

Chapter 18: Catalytic C-H Functionalization

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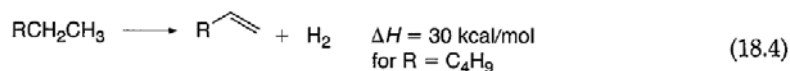
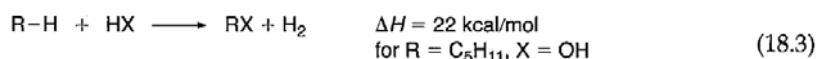
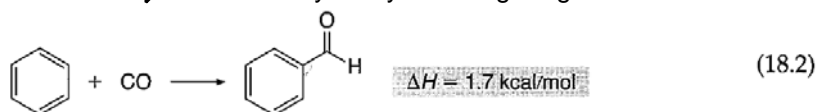
18.1. Overview

C-H activation: Catalytic or stoichiometric reactions of transition metal complexes with the unreactive C-H bonds of alkanes, arenes, or alkyl chains to form products containing a new metal-carbon bond.
(Fiedel-Crafts reaction or ortho lithiation are not C-H activation.)

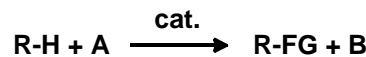
- major challenge:**
- selective activation
 - catalytic process
 - terminal C-H bond functionalization (sec. or tert. C-H: radical approach)
 - methane to methanol

Difficulties

- The reactions are thermodynamically unfavored in many cases.
- ⇒ Oxidation by many oxidizing reagents is downhill.



- The products are typically more reactive than the reactants.
- ⇒ Protect the products by steric or electronic effect.



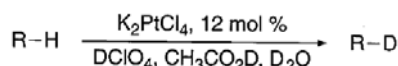
reactive site

18.2. 18.3. Oxidations

Platinum catalyst

Shilov's system

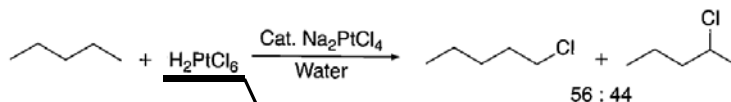
H-D exchange



Alkane	Time (h)	D found (%)	D in ^a		
			Me- (%)	-CH ₂ - (%)	-CH- (%)
Methane	95	25	—	—	—
Ethane	137	91	91	—	—
Pentane	137	75	92	57	—
2-Methylbutane	137	69	83	37	9

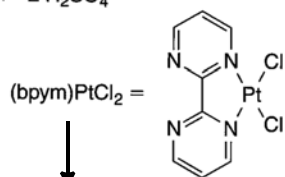
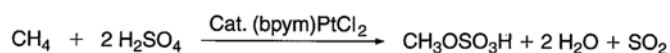
primary C-H selective

functionalization



Pt(IV) as oxidant : impractical

Periana's improvement



TOF = 10⁻² s⁻¹
TON > 500

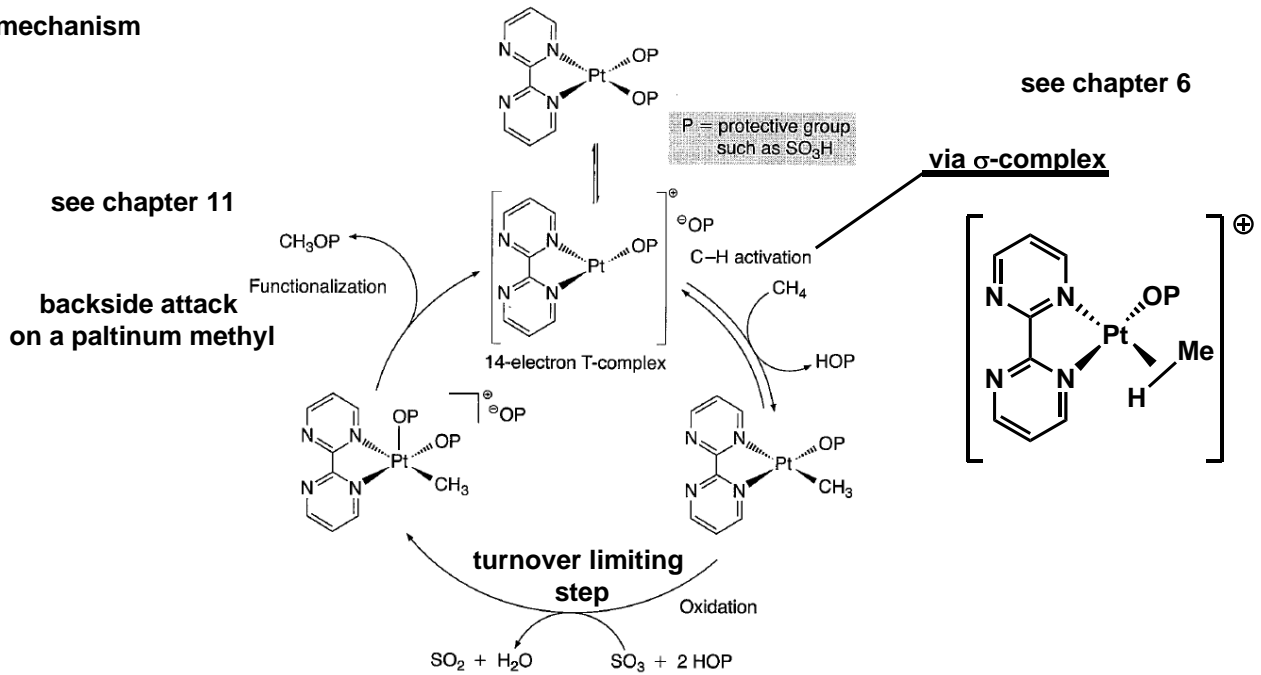
H₂SO₄: corrosive...

