## 3-2. Cross-coupling and related reactions

### (1) General

R–X + M–R' $\xrightarrow{\text{catalyst}}$ R–R'

X = I, Br, Cl, OTf *etc.*
M = MgX, B(OH)$_2$, ZnCl *etc.*

See: *J. Organomet. Chem.*, **653**, 1–303 (2002) (special issue).
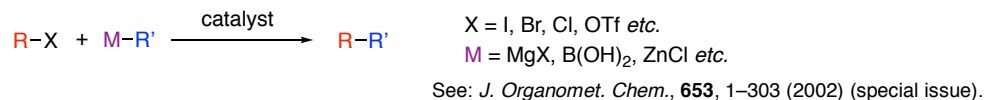
- Nucleophilic substitution of aryl or alkenyl halide, which is believed inert to nucleophilic substitution, took place in the presence of a transition metal complex, such as palladium and nickel.
- The reaction between organohalide and organometal is called 'cross-coupling reaction'.
- The cross-coupling reactions are named according to the organometallic substrate.

<u>Typical mechanism</u>
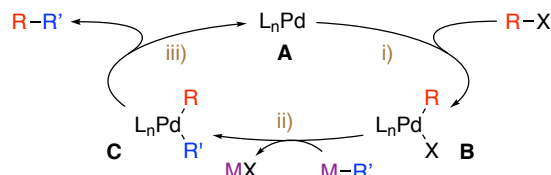


i) Oxidative addition of R–X to palladium(0) **A**:   This step is commonly rate-determining.
ii) Transmetalation between Pd–X and R'–M
iii) Reductive elimination from **C** to form the coupling product R–R' and regenerate **A**

### (2) Kumada–Tamao–Corriu reaction (M = MgX)



X = Cl. Br
R = aryl, alkenyl, 1° alkyl

DPPP = Ph$_2$P⌒⌒PPh$_2$
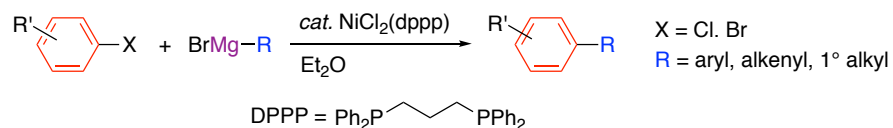
K. Tamao, M. Kumada, *J. Am. Chem. Soc.*, **94**, 4374 (1972); *Bull. Chem. Soc. Jpn.*, **49**, 1958 (1976).
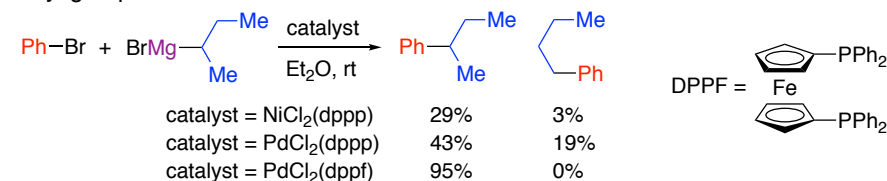R. J. P. Corriu, *Chem. Commun.,* 144 (1972).

<u>General</u>
- When Grignard reagent is used as the organometallic substrate, the cross-coupling reaction is called Tamao–Kumada–Corriu reaction.
- Phosphine–nickel complex is commonly used as the catalyst for the coupling reaction. Other metal complexes, *e.g.* palladium, iron, cobalt, also catalyze the reaction.
- The catalyst precursor, NiCl$_2$(dppp), is reduced to the nickel(0) species through twice transmetalations and following reductive elimination.
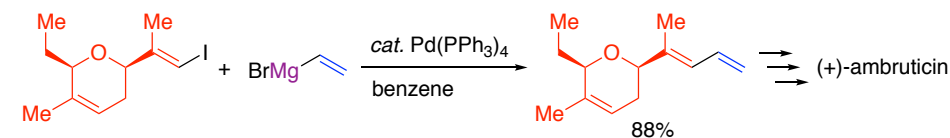
<u>Considerations for organic synthesis</u>
- In the formation of C($sp^2$)–C($sp^3$) bond, alkyl magnesium halides should be chosen as the alkyl substrate to avoid the β-hydride elimination from alkylnickel(II) species.
- The reaction of secondary alkyl magnesium is accompanied with the isomerization of the
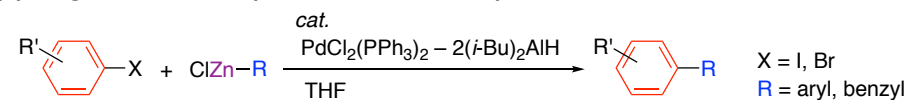
alkyl group.



