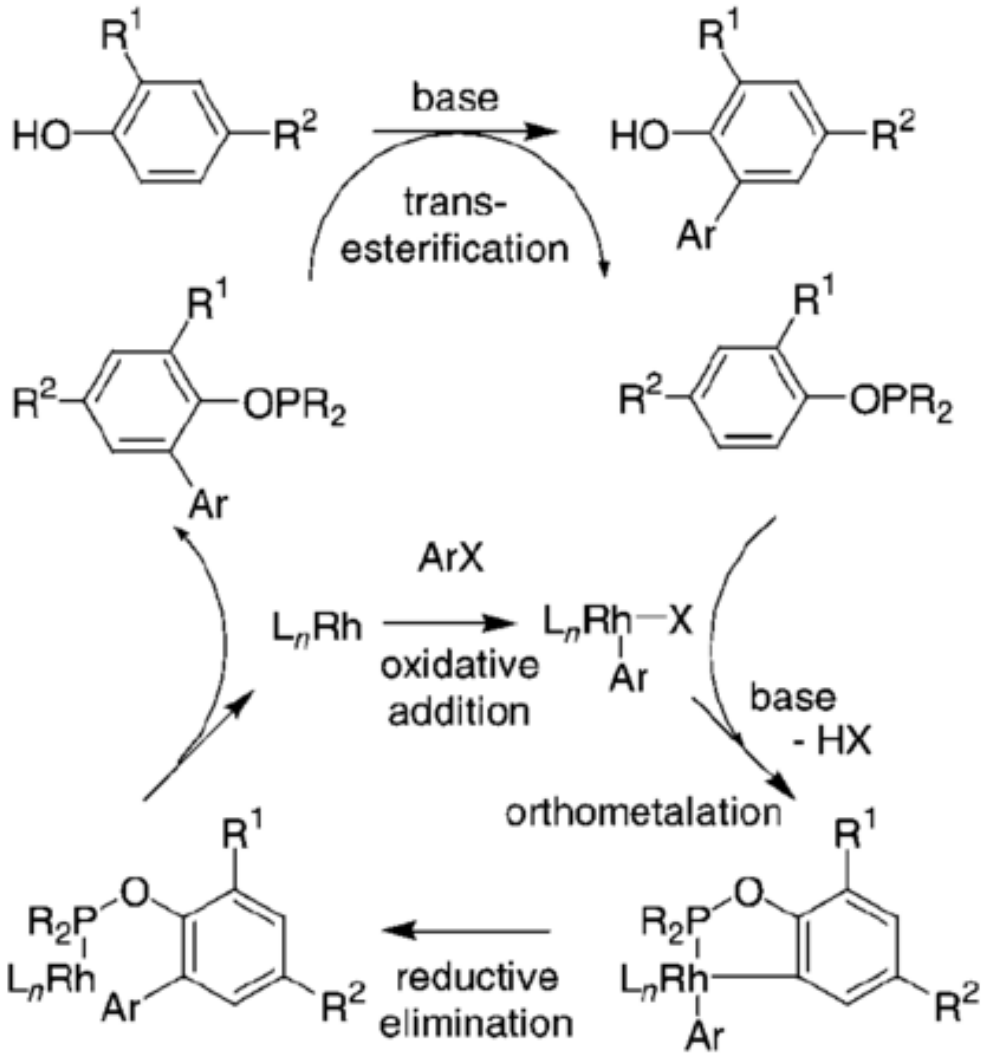
- **DG is useful to achieve regioselective, high-yield C-H activation.**
- **Outer DG enables chelation-assisted C-H activation to substrate that doesn't contain DG.**
- **Concept of MOCC is helpful for greener, shorter-step C-H activation.**
- **But, to achieve MOCC, one have to take account of the combination of substrate and DG, in addition to reactant, metal, and ligand.**