remarkable stability

EWG: prevent the further reaction

cf. Polyoxometallate (H₄PV₂Mo₁₀O₄₀) can act as a mediator of oxidation by O₂.

mechanism



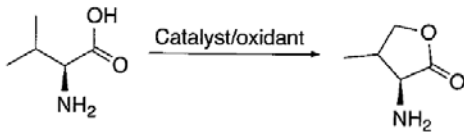
Directed functionalizations

Scheme 18.2

Role of directing group

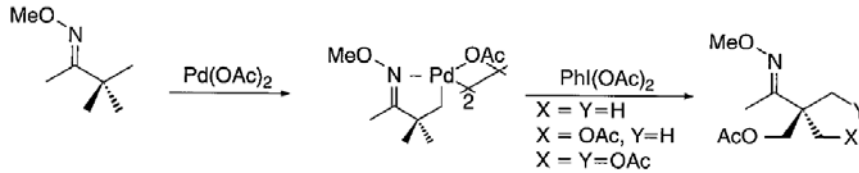
- trigger C-H bond cleavage
- regioselective functionalization

Sames (Shilov's system)

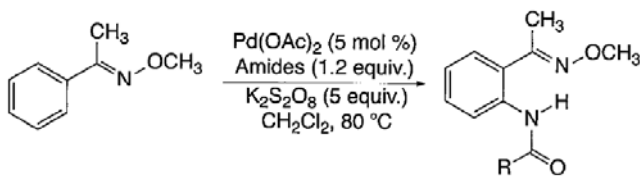


Catalyst/oxidant	Yield	Syn : anti
16% $\text{K}_2\text{PtCl}_4/\text{K}_2\text{PtCl}_6$	21%	5 : 1
10% $\text{K}_2\text{PtCl}_4/\text{CuCl}_2$	67	3 : 1
1% $\text{K}_2\text{PtCl}_4/5\% \text{CuCl}_2$	20	3 : 1