| catalyst | | |
|---|---|---|
| catalyst = NiCl$_2$(dppp) | 29% | 3% |
| catalyst = PdCl$_2$(dppp) | 43% | 19% |
| catalyst = PdCl$_2$(dppf) | 95% | 0% |

T. Hayashi, M. Kumada, *J. Am. Chem. Soc.*, **106**, 158 (1984).

<u>Application</u>



E. N. Jacobsen, *J. Am. Chem. Soc.*, **123**, 10772 (2001).

### (3) Negishi reaction (M = ZnX, Al, Zr *etc.*)



X = I, Br
R = aryl, benzyl

E.-i. Negishi, *J. Org. Chem.*, **42**, 1821 (1977) (Zn, Al); *J. Am. Chem. Soc.*, **99**, 3168 (1977) (Zr).
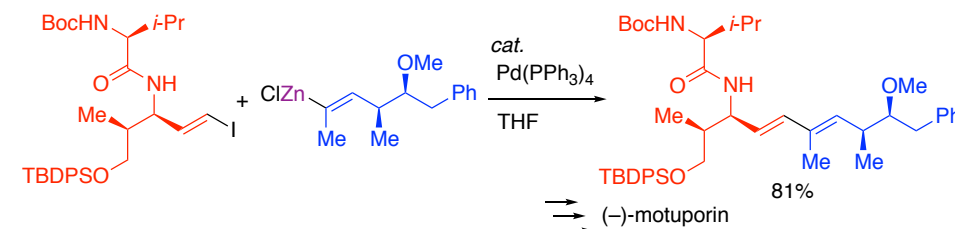
<u>General</u>
- Negishi reaction commonly indicates the cross-coupling reaction between organohalides and organozinc compounds.
- The reaction using organoaluminium or zirconium is also called Negishi reaction.
- Palladium complex is commonly used as the catalyst for Negishi coupling.
- In the original procedure, PdCl$_2$(PPh$_3$)$_2$ was used as the catalyst precursor.   The precursor was reduce to the palladium(0) species through the reduction of the palladium(II) with 2 equiv of (*i*-Bu)$_2$AlH (DIBAH).
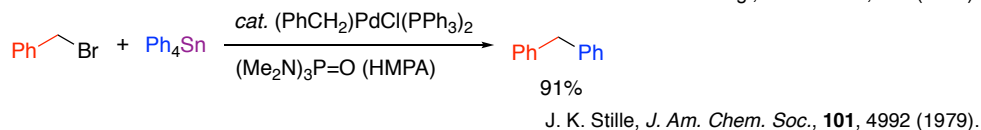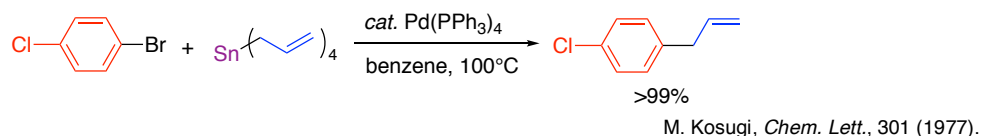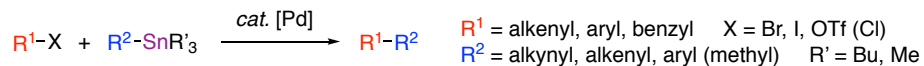
<u>Considerations for organic synthesis</u>
- Commonly, the organozinc reagents are generated from the transmetalation between other reactive organometal (Li or Mg) and zinc chloride, Rieke's, or Knochel's direct method.
- This reaction is compatible with various reactive functionalities, *e.g.* carboxylate, ketone, nitro, cyano groups.

