

Ketone α C-H Alkylation with Alkenes

2018/5/26 Takumi Fukuda

Contents

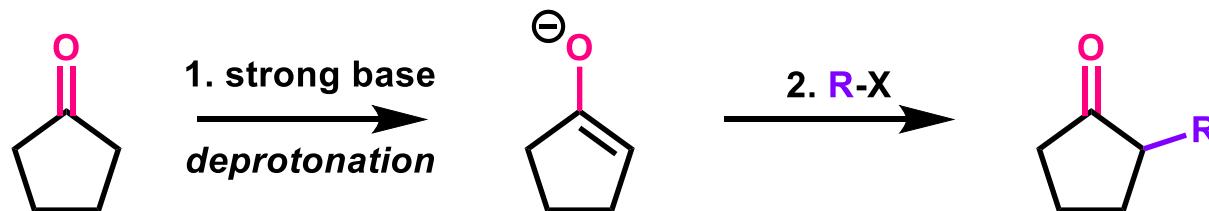
1. Introduction
2. Linear selective ketone α -alkylation (Dong, 2014)
3. Branched selective ketone α -alkylation (Dong, 2017)

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α Alkylation of Ketone

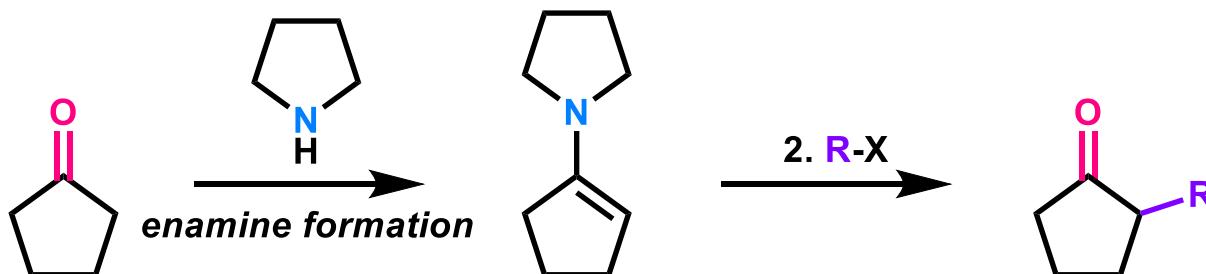
(1) enolate alkylation



Problems

1. Strong bases (such as LDA) and alkyl halides are required.
2. Self-condensation, over-alkylation and E2 elimination could compete.

(2) Stork enamine reaction



Problem

1. Reactive alkyl halides is still required due to the reduced nucleophilicity of enamines versus metal enolates.
2. N-alkylation compete with C-alkylation.

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1. Introduction
2. Linear selective ketone α -alkylation (Dong, 2014)
3. Branched selective ketone α -alkylation (Dong, 2017)

Guangbin Dong



- 2003 : BS Peking University (Prof. Zhen Yang and Prof. Jiahua Chen)**
- 2009 : Ph.D. Stanford University (Prof. Barry M. Trost)**
- 2009 - 2011 : Postdoc. Caltech (Prof. Robert H. Grubbs)**
- 2011 - 2016: Assistant Prof. University of Texas at Austin**
- 2016 - : Professor of Chemistry, University of Chicago**

Research Topic:

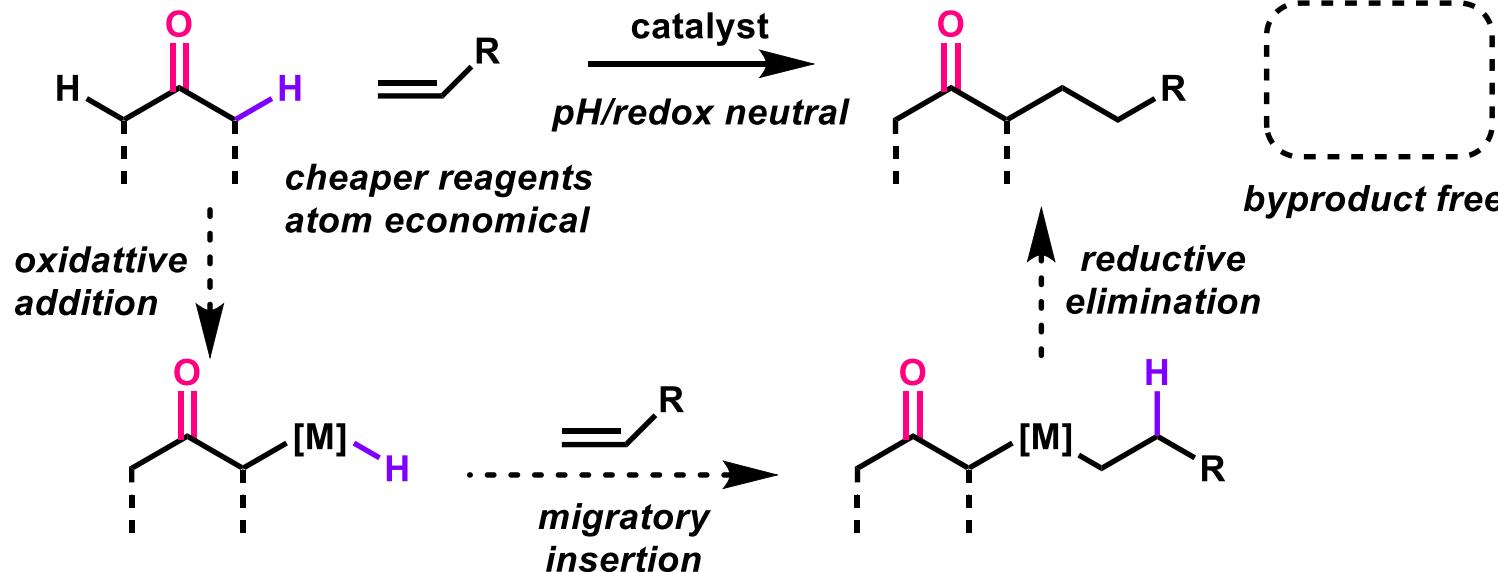
**1. Catalytic C-H and C-C Bond Activation
170121_LS_Tsukasa_Shimakawa**

2. Methane Activation

3. Total Synthesis

4. Functionalized Materials

Approaches to Ketone Alkylation

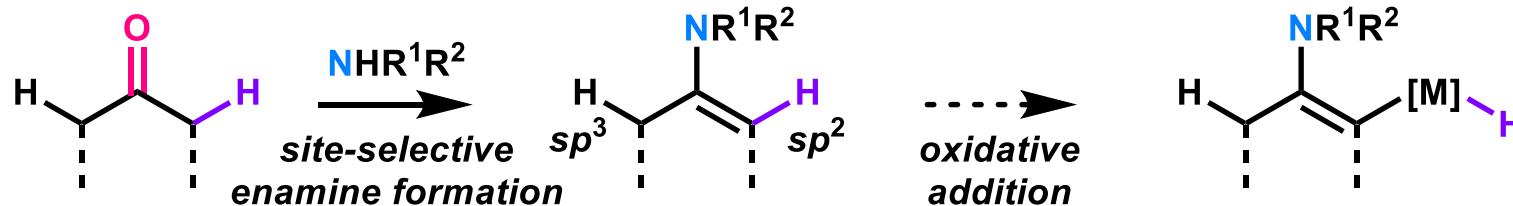


Problems

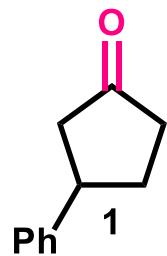
1. Oxidative addition of ketone α C-H bond (sp^3) was difficult.
2. Site-selective oxidative addition was needed.

inspired by the Stork enamine reaction.

To solve these problems, a secondary amine was used as a cocatalyst.



Optimization for Reaction Conditions

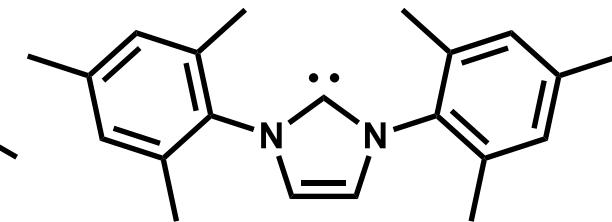
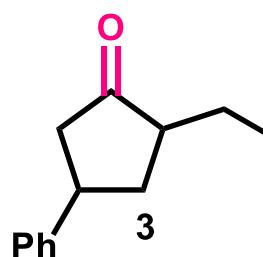


$\text{H}_2\text{C}\equiv\text{CH}_2$
2
300 psi
(≈ 20 atm)

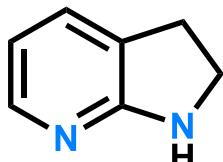
Rh catalyst
ligand (5 mol%)
 $\text{TsOH}\cdot\text{H}_2\text{O}$ (10 mol%)
amine cocatalyst
toluene (0.2 M)

130 °C, time

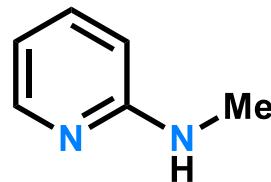
coe = cyclooctene



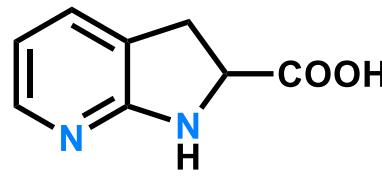
entry	Rh catalyst (mol%)	ligand	amine cocatalyst (mol%)	time	NMR yield of 3 (%)
1	$[\text{Rh}(\text{coe})_2\text{Cl}]_2$ (2.5)	IMes	L1 (50)	24	> 99
2	$[\text{Rh}(\text{coe})_2\text{Cl}]_2$ (2.5)	IMes	L1 (25)	48	87
3	$[\text{Rh}(\text{coe})_2\text{Cl}]_2$ (2.5)	IMes	L2 (25)	48	0
4	$[\text{Rh}(\text{coe})_2\text{Cl}]_2$ (2.5)	IMes	L3 (25)	48	0
5	$[\text{Rh}(\text{coe})_2\text{Cl}]_2$ (2.5)	IMes	L4 (25)	48	0
6	$[\text{Rh}(\text{coe})_2\text{Cl}]_2$ (2.5)	IMes	L5 (25)	48	0
7	$\text{RhCl}(\text{PPh}_3)_3$ (5.0)	—	L1 (100)	48	37



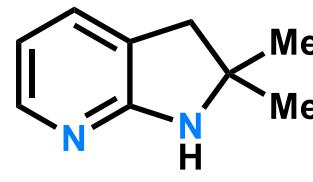
L1



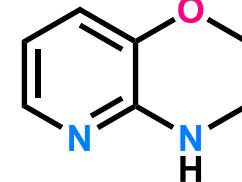
L2



L3



L4



L5

- Several amine cocatalysts (L1-L5) were examined, but only L1 acted efficiently (entry 2-6).
- The Wilkinson's catalyst $\text{RhCl}(\text{PPh}_3)_3$, which was commonly used as a MOCC catalyst, performed poorly in this case (entry 7).