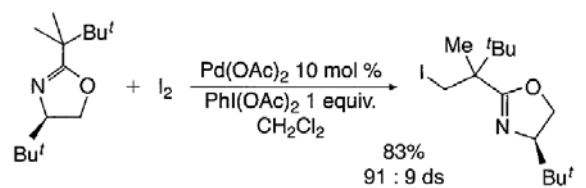
acetoxylation



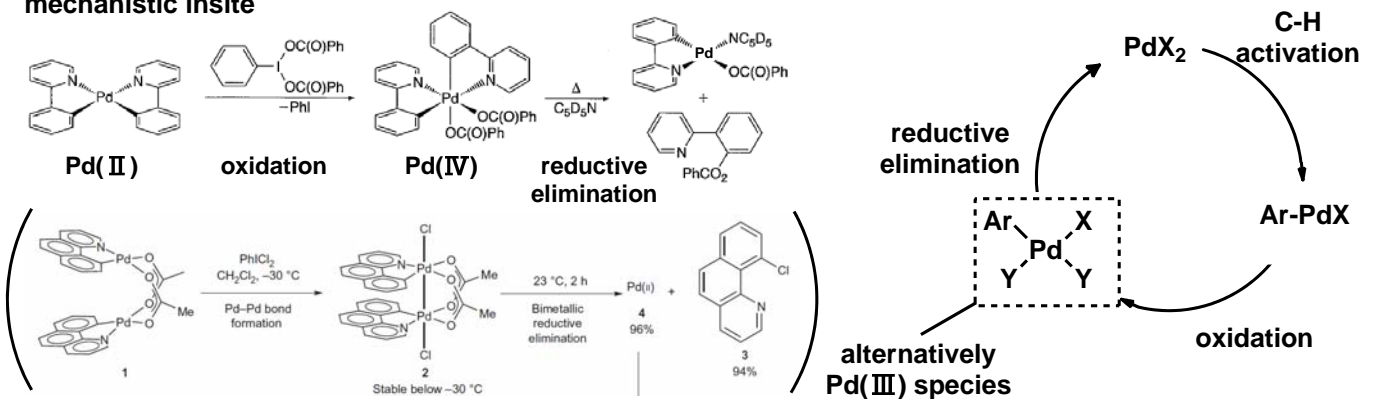
amination



halogenation



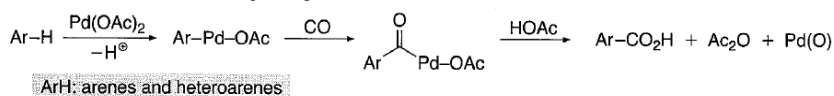
mechanistic insight



18.4. Carbonylation of Arenes and Alkanes

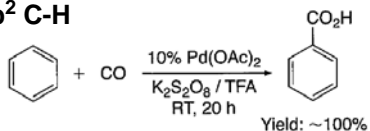
oxidative carbonylation

stoichiometric in Pd by Fujiwara

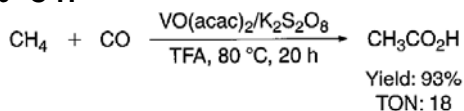


catalytic in Pd

sp² C-H

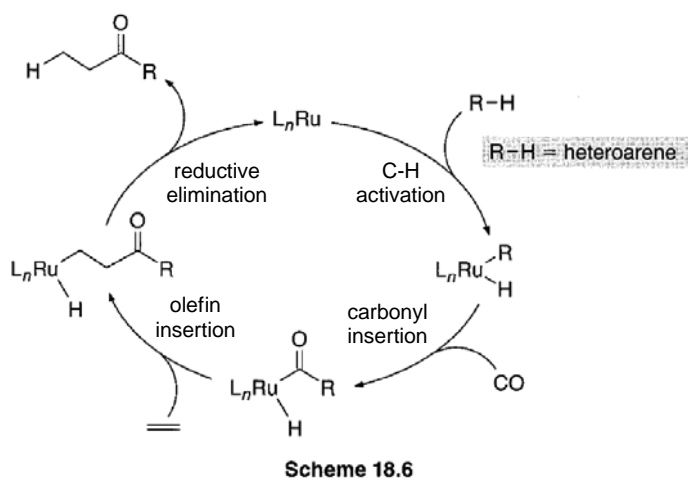


sp³ C-H

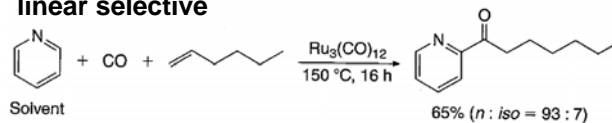


alkylative carbonylation

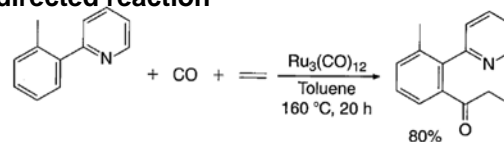
mainly by Ru



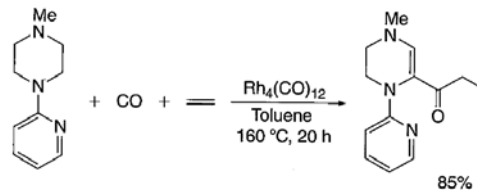
linear selective



directed reaction



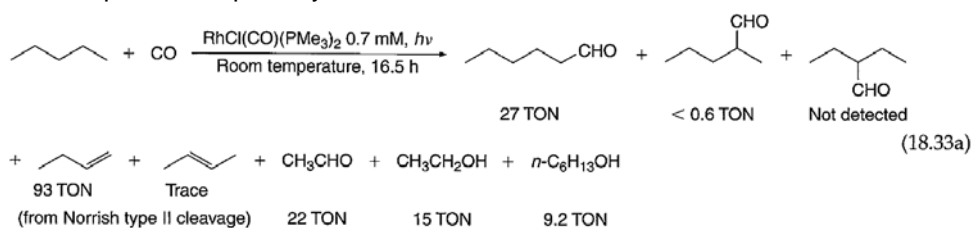
sp³ C-H



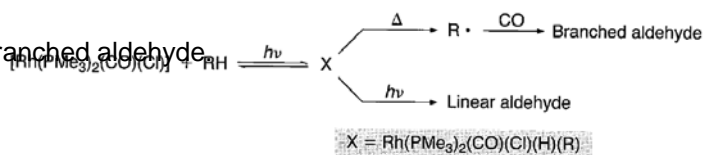
direct carbonylation to aldehyde

endothermic process (thermal conditions were inefficient)

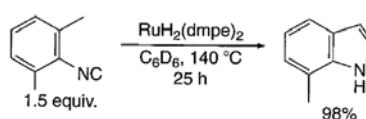
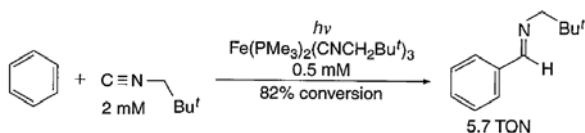
Photochemical processes partially succeeded the reaction.



A radical trap inhibited the formation of the branched aldehyde.

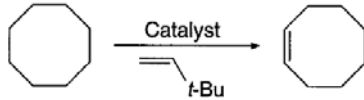


alternative use of isocyanide (weaker multiple bond)



18.5. Dehydrogenation

Early works by Crabtree and Felkin

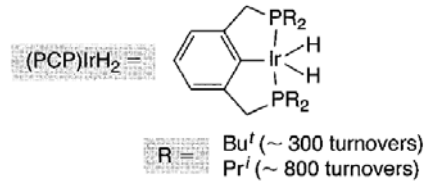
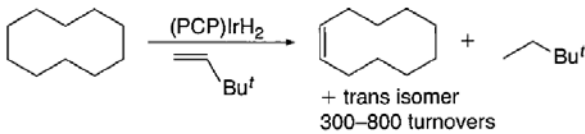


Crabtree: Catalyst = $[\text{Ir}(\text{PR}_3)_2(\kappa^2\text{-O}_2\text{CC}_2\text{F}_5)_2\text{H}_2]^+$ R = Cy or $\text{C}_6\text{H}_4\text{CF}_3$
 35 turnovers with acceptor; 35 turnovers without acceptor in open reflux
 Felkin: Catalyst = $(i\text{-Pr}_3\text{P})_2\text{IrH}_5$, $[(p\text{-FC}_6\text{H}_4)_3\text{P}]_2\text{IrH}_5$, or $[(p\text{-FC}_6\text{H}_4)_3\text{P}]_3\text{RuH}_4$
 45–70 turnovers with acceptor

high temperature condition

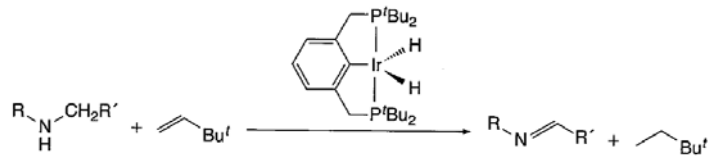
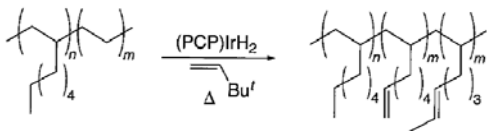
catalyst stability limits turnover numbers