<u>Application</u>



81%

(–)-motuporin

## (4) Kosugi–Migita–Stille reaction (M = Sn)

J. S. Panek, *J. Org. Chem.*, **64**, 3000 (1999).

$$R^1\text{-}X \ + \ R^2\text{-}SnR'_3 \xrightarrow{\textit{cat.} \ [Pd]} R^1\text{-}R^2$$

$R^1$ = alkenyl, aryl, benzyl     X = Br, I, OTf (Cl)
$R^2$ = alkynyl, alkenyl, aryl (methyl)     R' = Bu, Me



>99%

M. Kosugi, *Chem. Lett.*, 301 (1977).



91%

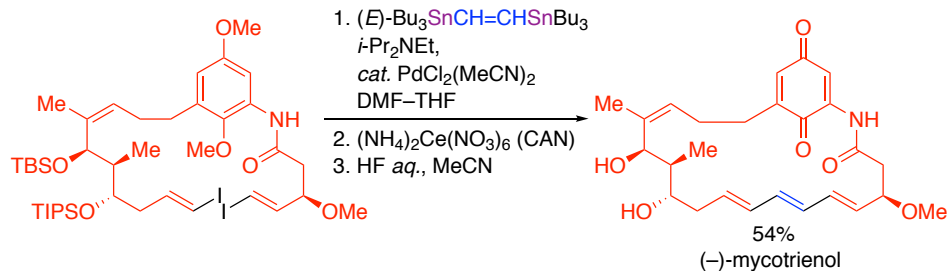J. K. Stille, *J. Am. Chem. Soc.*, **101**, 4992 (1979).

General
· Organostannnane is used as the organometallic substrate in Kosugi–Migita–Stille reaction.
· Palladium complex is the catalyst of choice for the cross-coupling reaction.   In particular, Pd(PPh$_3$)$_4$ or the in-situ-generated palladium(0) from Pd$_2$(dba)$_3$ and a phosphine ligand is commonly employed as the catalyst.
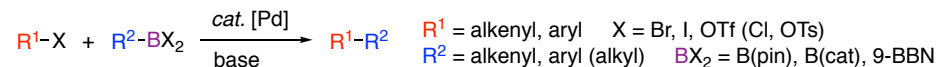· Additive, *e.g.* CuI or LiCl, often remarkably facilitates the Kosugi–Migita–Stille reaction.

Considerations for organic synthesis
· Organostannane substrates are ordinarily prepared through the transmetalation of reactive organometals with Bu$_3$SnCl or the hydrostannation of alkynes with Bu$_3$SnH.
· Tributylstannyl group is widely used as the tin substituent in the oraganometallic substrate.
· Tetraorganostannanes can be purified with extraction and/or silica-gel column chromatography, because they are commonly stable to oxygen and water in air.
· Kosugi–Migita–Stille reaction exhibits larger functional group compatibility than Negishi one.
· After the cross-coupling reaction, the reaction mixture is often treated with aqueous KF to remove the tin by-product.
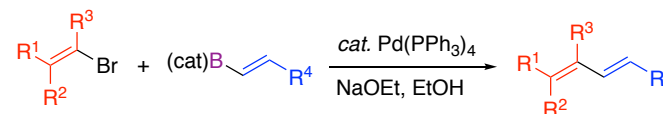· Organostannanes often have high toxicity for us.