C-H activation

Appendix -Outer DG Mechanism

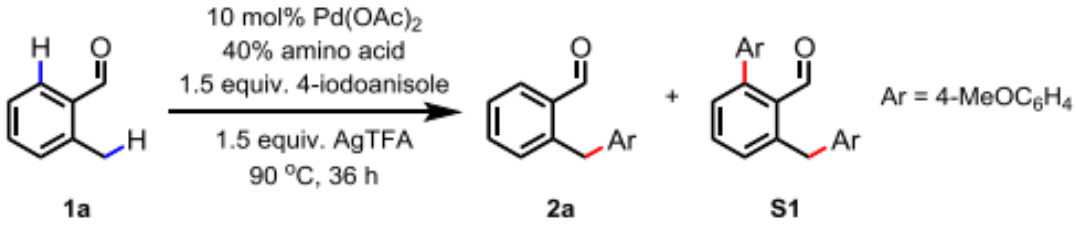


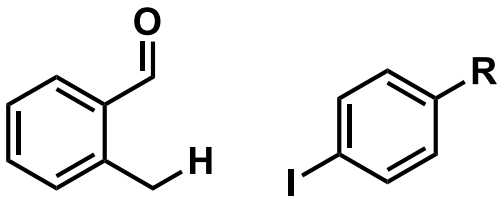
Appendix-MOCC ex1 Mechanism

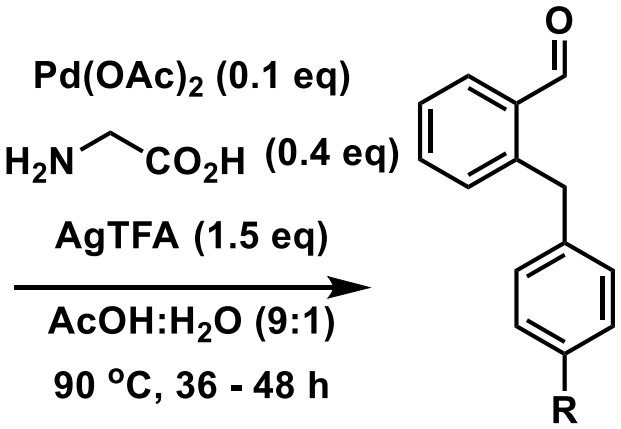


Scheme 2. Plausible reaction mechanism.