Pincer complex

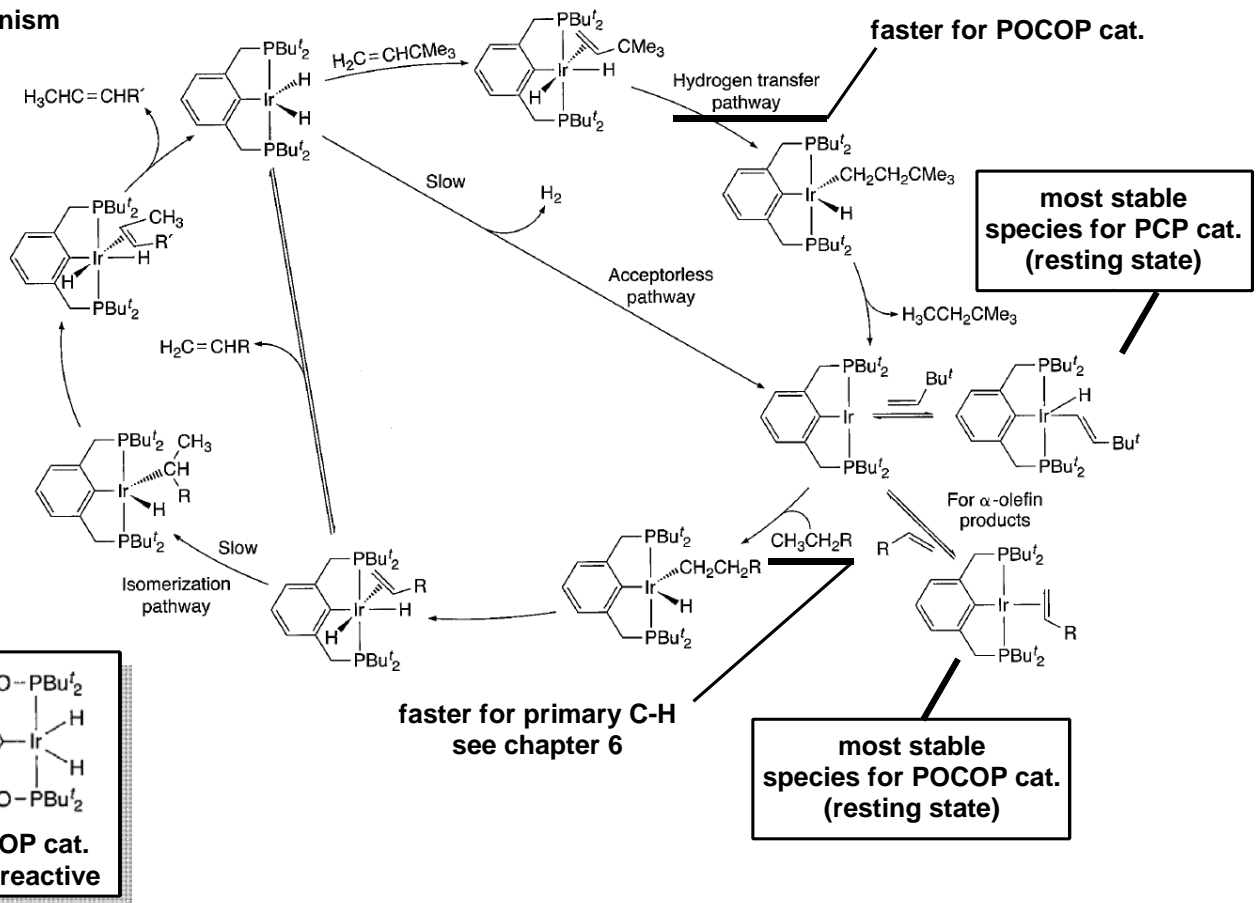


thermally stable complex

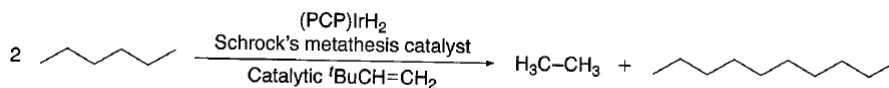
applicable to polymers and amines



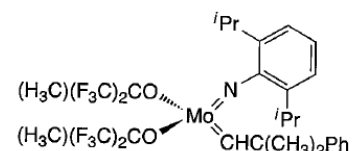
mechanism



dehydrogenation cat. + olefin metathesis cat. = alkane metathesis



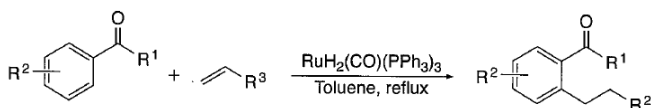
Schrock's metathesis catalyst:



18.6. Hydroarylation

overview

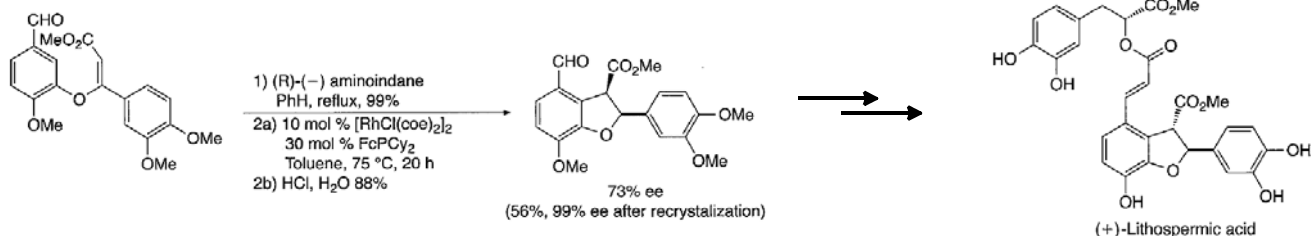
Murai *et al.* 1993



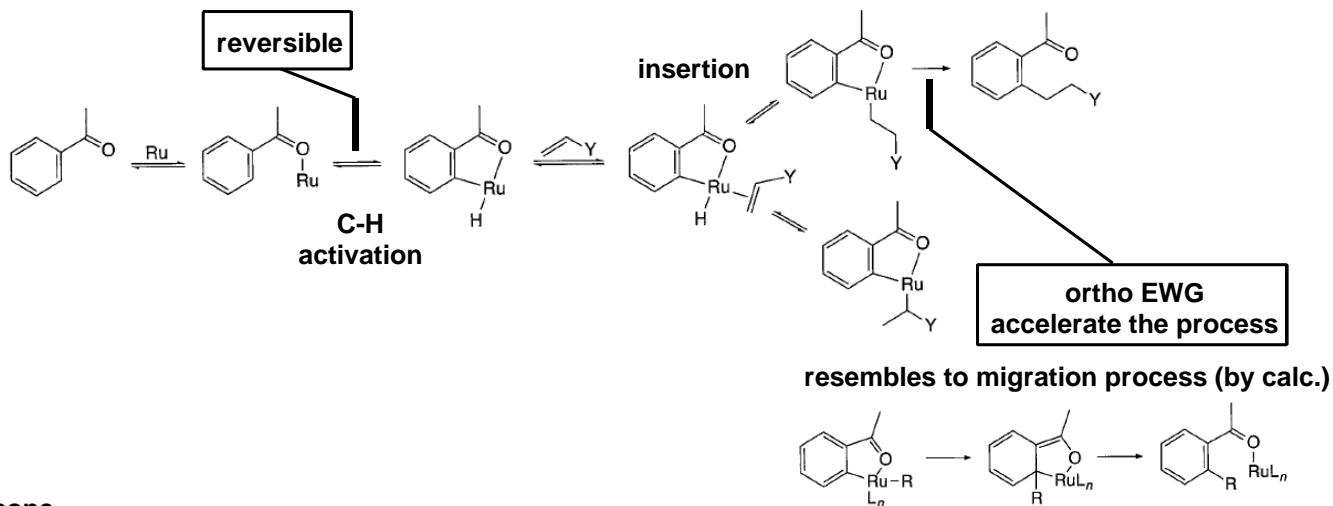
$\text{R}^1 = \text{Me or Bu}^t$; $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Si(OEt)}_3, \text{SiMe}_3, \text{Me or Ar}$

pioneering work

synthesis of lithospermic acid



mechanism



Scope

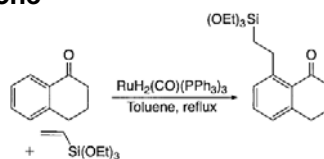
DG part: imine, pyridine, carbonyl, heterocycles

imine

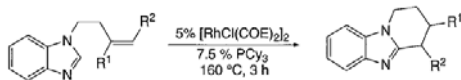


R = ^tBu , ^iBu , $^n\text{C}_4\text{H}_9$, $^n\text{C}_6\text{H}_{13}$, $^n\text{C}_{10}\text{H}_{21}$, Cy , C_6F_5 , Ph , SiMe_3 , $(\text{CH}_2)_8\text{CH}=\text{CH}_2$

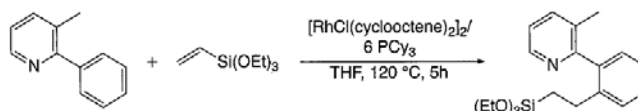
ketone



heterocycle



pyridine



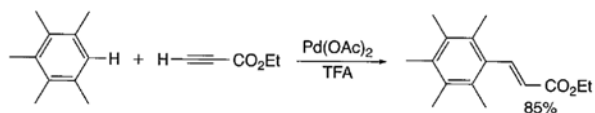
catalyst

ketone DG: $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$, $[\text{RuH}_2(\text{H}_2)(\text{PCy}_3)_2]$, $[\text{Cp}^*\text{Rh}(\text{C}_2\text{H}_3\text{SiMe}_3)_2]$

imine DG: $\text{Ru}_3(\text{CO})_{12}$, $[\text{Rh}(\text{PPh}_3)_3\text{Cl}]$

pyridine DG: $[\text{RhCl}(\text{COE})] + \text{PCy}_3$

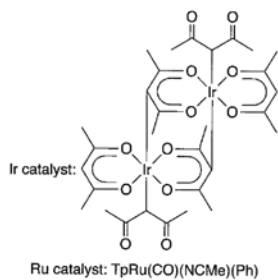
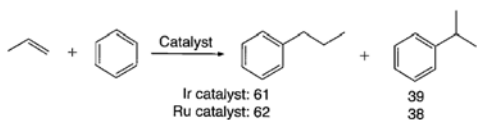
alkynes