Application



1. (*E*)-Bu$_3$SnCH=CHSnBu$_3$
   *i*-Pr$_2$NEt,
   *cat.* PdCl$_2$(MeCN)$_2$
   DMF–THF

2. (NH$_4$)$_2$Ce(NO$_3$)$_6$ (CAN)
3. HF *aq.*, MeCN

54%
(–)-mycotrienol

J. S. Panek, *J. Am. Chem. Soc.*, **120**, 4123 (1998).

## (5) Suzuki–Miyaura reaction (M = B)

$$R^1\text{-}X \ + \ R^2\text{-}BX_2 \xrightarrow[\text{base}]{\textit{cat.} \ [Pd]} R^1\text{-}R^2$$

$R^1$ = alkenyl, aryl     X = Br, I, OTf (Cl, OTs)
$R^2$ = alkenyl, aryl (alkyl)     BX$_2$ = B(pin), B(cat), 9-BBN

Review: N. Miyaura, A. Suzuki, *Chem. Rev.*, **95**, 2457 (1995).



N. Miyaura, A. Suzuki, *Tetrahedron Lett.*, **20**, 3437 (1979); *Synth. Commun.*, **11**, 513 (1981).
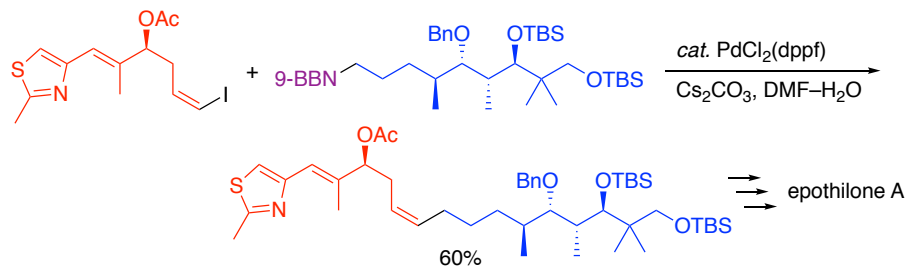
General
· Organoboron is used as the organometallic substrate in Suzuki–Miyaura reaction.
· Phosphine-ligated palladium complex is commonly chosen as the catalyst for the cross-coupling reaction, while nickel and iron complexes can catalyze the reaction.
· Stoichiometric addition of base, such as hydroxide and alkoxide, is required for the Suzuki–Miyaura reaction to facilitate the transmetalation process.
· The base, such as alkoxide, interacts with the boron atom to enhance the reactivity of the organometallic substrates (path a).   Alternatively, the base is replaced by the halide on arylpalladium(II) species (path b).   Alkoxopalladium is more reactive to the transmetalation process than halopalladium.
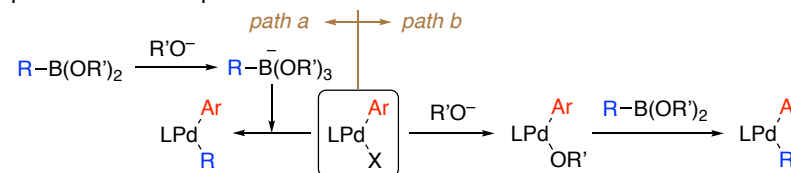


Considerations for organic synthesis
· Organoboron substrates are ordinarily prepared through the transmetalation of reactive organometals with B(OMe)$_3$ or the hydroboration of alkynes with 9-BBN-H.
· Most of organoboranes are sufficiently stable to oxygen and water in air.   Therefore, the organometallic substrates can be purified with extraction and/or silica-gel column chromatography.
· Suzuki–Miyaura reaction also exhibits excellent functional group compatibility as with Kosugi–Migita–Stille one.
· Commonly, the boron waste is less toxic than the tin one from Kosugi–Migita–Stille coupling.
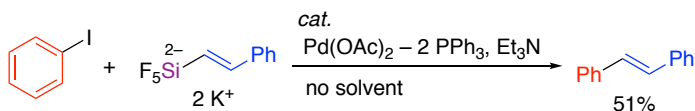
## Application



cat. PdCl$_2$(dppf)