Substrate Scope (1)

[Rh(cod)₂Cl]₂ (2.5 mol%)

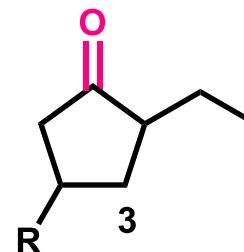
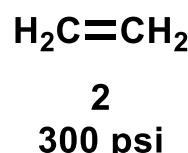
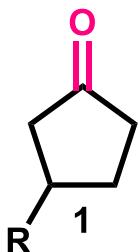
IMes (5 mol%)

TsOH·H₂O (10 mol%)

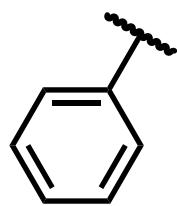
L1 (25 mol%)

toluene (0.2 M)

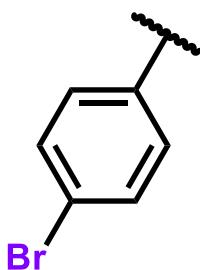
130 °C, 48 h



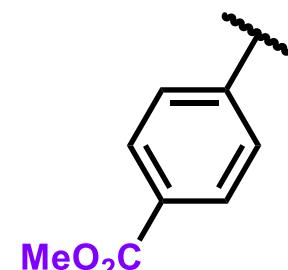
R =



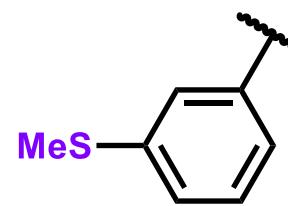
82%
dr = 1.7:1



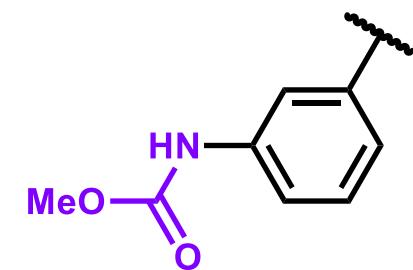
71%
dr = 2:1



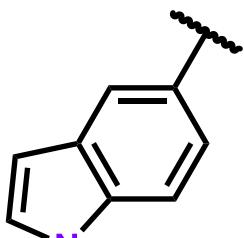
71%
dr = 2:1



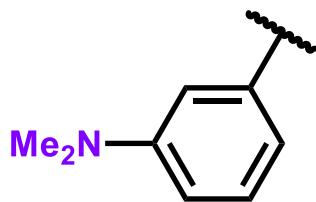
60%
dr = 1.8:1



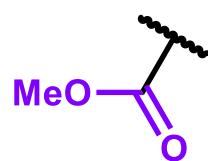
84%
dr = 1.9:1



52%
dr = 2:1



62%
dr = 1.3:1



96%
dr = 1.3:1

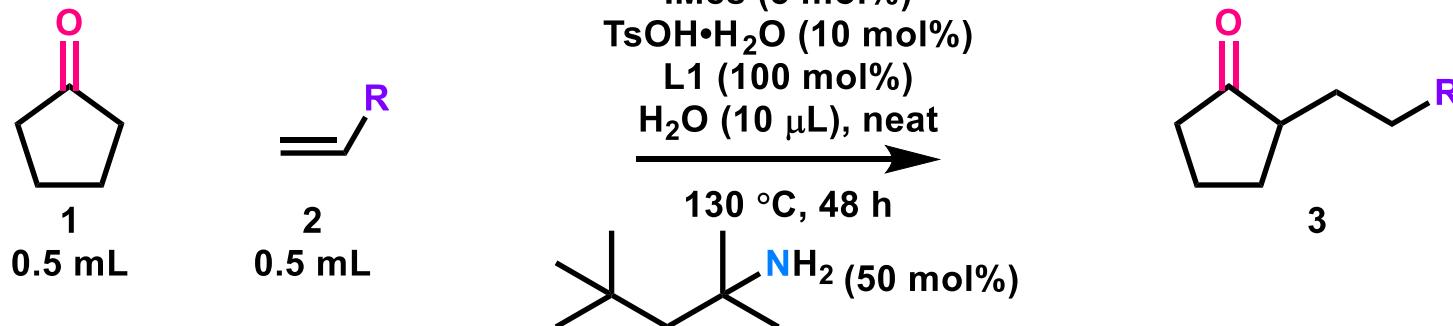


95%
dr = 1.6:1

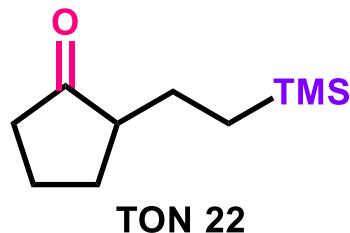
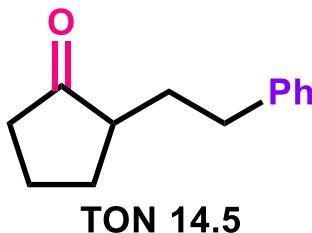
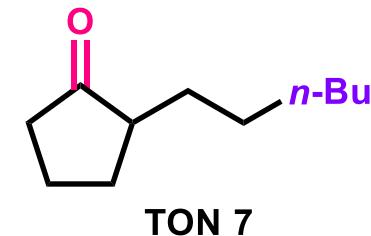
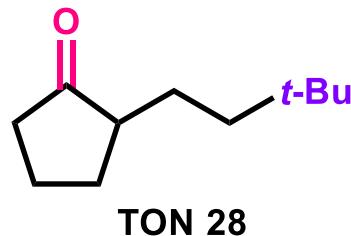
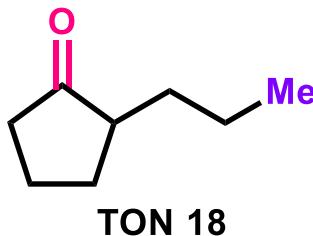


62%
dr = 1:1

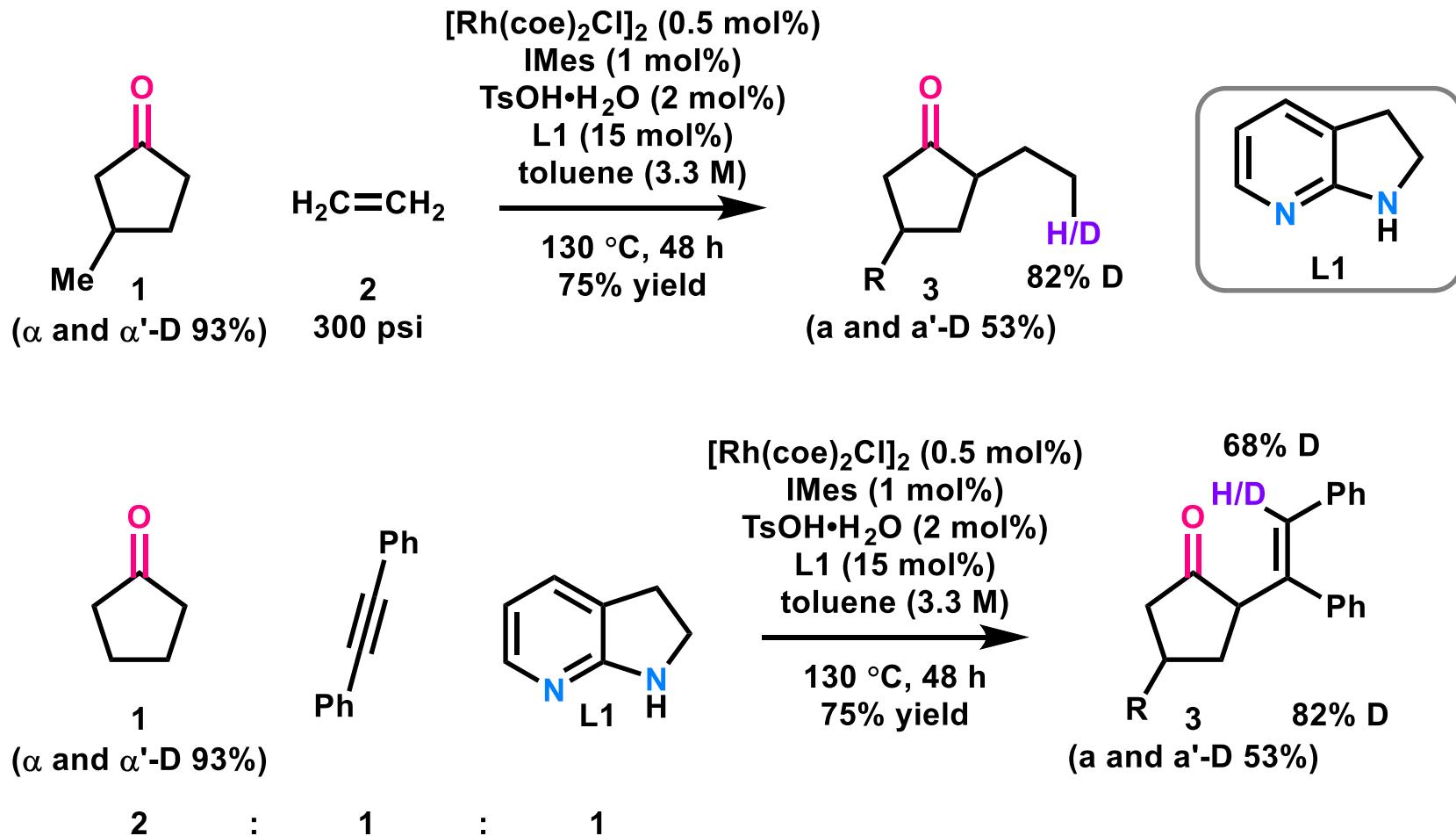
Substrate Scope (2)



$$\text{TON} = 3 \text{ (mol)} / [\text{Rh}] \text{ monomer (mol)}$$

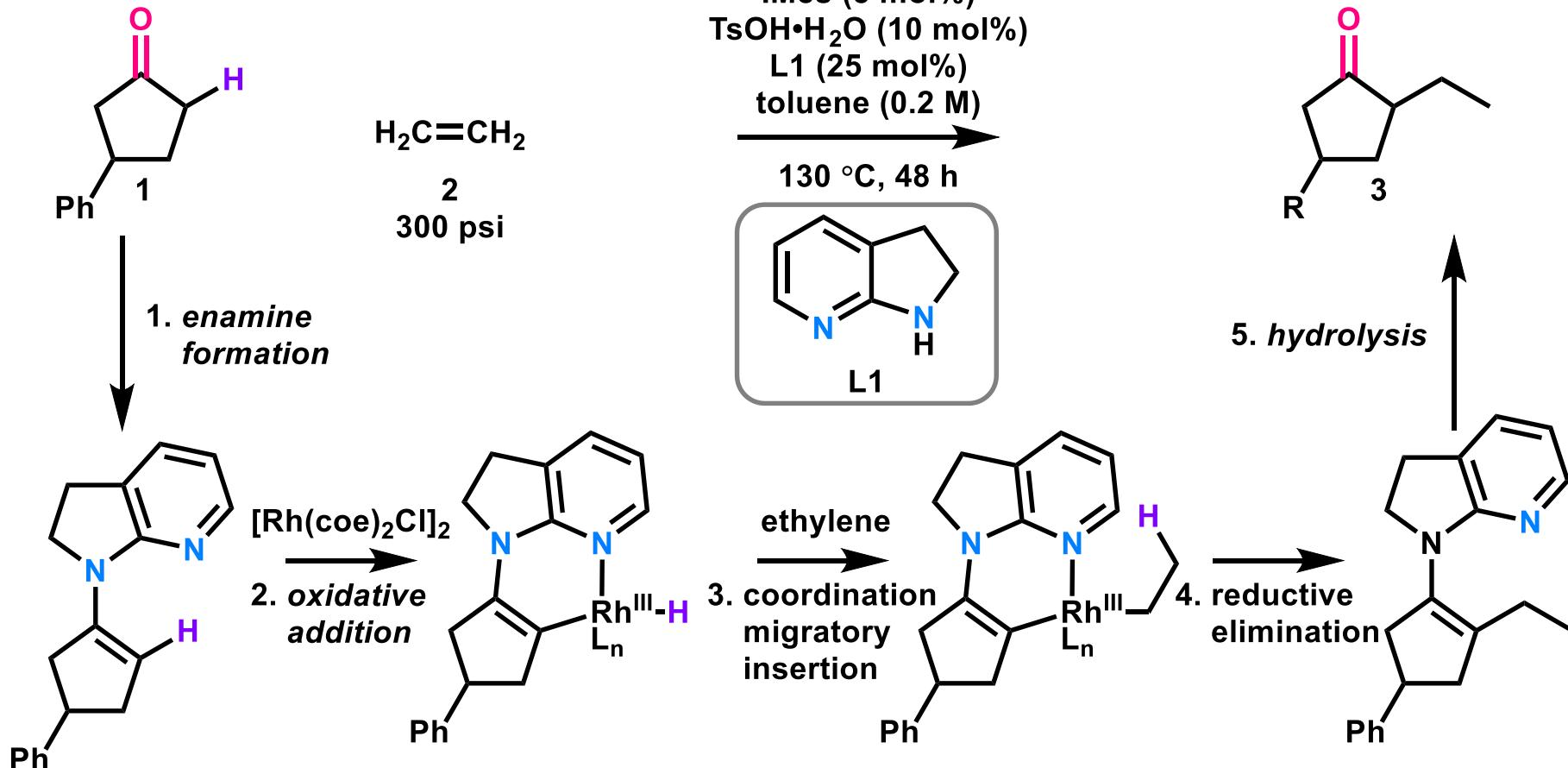


Deuterium Experiments



These experiments suggest that an α hydrogen of the ketone substrate transfer to the terminal position of the product.