more likely via electrophilic substitution

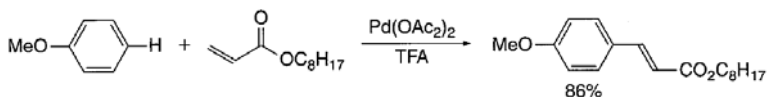
without directing group

hydroarylation



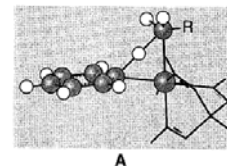
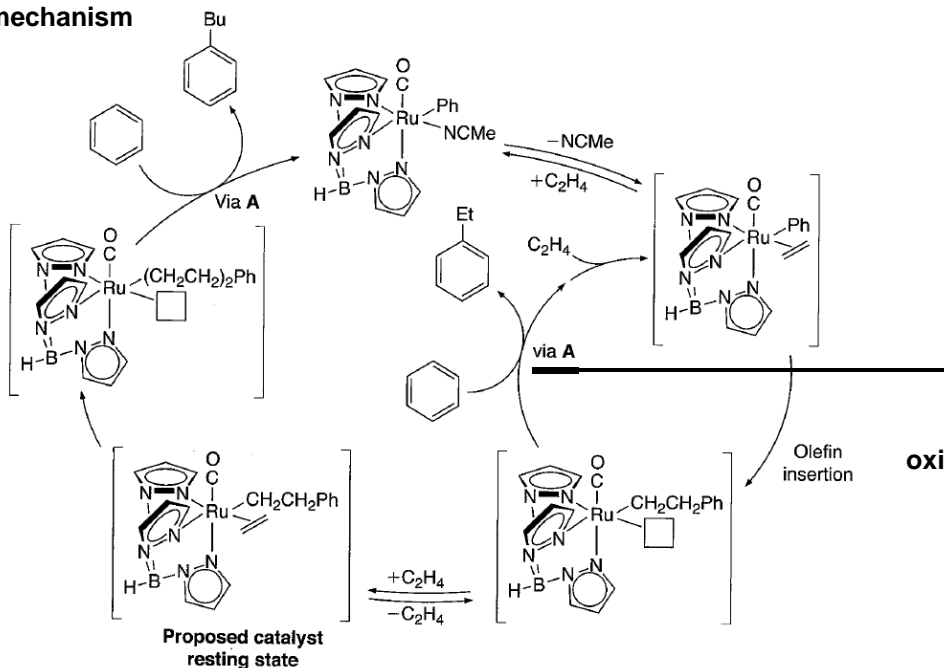
anti-Markovnikov selectivity

oxidative arylation



alternative to the Heck reaction

mechanism

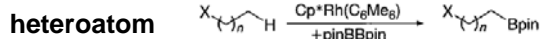
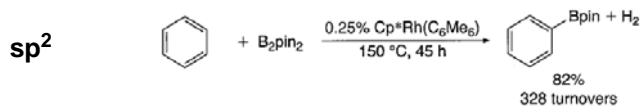
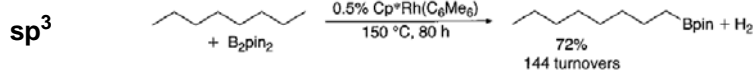


oxidative hydrogen migration

18.7. Functionalization of Alkanes and Arenes with Main Group Reagents

Borylation of Alkanes

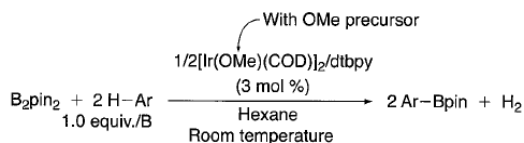
Hartwig's land mark reaction



pin = Pinacolate
X = RO, RC(OR)₂, F, CF₃(CF₂)_m, or R₂N

terminal C-H selective
less hindered position
not at the α position of heteroatom

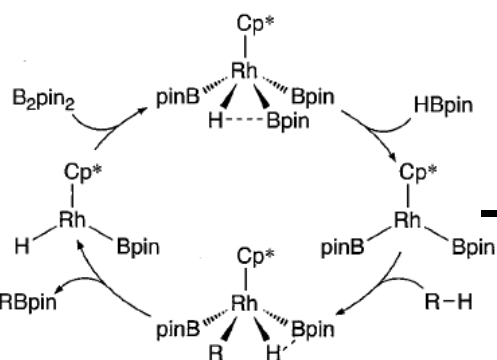
Ir catalyzed borylation of arenes



little electronic preference
controlled by steric effects
complements to electrophilic substitutions

mechanism

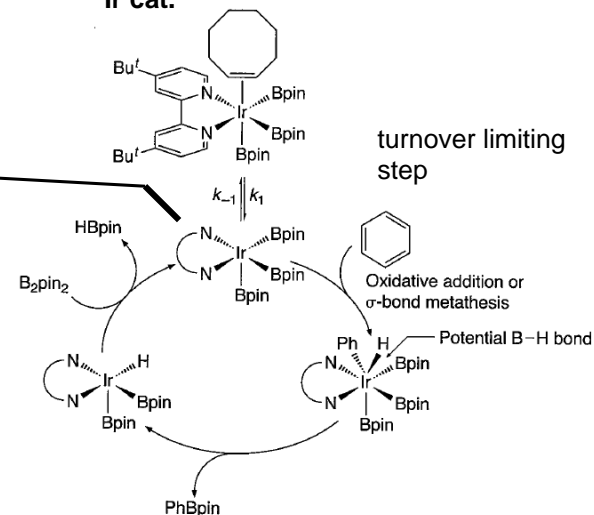
Rh cat. isolated (catalytically active)