Cs$_2$CO$_3$, DMF–H$_2$O

epothilone A

60%

J. S. Panek, *Org. Lett.*, **2**, 2575 (2000).

## (6) Hiyama reaction (M = Si *etc.*)

$R^1$–X  +  $R^2$–SiR'$_3$  $\xrightarrow[F^-]{\text{cat. [Pd]}}$  $R^1$–$R^2$

$R^1$ = alkenyl, aryl, allyl    X = Br, I, OTf
$R^2$ = alkenyl, aryl, allyl

Reviews: T. Hiyama, *Top. Curr. Chem.*, **219**, 61 (2002); *Chem. Soc. Rev.*, **40**, 4893 (2011).



cat.
Pd(OAc)$_2$ – 2 PPh$_3$, Et$_3$N

no solvent

51%

K. Tamao, M. Kumada, *Organometallics*, **1**, 542 (1982).



cat. [Pd($\eta^3$-C$_3$H$_5$)Cl]$_2$

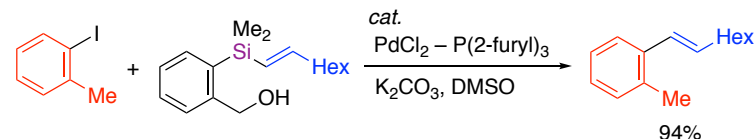[(Et$_2$N)$_3$S](Me$_3$SiF$_2$) (TASF)
HMPA

98%
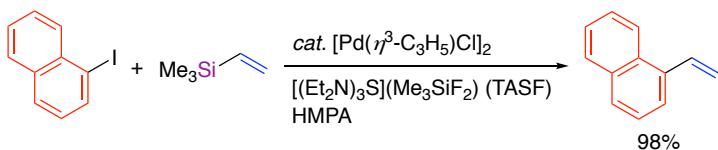
T. Hiyama, *J. Org. Chem.*, **53**, 918 (1988).

## General
· The cross-coupling reaction using organosilane as the nucleophilic substrate is commonly called Hiyama coupling reaction.
· Stoichiometric fluoride ion, F$^-$, is required for the efficient formation of the cross-coupling products.
· The fluoride ion bonds to the silicon atom to form silicate species.  The formation of silicates facilitates the transmetalation between the organosilyl compound and halopalladium.
· Hiyama reaction is possible to proceed in the absence of fluoride ion when the substituents on silicon are well-designed to activate the C–Si bond.



cat.
Pd(dba)$_2$

KOSiMe$_3$
DME

93%

DBA = 
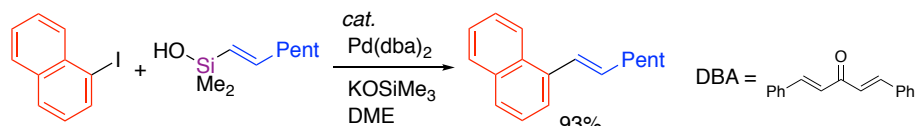
S. E. Denmark, *J. Am. Chem. Soc.*, **123**, 6439 (2001).



cat.
PdCl$_2$ – P(2-furyl)$_3$

K$_2$CO$_3$, DMSO

94%

Y. Nakao, T. Hiyama, *J. Am. Chem. Soc.*, **127**, 6952 (2005).

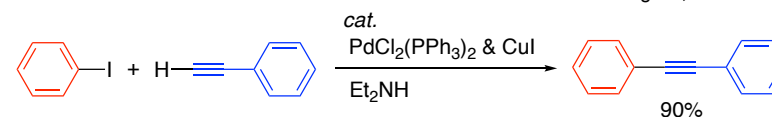## (7) Palladium-catalyzed coupling reaction with relatively acidic compounds
### General
· Organic compound bearing an acidic proton (p$K_a$ < 40), such as malonates, amines, and alcohols, can couple with haloarene or related compound through palladium catalysis.
· The cross-coupling reaction is conducted in the presence of a base, such as alkoxide or tertiary amines.  The base deprotonates the acidic substrate to generate the anionic species, which can work as the nucleophilic substrate in place of the organometallic substrate in the cross-coupling reaction.