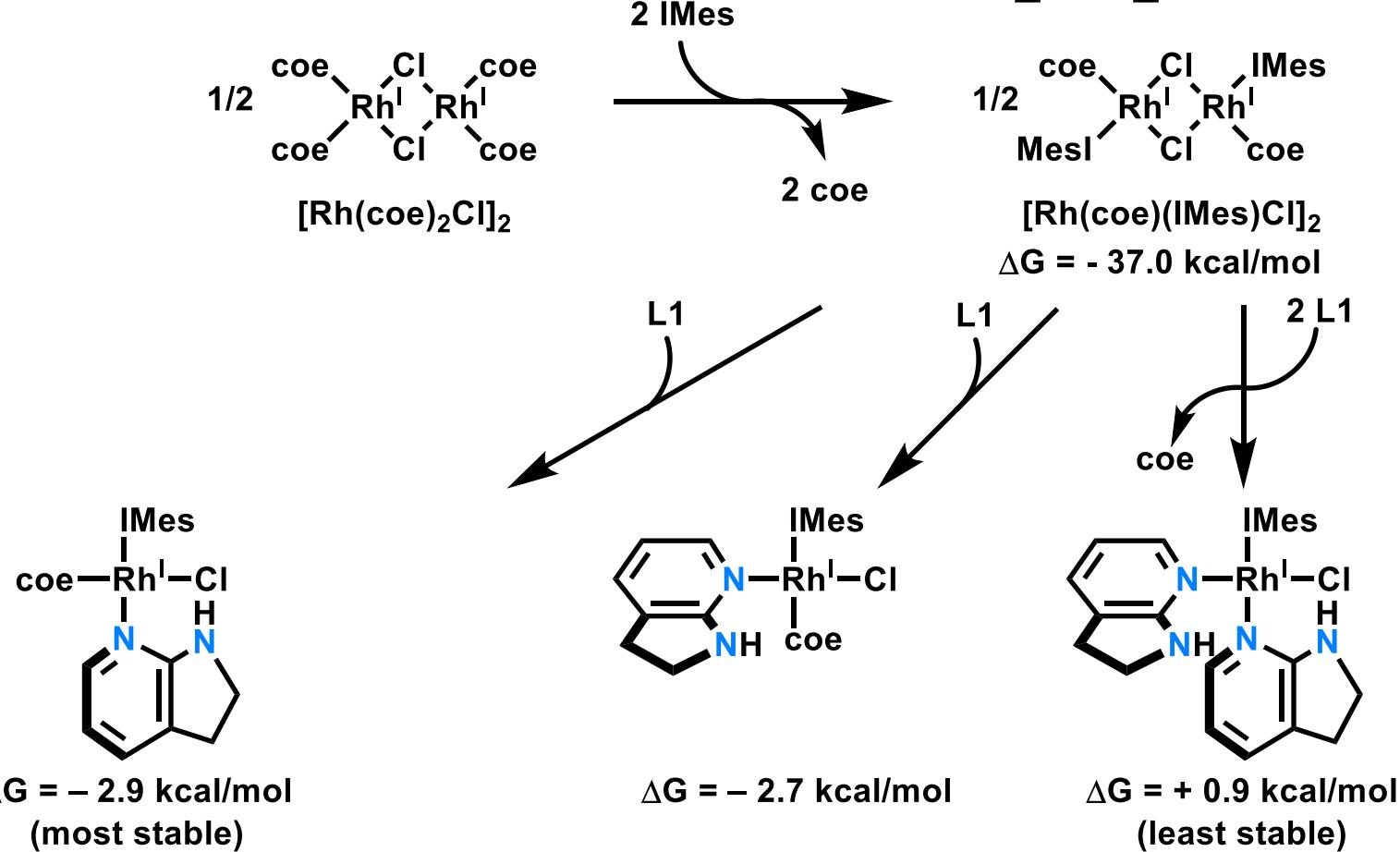
Mechanistic Study - Wang's Group -



Questions

1. Regioselectivity of enamine formation
2. Coordination mode of Rh intermediate.

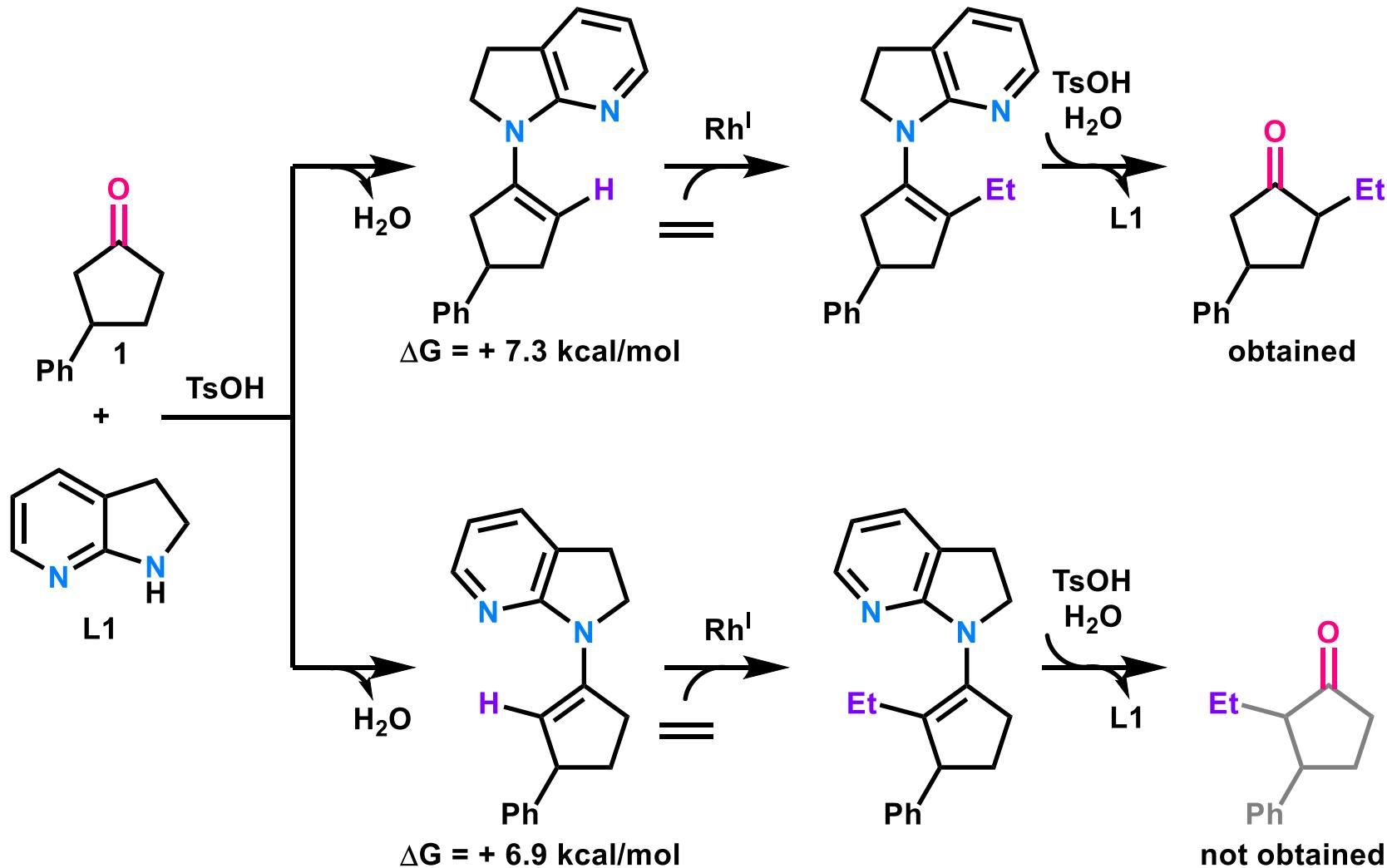
Initiation of $[\text{Rh}(\text{coe})_2\text{Cl}]_2$



Wang's group used the most stable 3cat as the initial active species to compute the catalytic mechanism.

Geometries were optimized and characterized by frequency analysis calculations to be minima or transition states (TSs) at the B3LYP/BSI level in the gas phase, where BSI denotes a basis set combining SDD for rhodium and 6-31G(d,p) for nonmetal atoms. The energies were then improved by M06/BSII//B3LYP//BSI single-point energy calculations with solvent effects simulated by the SMD solvent model, using the experimental solvent (toluene).

Enamine Formation



Enamine formation of **1** with **L1** giving **1b** and **1b'** is kinetically favorable and endergonic by 7.3 and 6.9 kcal/mol, respectively.

Therefore, the regioselectivity must be kinetically controlled by the late stage involving Rh catalyst.

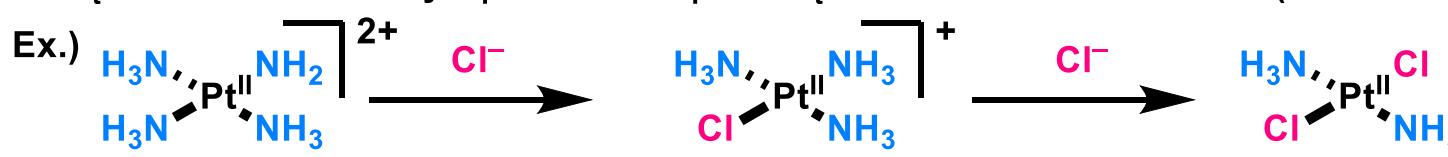
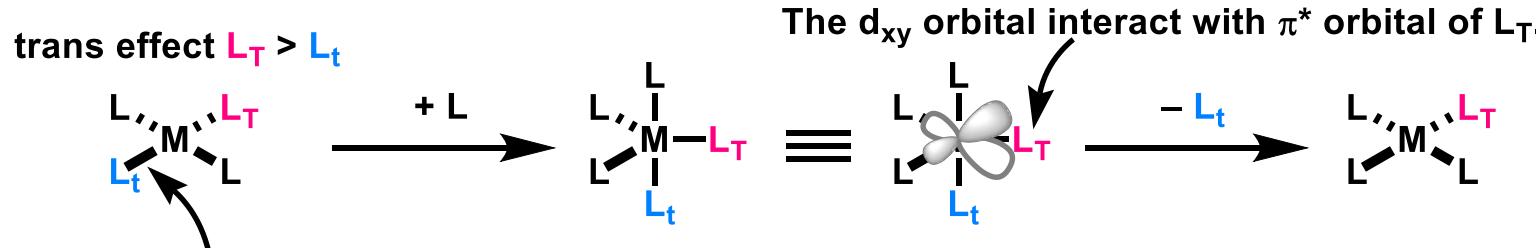
Trans Effect and Trans Influence

The trans effect refers to the observation that certain ligands increase the rate of ligand substitution when positioned trans to the departing ligand.

The trans influence refers to the impact of a ligand on the length of the bond trans to it in the ground state of a complex.