R=H : isolated
(catalytically active)

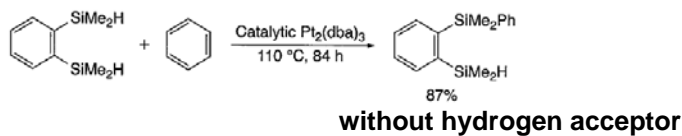
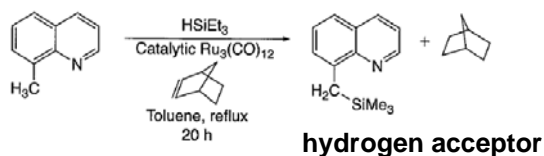
p-orbital on boron assists in the C-H bond cleavage step (chapter 6)

Ir cat.

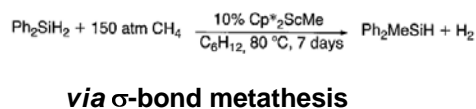
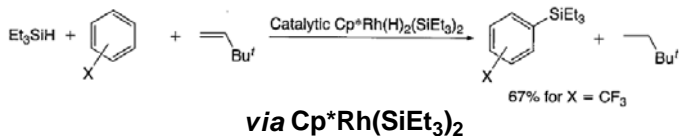


silylation of C-H bonds

with DG

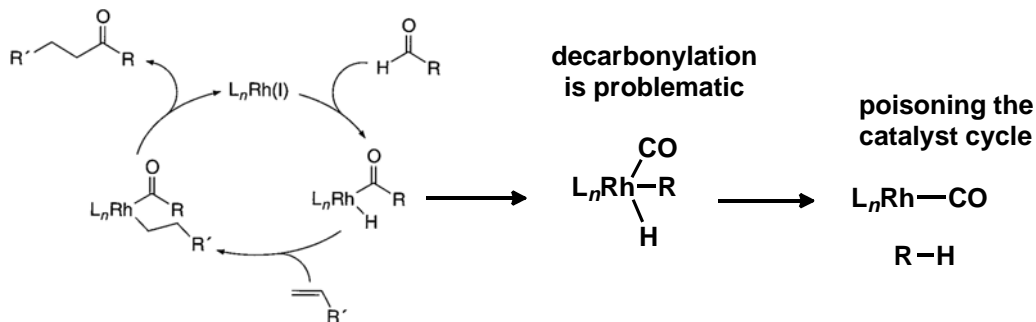


without DG

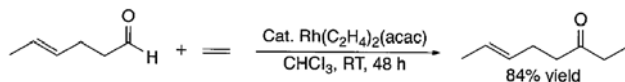


18.8. Hydroacylation

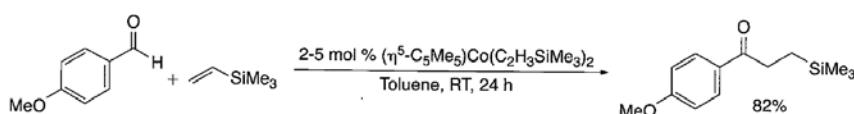
mechanism



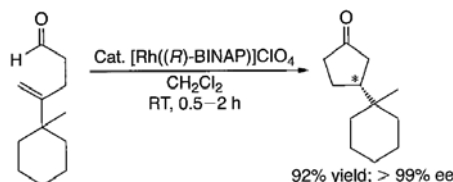
Rh cat.



Co cat.

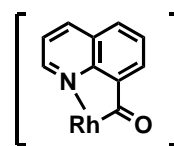
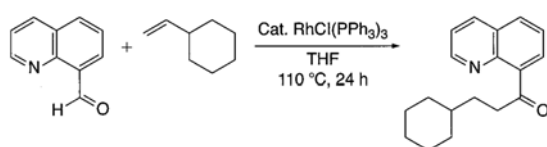


intramolecular asymmetric



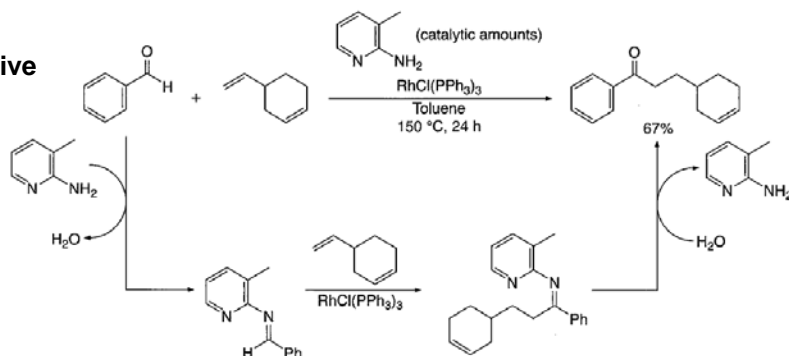
(The use of cationic Rh complex containing chelating ligand suppresses poisoning of the catalyst by decarbonylation.)