Appendix -MOCC ex2 Mechanism







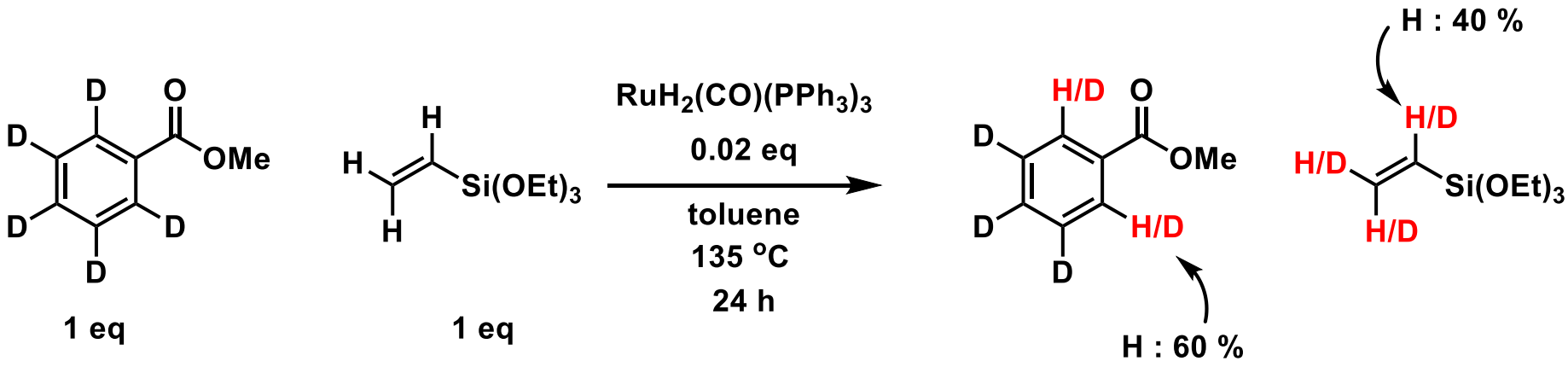
R = H, Me, OMe, OH, CHO, CO_2H, CO_2Me

Yield 70 ~ 82 %

entry	solvent	amino acid	conversion (%)	**2a** (%)	**S1** (%)
1	DCE	glycine	-	<2	<2
2	toluene	glycine	-	<2	<2
3	dioxane	glycine	-	<2	<2
4	MeCN	glycine	-	<2	<2
5	HFIP	glycine	60	18	11
6	AcOH	glycine	90	52	10
7	AcOH:HFIP (9:1)	glycine	94	59	6
8	AcOH:H_2O (9:1)	glycine	93	71	11
9	AcOH:H_2O (4:1)	glycine	84	63	11
10‡	**AcOH:H_2O (9:1)**	**glycine**	**95**	**81 (72)**§	**<3**
11‡	AcOH:H_2O (9:1)	L-alanine	-	76	<3
12‡	AcOH:H_2O (9:1)	L-valine	-	78	<3
13‡	AcOH:H_2O (9:1)	L-norvaline	-	76	<3
14‡	AcOH:H_2O (9:1)	Ac-Gly-OH	-	<2	<2

*Conditions: 0.1 mmol of **1a**, 1.5 equiv of 4-iodoanisole, 10 mol% of $Pd(OAc)_2$, 40 mol% of amino acid, 1.5 equiv of AgTFA, 1.0 mL of solvent, 90 °C, 36 h. †The yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard. ‡0.12 mmol of **1a** and 0.1 mmol of 4-iodoanisole were used. §isolated yield.