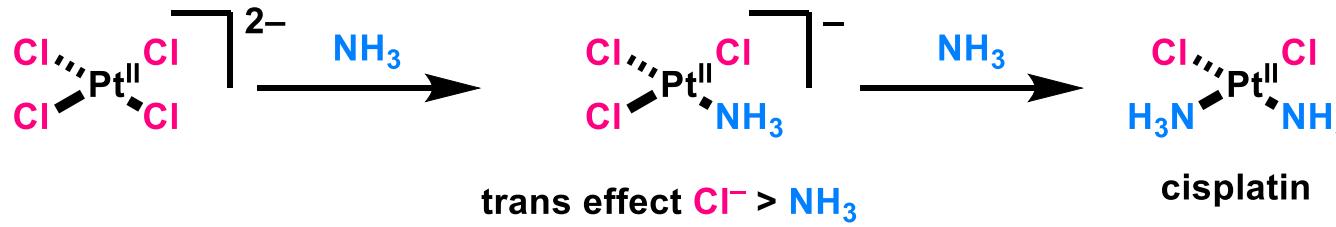


Strong trans effect = strong σ-donor + strong π-acceptor



trans effect Cl⁻ > NH₃

transplatin

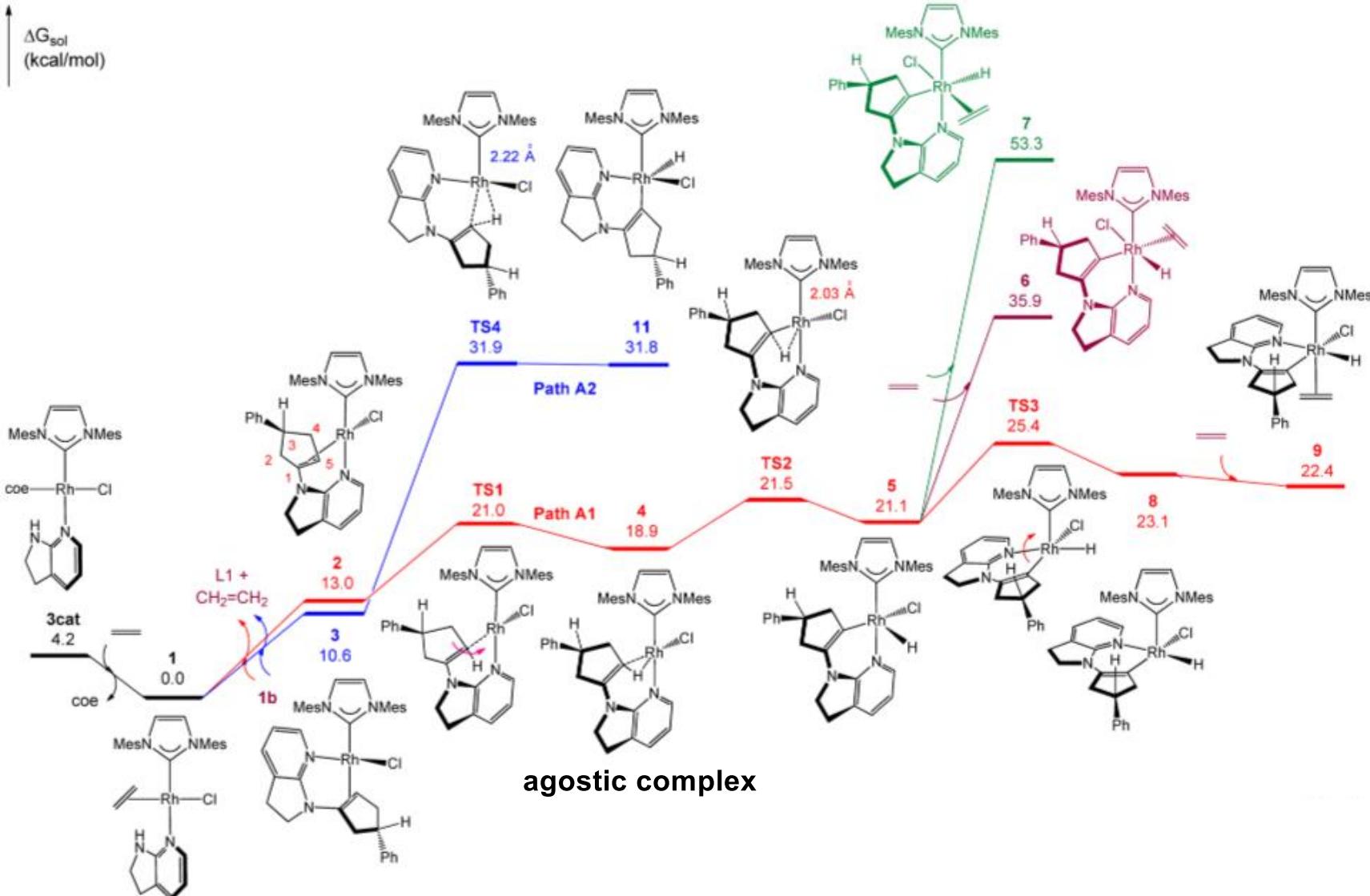


trans effect Cl⁻ > NH₃

cisplatin

1) Quagliano, J. V.; Schubert, L. *Chem. Rev.* **1952**, *50*, 201. 2) Appleton, T. G.; Clark, K. C.; Manzer, L. E. *Coord. Chem. Rev.* **1973**, *10*, 335

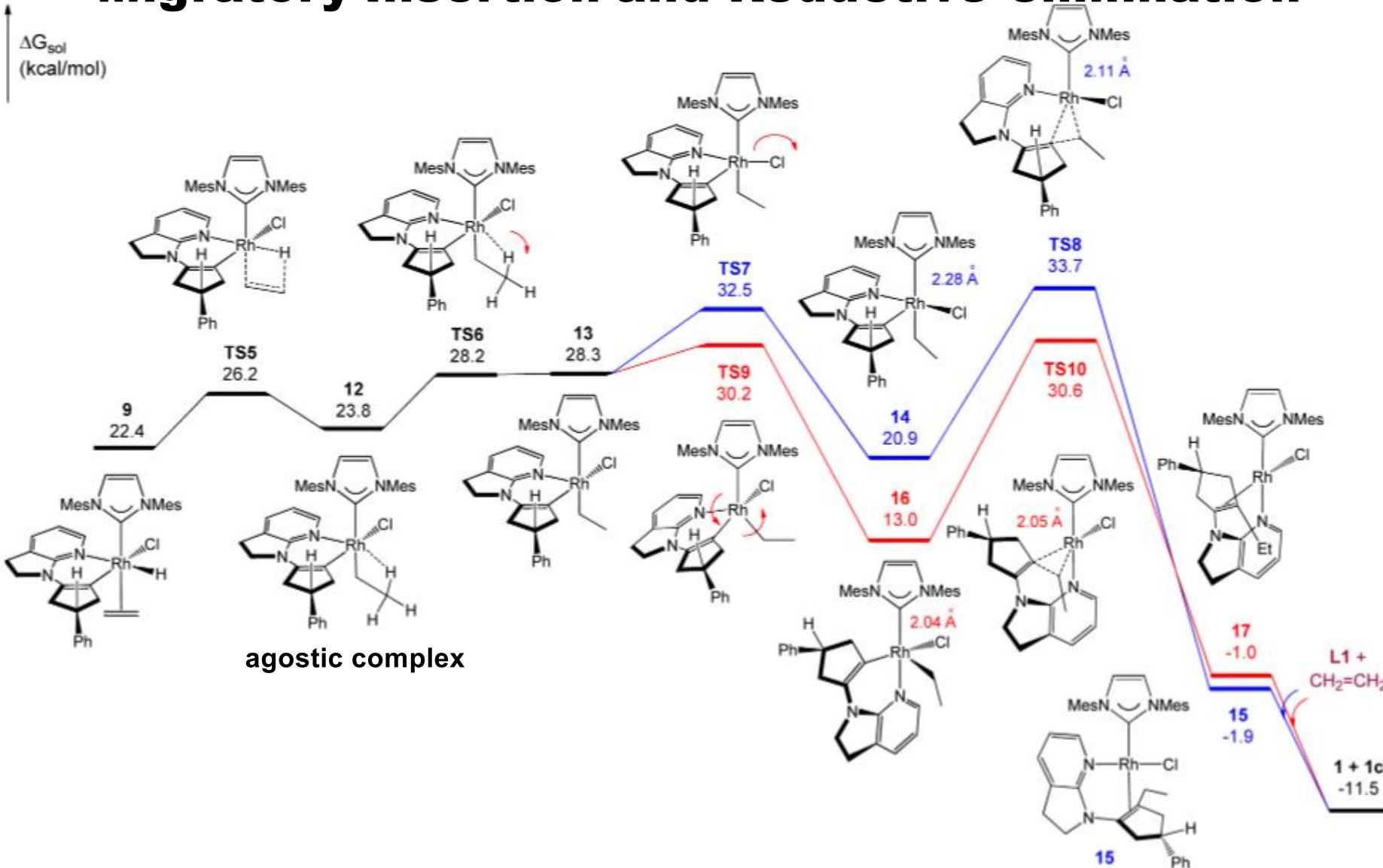
Oxidative Addition and Coordination



TS4 is 10.4 kcal/mol higher than TS2 owing to the strong trans-effect of IMes ligand.

The direct coordination of ethylene to the empty site of 5 is forbidden because 6 and 7 were high-energy structures. Therefore, the ligand in 5 rotates to give 8 with an empty site trans to IMes. Then, ethylene occupies the empty site of 8 to form an 18e Rh^{III} octahedral complex 9.

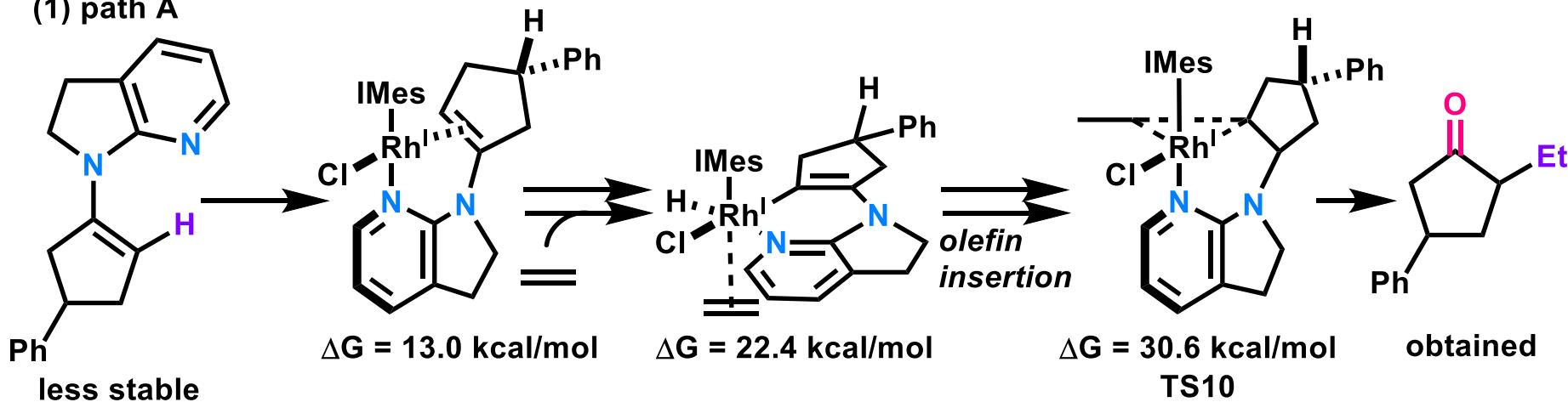
Migratory Insertion and Reductive elimination



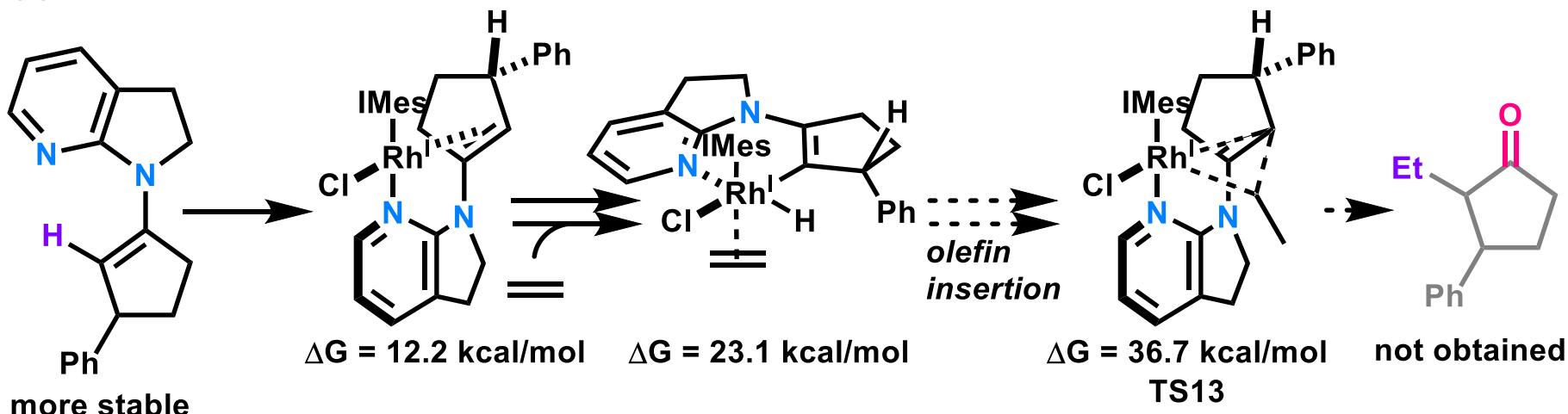
The higher 14 and TS8 than 16 and TS10, respectively, can be attributed to the strong trans-effect of IMes ligand and ethyl in 14 and TS8. The equatorial ligand in 13 first rotates to give 16 with an empty site cis to IMes. Subsequently, reductive elimination occurs to form Rh^I complex 17.