### (a) Sonogashira reaction

$R^1$–X  +  H—≡—$R^2$  $\xrightarrow[\text{base}]{\text{cat. [Pd] \& CuI}}$  $R^1$—≡—$R^2$

$R^1$ = alkenyl, aryl
X = Br, I, OTf
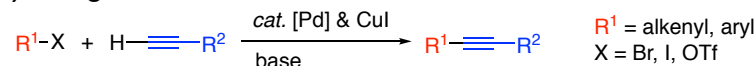
Review: E.-i. Negishi, *Chem. Rev.*, **103**, 1979 (2003).



cat.
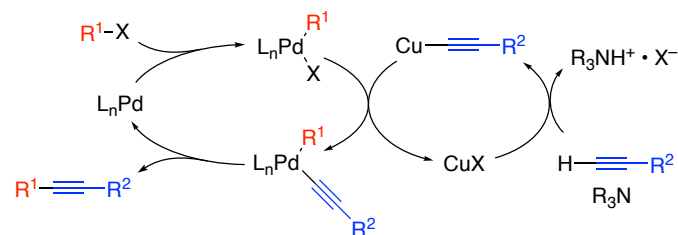PdCl$_2$(PPh$_3$)$_2$ & CuI

Et$_2$NH

90%

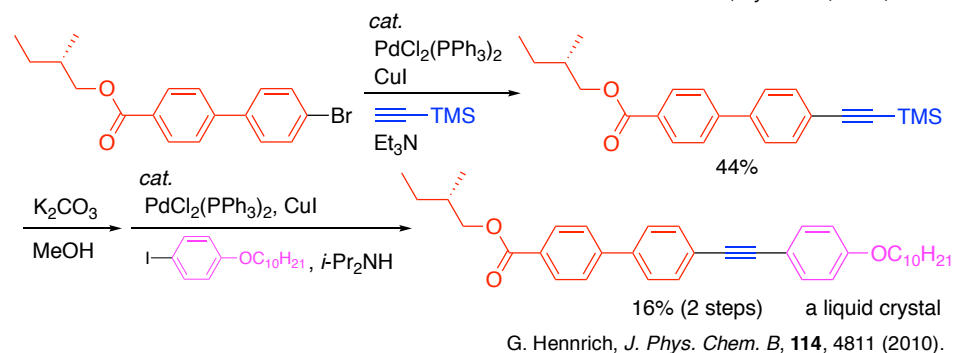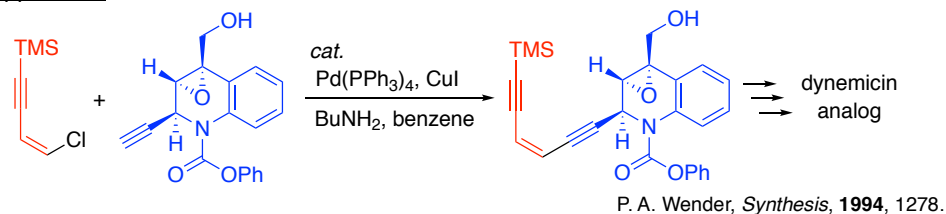K. Sonogashira, *Tetrahedron Lett.*, **36**, 4467 (1975).