C-H activation –deuterium labeling experiment



No coupling product

- **H/D scrambling occurred among two ortho and three olefinic position.**

  → **Oxidative addition and Olefin insertion occurs.**

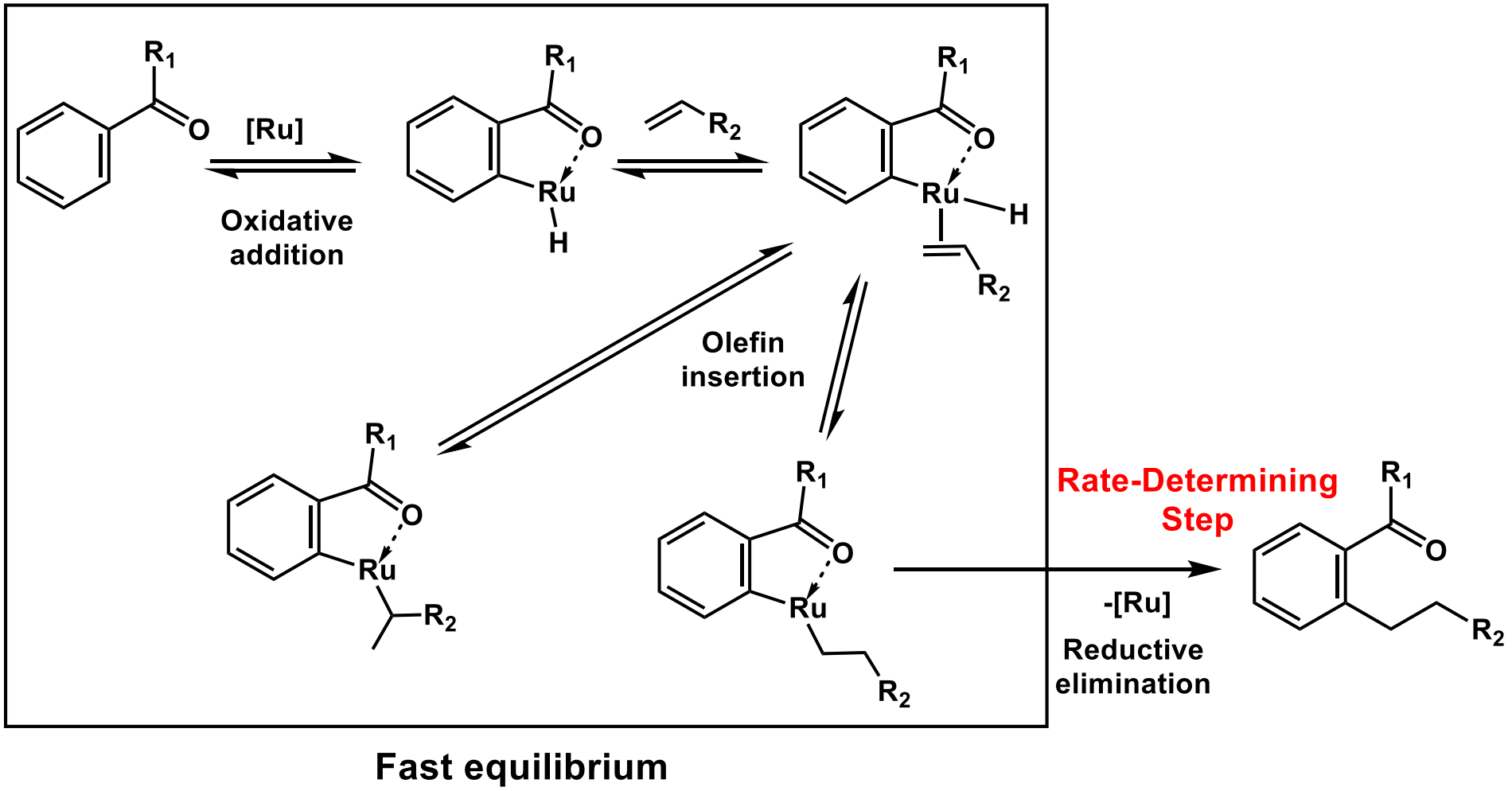
- **Not among meta and para position.**

  → **Directing is necessary for C-H bond cleavage.**

- **Product wasn't gained.**

  → **Reductive elimination doesn't occur.**

C-H activation –detailed mechanism (2)



C-H activation -13C kinetic effect(1)

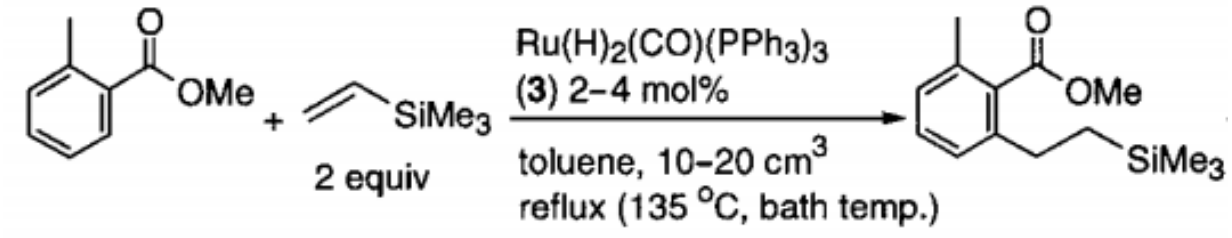
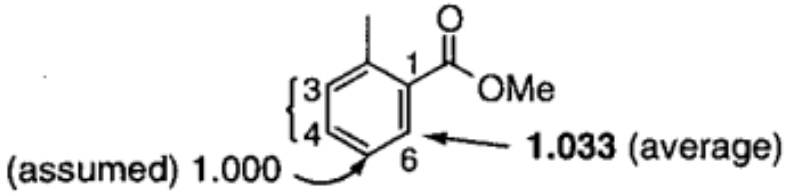


Table 1. Experimental ^{13}C kinetic isotope effect



Run	Conversion	KIEs				
		C1	C2	C3+C4	C5	C6
1	64%	0.996(1)	1.001(3)	1.003(1)	1.000	1.034(1)
2	69%	0.999(2)	0.996(3)	1.000(1)	1.000	1.032(1)
3	79%	0.997(1)	0.996(1)	1.004(1)	1.000	1.034(1)

KIE = $k_{12}C/k_{13}C$

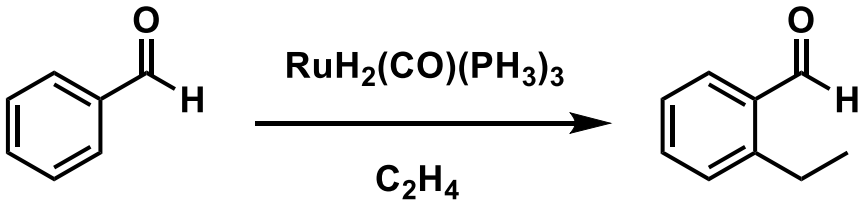
SM contains ^{13}C at C6 reacts slower than that of ^{12}C

⟹ **rate-determing step incrudes C-X bond cleavage**

⟹ **Oxidative addition or reductive elimination is rate-determing step.**

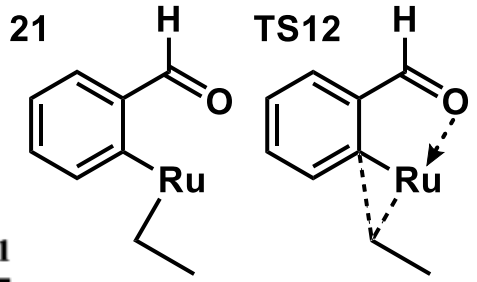
Murai et. al. *Chem. Lett.* **1996**, 109-110

C-H activation -calculation



Reductive elimination is difficult.