Regioselectivity of Alkylation

(1) path A

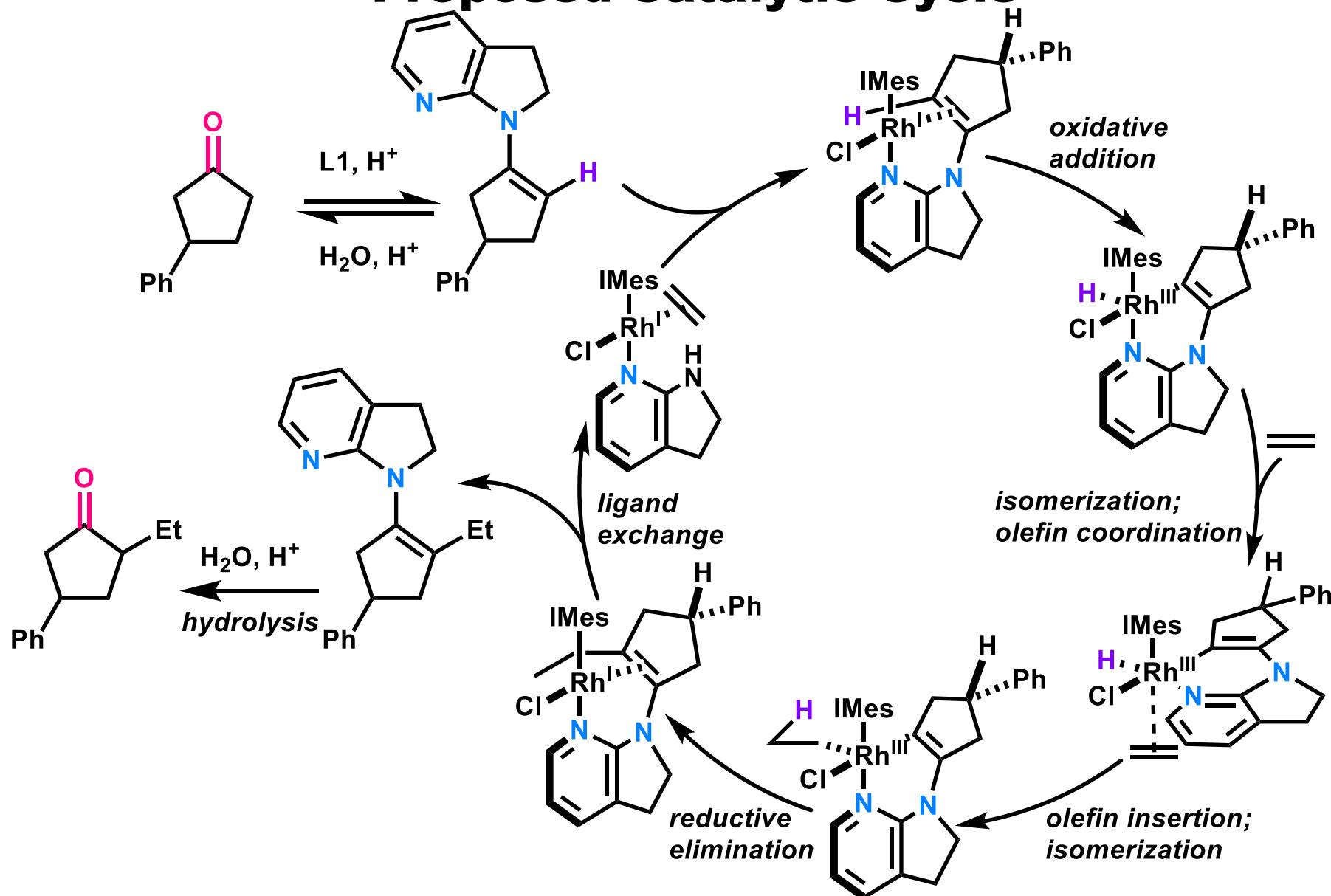


(2) path B



The rate-determining TS10 in path A is 6.1 kcal/mol lower than TS13 in path B, well accounting for the experimental regioselectivity.

Proposed Catalytic Cycle

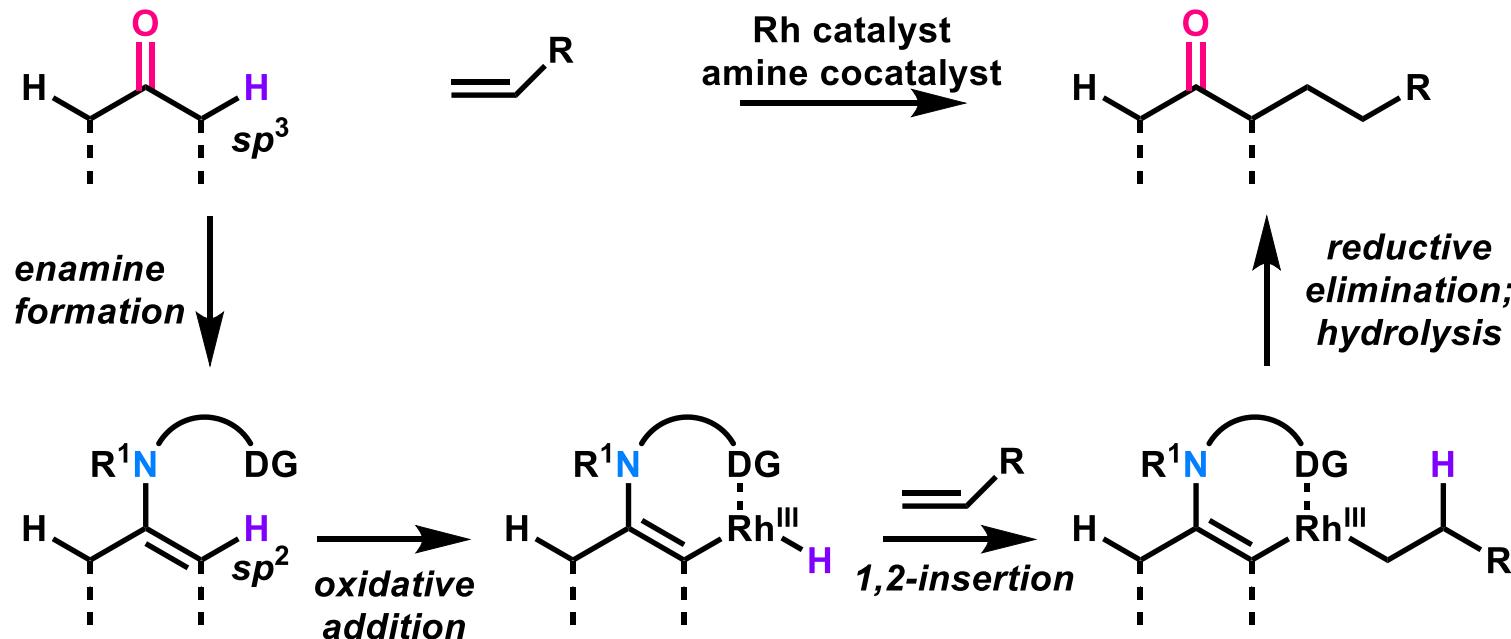


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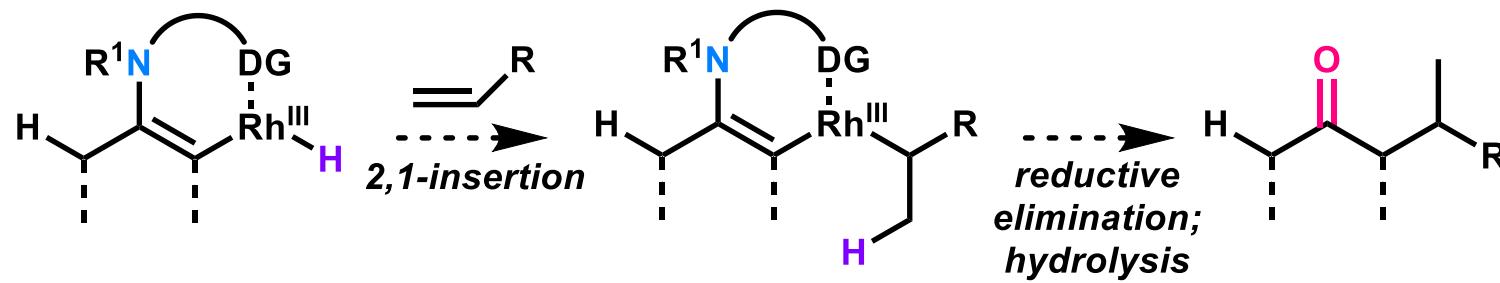
Concepts

(1) Previous results: linear selective alkylation

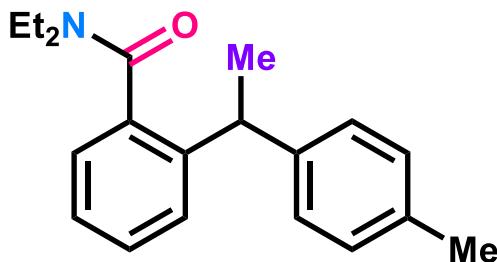
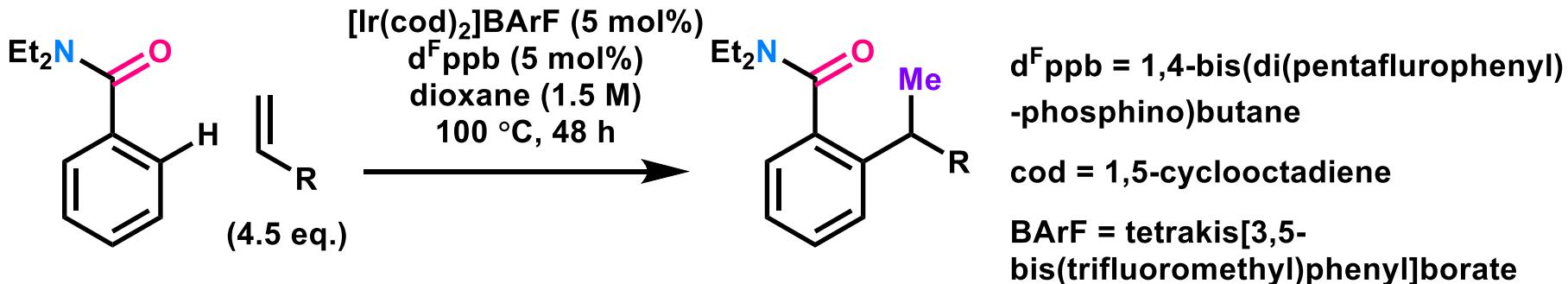


(2) Branched selective alkylation

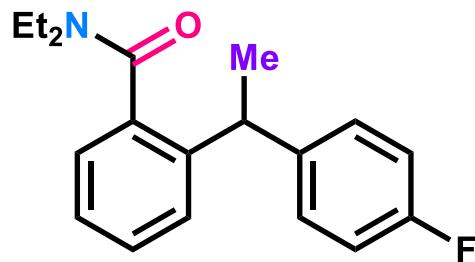
If 1,2-insertion occurred instead of 2,1-insertion, branched alkylated products would be obtained.