directing group



stable metallacycle

imine derivative



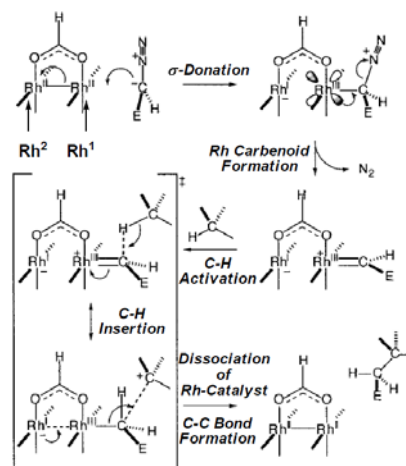
stable metallacycle + less favorable de-insertion of an isocyanide

18.9. Functionalization of C-H Bonds by Carbene Insertions

secondary C-H > tertiary C-H > primary C-H ——— { bond energy
steric factor

favorable at sites that stabilize a buildup positive charge
(favored: α to O, N disfavored: α to ester, OAc)

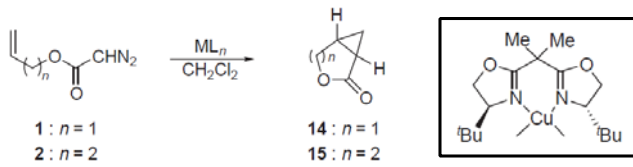
aliphatic C-H > aromatic C-H



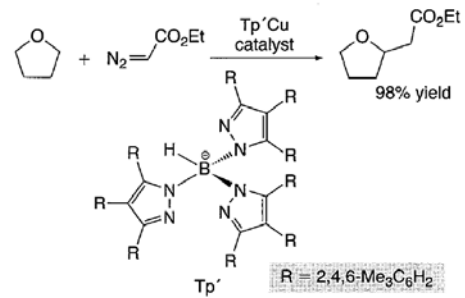
Cu catalyst

The first work was conducted with copper complexes.

intramolecular



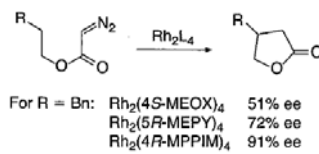
intermolecular



Rh catalyst

intramolecular reaction

asymmetric reaction



for total synthesis

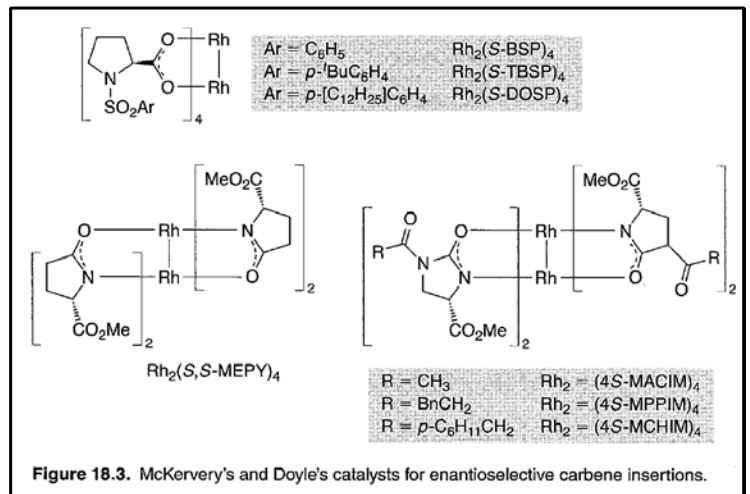
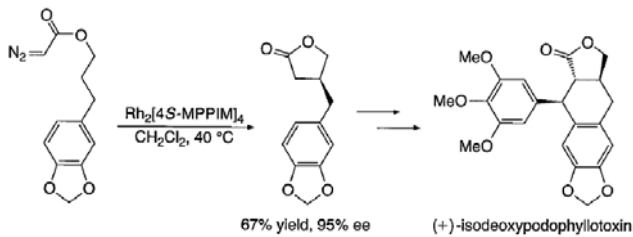
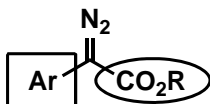


Figure 18.3. McKervery's and Doyle's catalysts for enantioselective carbene insertions.

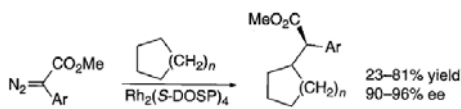
intermolecular reaction (see Mr. Takasu's lit. seminar (D₂))

major problem: self coupling to form olefins

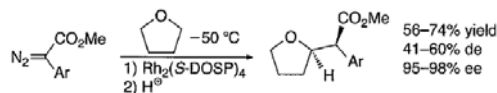


Donor Acceptor

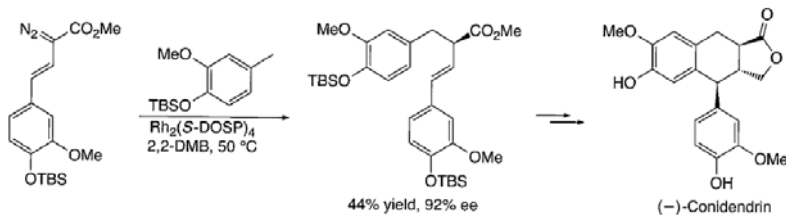
π -Donor- π -acceptor type carbenoids have moderate reactivity. It worked well for intermolecular C-H functionalization.



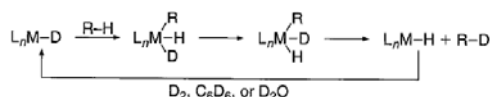
α to heteroatom



for total synthesis



18.10. H/D Exchange



Label compounds directly from natural products or synthetic products.