1 = $Ru(CO)(PH_3)_2$



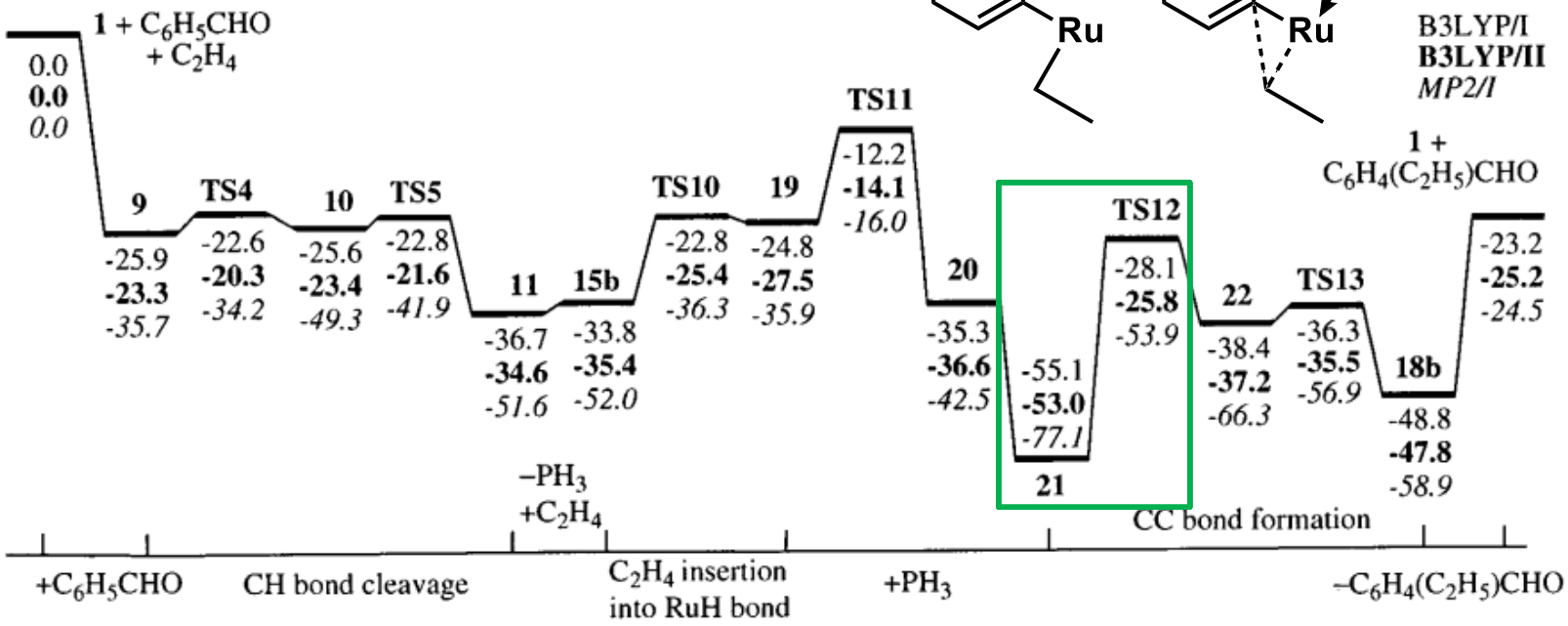


Figure 10. Entire potential energy surface (in kcal/mol) of the catalytic ortho-CH bond addition of benzaldehyde to ethylene by $Ru(CO)(PH_3)_2$ along the most favorable reaction path. The values in plain, bold, and italic are calculated at the B3LYP/I, B3LYP/II, and MP2/I level, respectively.

Matsubara et al. *Organomatallics* **2000**, 19, 2318-2329