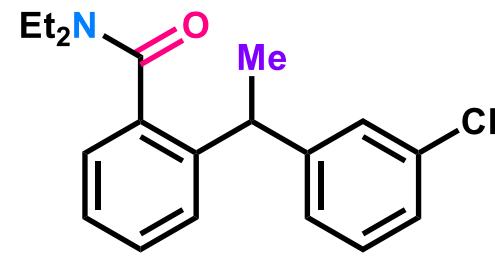
Branched-Selective Alkylation by Bower's Group



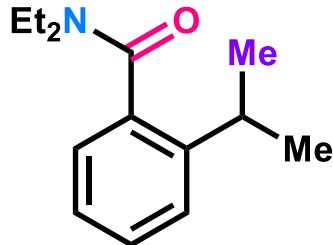
78%
branched : linear >25:1



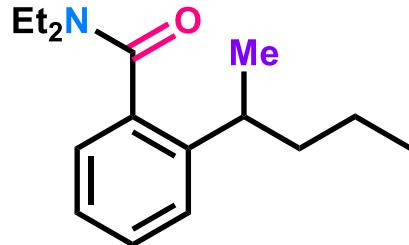
quant.
branched : linear >25:1



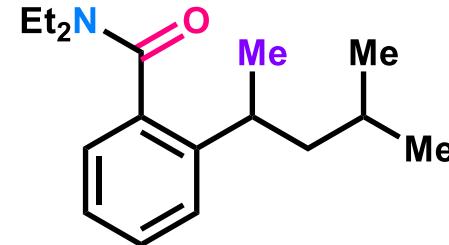
92%
branched : linear >25:1



79%
branched : linear >25:1

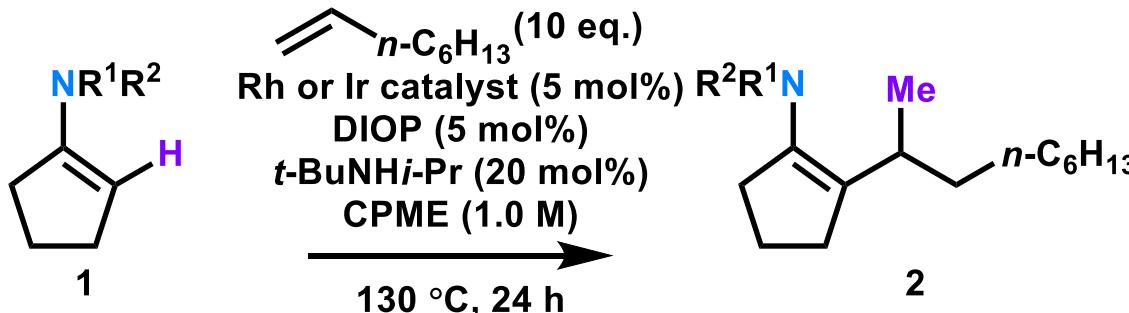


78%
branched : linear >25:1

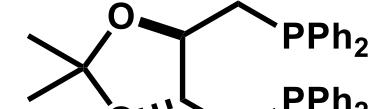
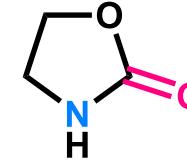
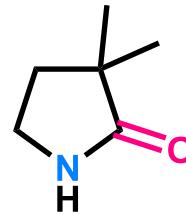
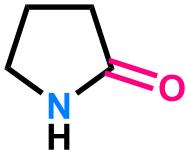
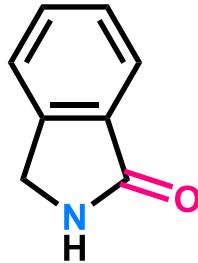


quant.
branched : linear >25:1

Optimization for Catalysts

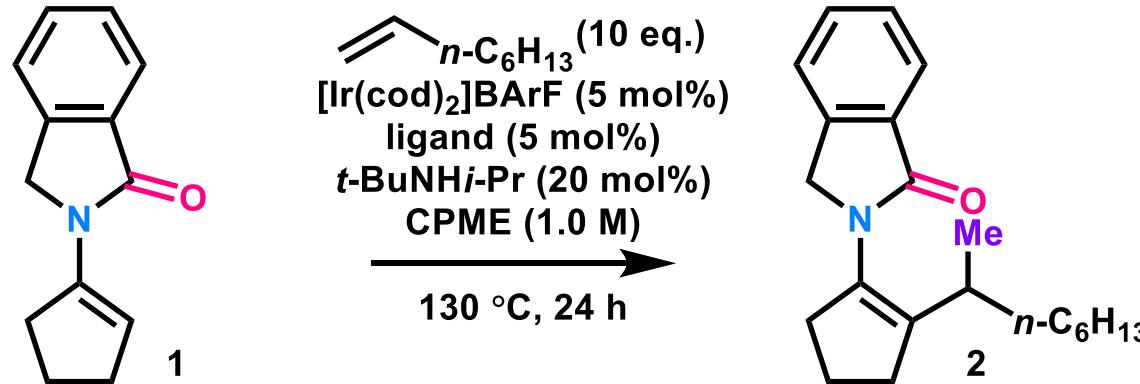


entry	Rh or Ir catalyst	amide	NMR yield of 2 (%)	branched/linear
1	$[\text{Ir}(\text{cod})_2]\text{BArF}$	A1	91	> 20:1
2	$[\text{Ir}(\text{cod})_2]\text{BArF}$	A2	56	17:1
3	$[\text{Ir}(\text{cod})_2]\text{BArF}$	A3	56	> 20:1
4	$[\text{Ir}(\text{cod})_2]\text{BArF}$	A4	21	> 20:1
5	$[\text{Rh}(\text{cod})_2]\text{BArF}$	A1	< 5	—

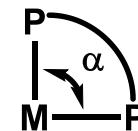


- The desired 2 was obtained with high selectivity (entry 1-4). A1 gave the best results.
- By using $[\text{Rh}(\text{cod})_2]\text{BArF}$ as a catalyst instead of $[\text{Ir}(\text{cod})_2]\text{BArF}$, almost no desired product was obtained (entry 5).

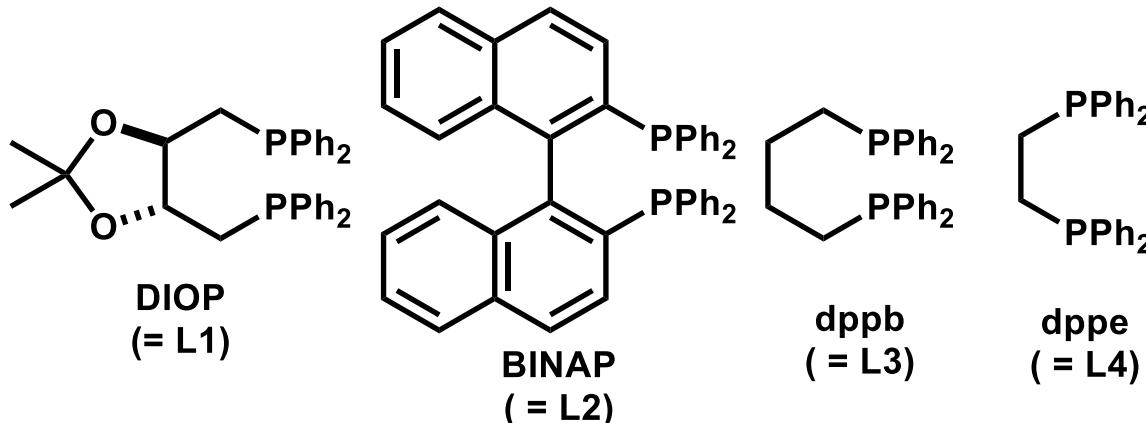
Optimization for Ligands



entry	ligand	bite angle	NMR yield of 2 (%)	branched/linear
1	L1	98°	91	> 20:1
2	L2	92°	37	5:1
3	L3	98°	60	17:1
4	L4	85°	56	4:1
5	d ^F ppb (= L5)	–	< 5	–



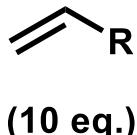
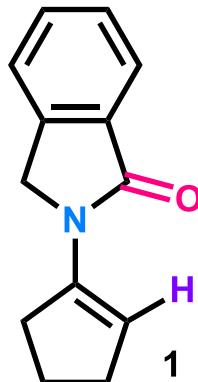
bite angle = α°



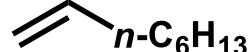
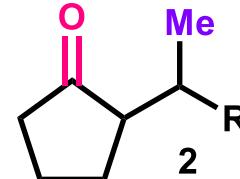
1. Ligands with a large bite angle gave excellent branched selectivity (entry 1, 3).
 2. L5 gave a low conversion (entry 5). Electron-rich ligands were required for this reaction.

1) Xing, D.; Dong, G. *J. Am. Chem. Soc.* **2017**, *139*, 13664. 2) Dierkes, P.; van Leeuwen, P. *J. Chem. Soc., Dalton Trans.* **1999**, 1519.

Substrate Scope

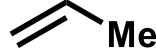


$[\text{Ir}(\text{cod})_2]\text{BArF}$ (5 mol%)
 ligand (5 mol%)
 $t\text{-BuNH}_i\text{-Pr}$ (20 mol%)
 CPME (1.0 M)
 130 °C, 24 h;
 $\xrightarrow{\quad}$
 HCl, toluene, 1 h



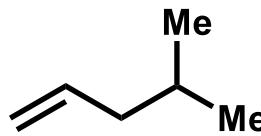
71%

branched:linear > 20:1
dr = 1.2:1



52%

branched:linear > 20:1



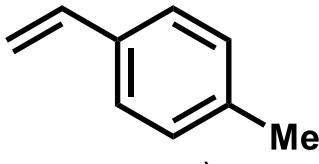
55%

branched:linear > 20:1
dr = 1.7:1



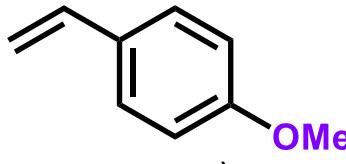
37%

branched:linear > 20:1
dr = 1.3:1



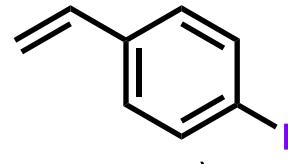
70%^{a)}

branched:linear > 20:1
dr = 1.1:1



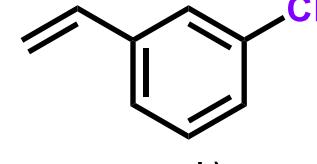
66%^{a)}

branched:linear > 20:1
dr = 1.1:1



53%^{a)}

branched:linear = 19:1
dr = 1.1:1

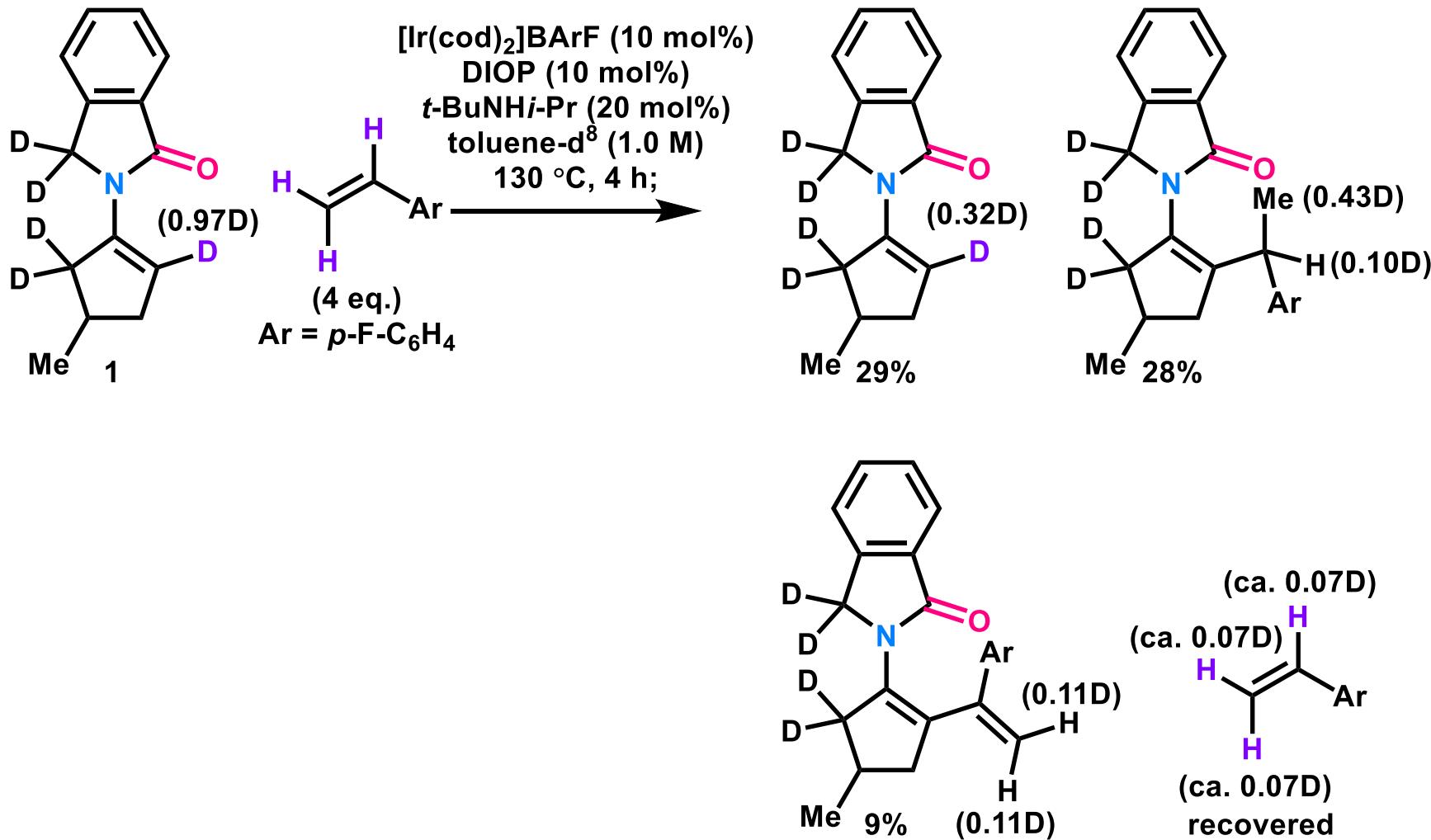


38%^{b)}

branched:linear > 20:1
dr = 1.1:1

a) The crude mixture was treated with Pd/C under H_2 (balloon) to convert oxidative olefination product to the alkylation product. b) The corresponding enamide was isolated before hydrolysis.