### General
· Sonogashira reaction is the cross-coupling reaction of terminal alkynes with haloarenes or haloalkenes.
· Palladium complex, *e.g.* PdCl$_2$(PPh$_3$)$_2$, is used as the catalyst.
· Commonly, the reaction is carried out in the presence of an amine and copper(I) iodide.
· The stoichiometric amount of amine base is required for neutralizing the hydrogen halide by-product.
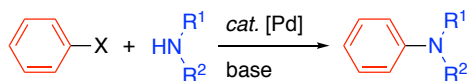
### Mechanism
· The copper(I) salt facilitates the deprotonation from the terminal alkynes with the amine base.  The resulting copper acetylide readily undergoes the transmetalation with halopalladium(II) species.
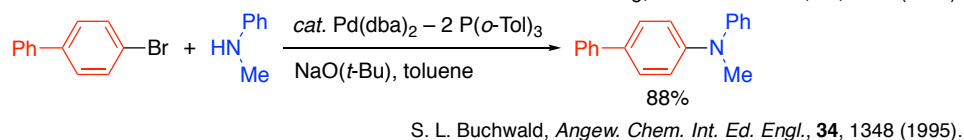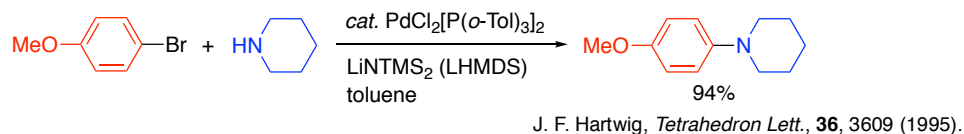
## Application



P. A. Wender, *Synthesis*, **1994**, 1278.



44%



16% (2 steps)     a liquid crystal

G. Hennrich, *J. Phys. Chem. B*, **114**, 4811 (2010).

## (b) Buchwald–Hartwig reaction (amination of haloarenes)



Reviews: J. F. Hartwig, *Acc. Chem. Res.*, **31**, 851 (1998); *Angew. Chem. Int. Ed.*, **37**, 2046 (1998).
S. L. Buchwald, *Acc. Chem. Res.*, **31**, 805 (1998); *Angew. Chem. Int. Ed.*, **47**, 6338 (2008).



94%

J. F. Hartwig, *Tetrahedron Lett.*, **36**, 3609 (1995).



88%

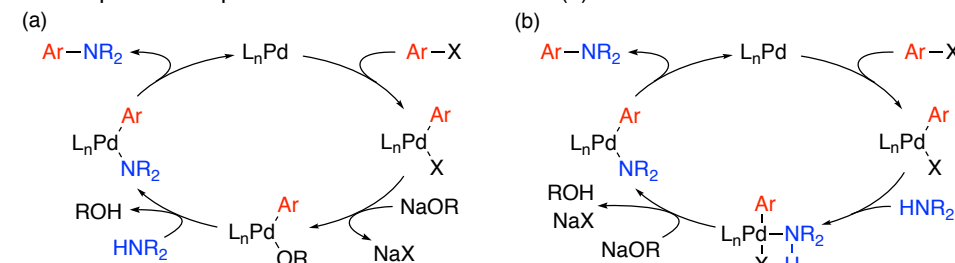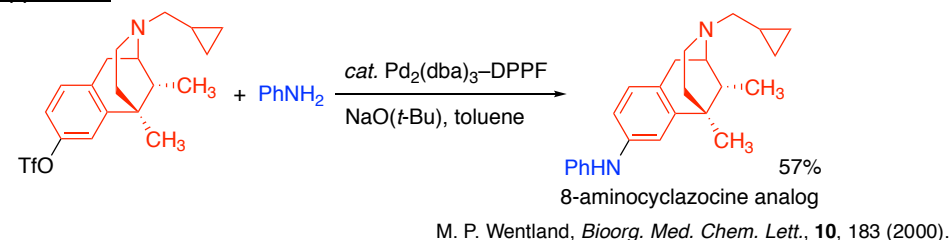S. L. Buchwald, *Angew. Chem. Int. Ed. Engl.*, **34**, 1348 (1995).