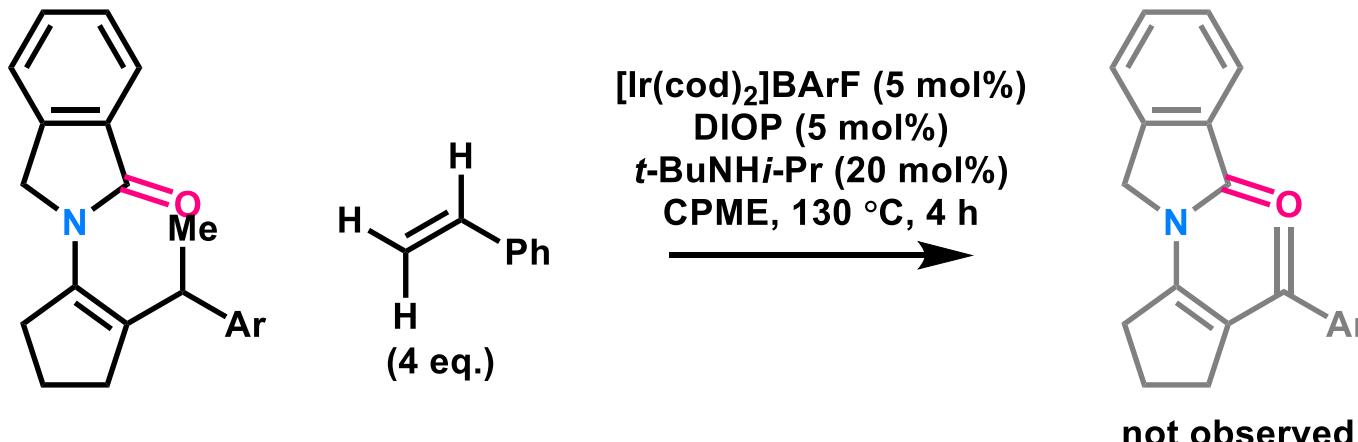
Deuterium Experiments (1)



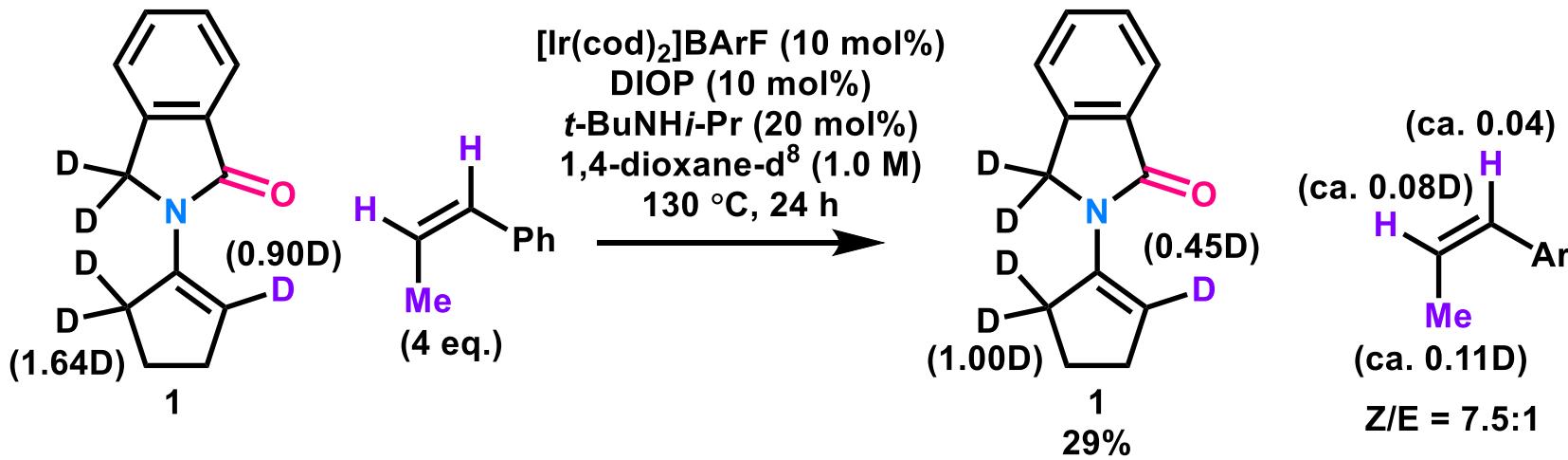
1. Oxidative addition into vinyl C-H bond is reversible.

2. Ir-H insertion into alkenes does occur and is reversible.

Deuterium Experiments (2)

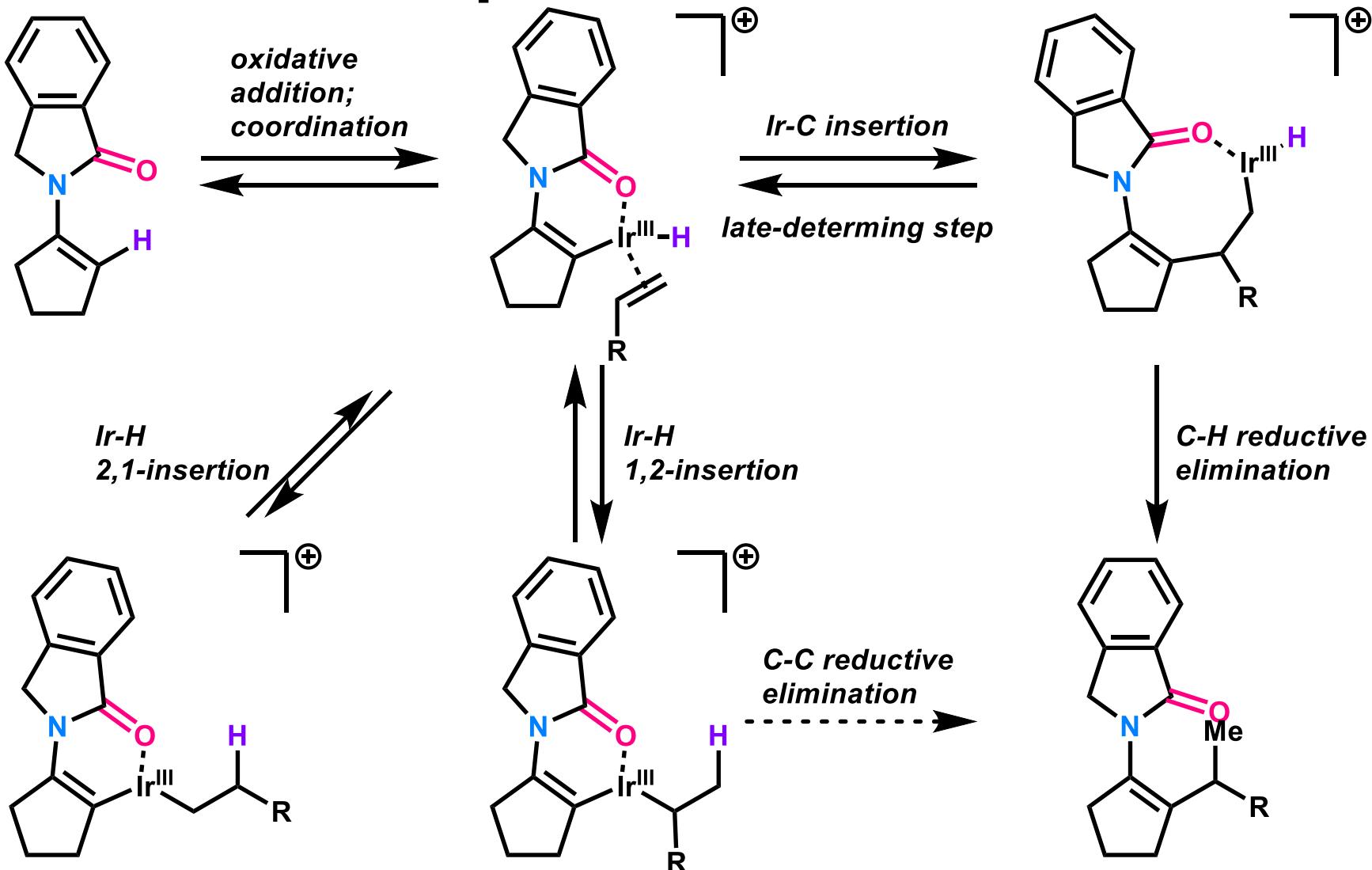


1. Alkenylation product did not come from dehydrogenation of alkylation product.
2. Ir-C insertion into alkenes also occurs and subsequent $\beta\text{-H}$ elimination happens and is reversible.



1. Oxidative addition into vinyl C-H bond, Ir-H insertion into alkenes seemed to occur, but no alkylation product was obtained.
2. Ir-C insertion into alkenes seems to be the main productive pathway.

Proposed Mechanism



Questions:

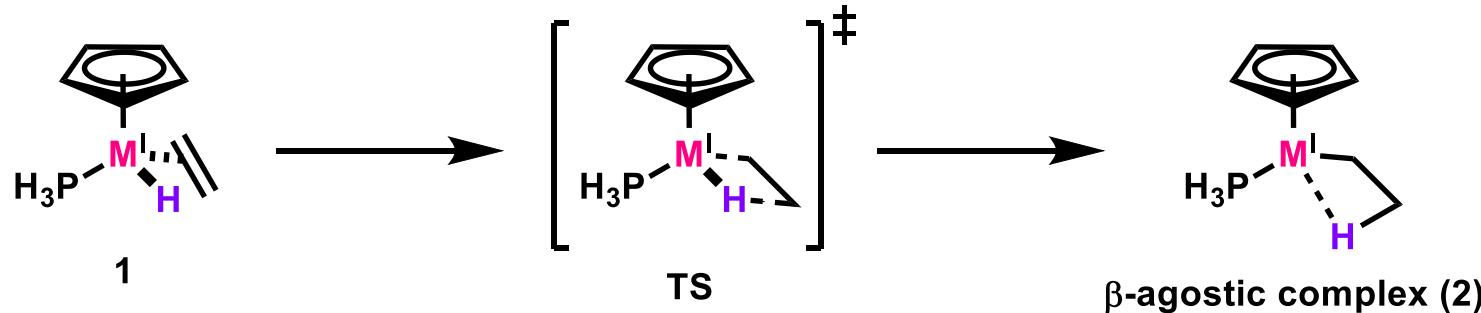
1. What is the difference between Rh and Ir?
2. How do the ligands control regioselectivity?

Rh v.s. Ir - My Opinion -

1. M-H insertion

Ziegler's group studied the hydride migratory insertion processes in $\text{CpM}^{\text{I}}(\text{PH}_3)(\text{CH}_2\text{CH}_2)\text{H}$ ($\text{M} = \text{Co, Rh, Ir}$) by relativistic density functional theory.¹⁾

Relative energies (relative to 1) of species were shown below.



Co	0.0 kcal/mol	+ 0.3 kcal/mol	- 3.4 kcal/mol
Rh	0.0 kcal/mol	+ 2.7 kcal/mol	- 1.0 kcal/mol
Ir	0.0 kcal/mol	+ 6.1 kcal/mol	+ 3.7 kcal/mol

The migratory insertion of ethylene into Rh-H is faster than Ir-H.

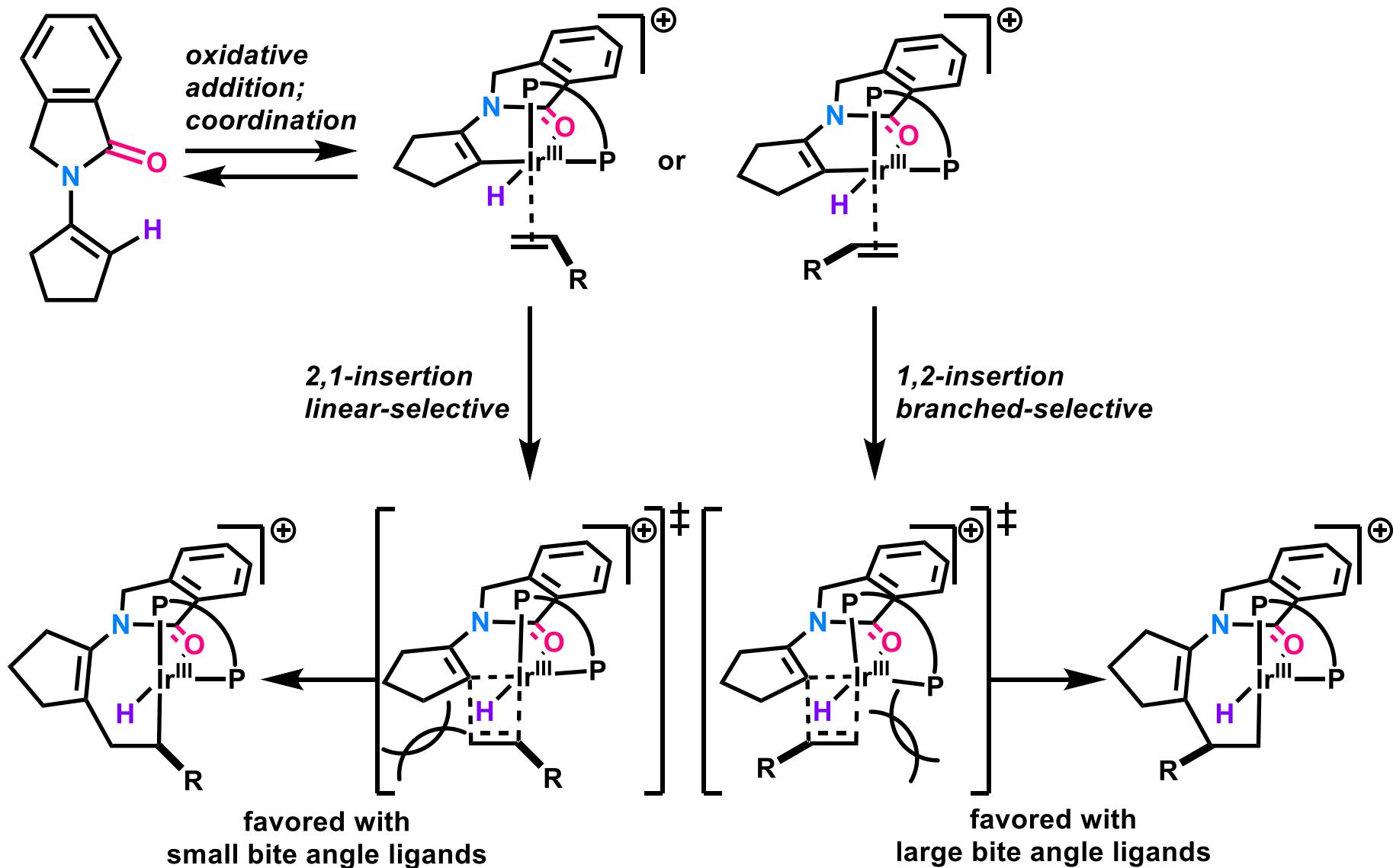
2. M-C insertion

Bond length

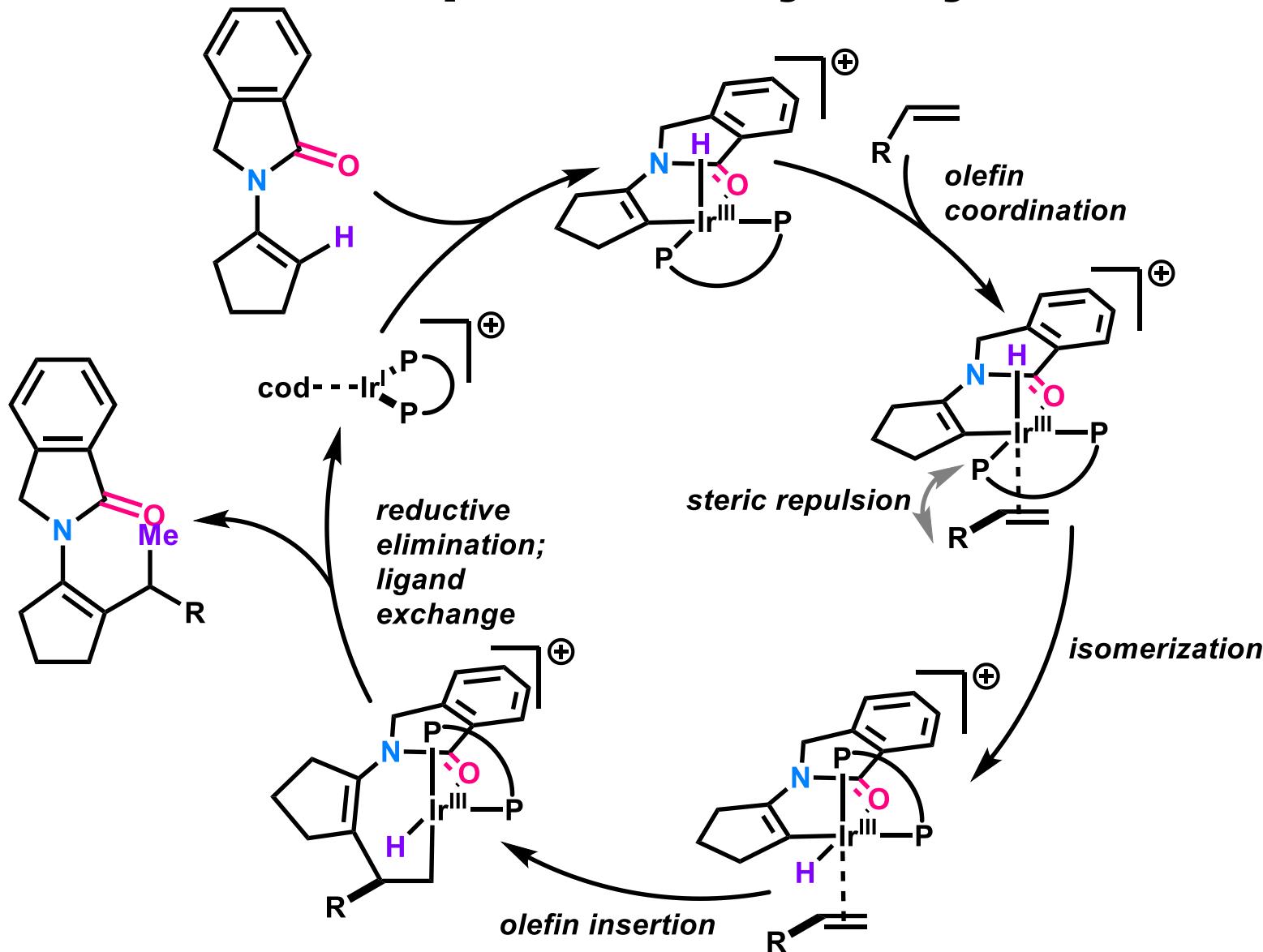
Rh-C < Ir-C

The migratory insertion of alkenes into Ir-C is faster than Rh-C.

Effects of Bisphosphine Ligands

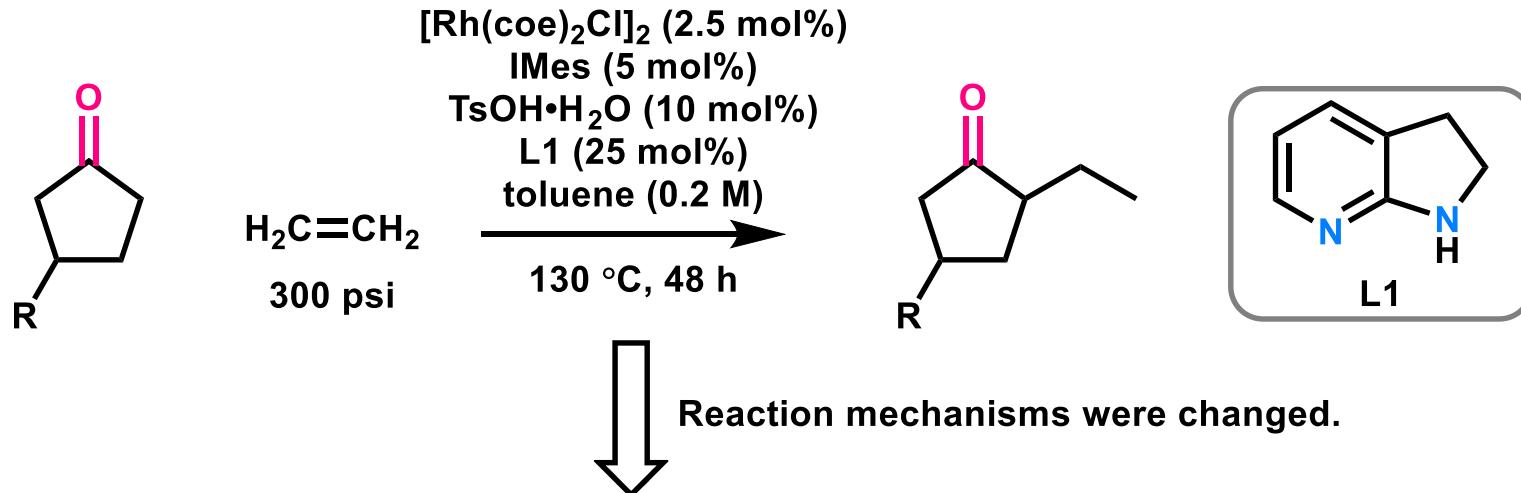


Proposed Catalytic Cycle

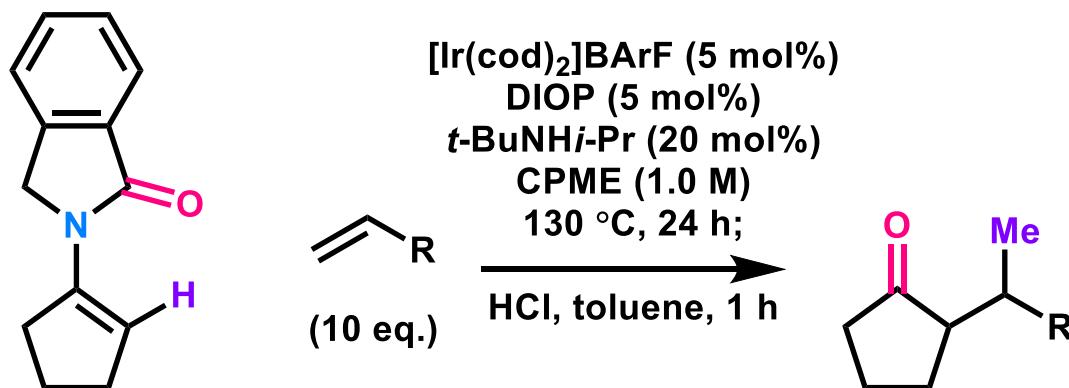


Summary

(1) Linear selective ketone a C-H alkylation



(2) Branched selective ketone a C-H alkylation



1) Mo, F.; Dong, G. *Science* **2014**, *345*, 68. 2) Xing, D.; Dong, G. *J. Am. Chem. Soc.* **2017**, *139*, 13664.