## General

- Buchwald–Hartwig reaction is the palladium-catalyzed cross-coupling reaction of amines with haloarenes. This reaction is applicable to the synthesis of a broad range of substituted anilines.
- Copper complex is known to work as the catalyst for the amination of haloarenes. The copper-catalyzed reaction is called Goldberg amination.
- The amination of haloarenes requires a stoichiometric base, such as KO(*t*-Bu) or $Cs_2CO_3$ for the efficient formation of C–N bond.
- The palladium catalysis is applicable to the formation of C–O and C–S bonds.
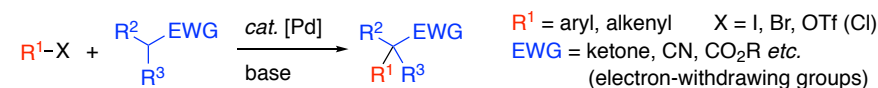
## Mechanism

- In mechanism (a), the alkoxide base is replaced by the halide on arylpalladium(II) species. The resulting alkoxy ligand on palladium abstracts a proton from the amine substrate to form amidopalladium species and release the alcohol.
- Alternatively, the coordination of the nitrogen on palladium enhance the acidity of the amine substrate. The proton on the nitrogen is readily abstracted by the base to form amidopalladium species as shown in mechanism (b).
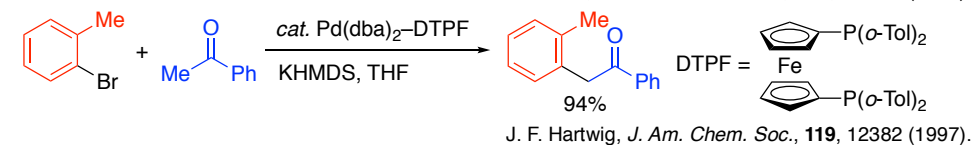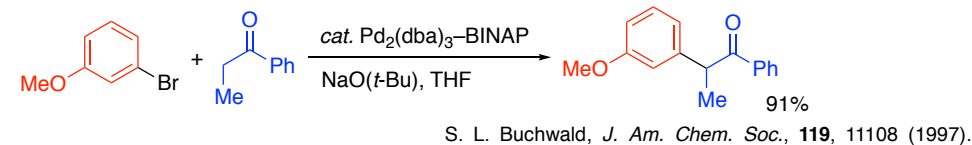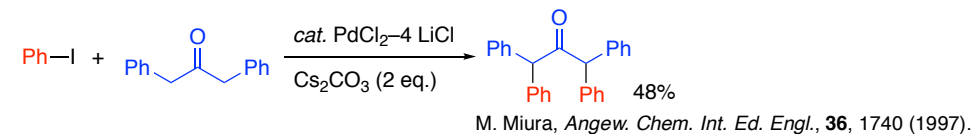
(a)



(b)

## Application



57%
8-aminocyclazocine analog

M. P. Wentland, *Bioorg. Med. Chem. Lett.*, **10**, 183 (2000).

## (c) α-Arylation of carbonyl and related compounds



$R^1$ = aryl, alkenyl     X = I, Br, OTf (Cl)
EWG = ketone, CN, $CO_2R$ *etc.*
(electron-withdrawing groups)

Reviews: J. F. Hartwig, *Acc. Chem. Res.*, **36**, 234 (2003).



48%

M. Miura, *Angew. Chem. Int. Ed. Engl.*, **36**, 1740 (1997).



91%

S. L. Buchwald, *J. Am. Chem. Soc.*, **119**, 11108 (1997).



94%

J. F. Hartwig, *J. Am. Chem. Soc.*, **119**, 12382 (1997).

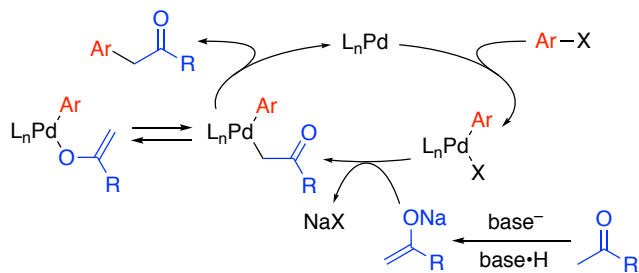## General

- Palladium catalysis allows the arylations of enolates and related soft carbanions with haloarenes.
- The palladium-catalyzed α-arylation requires a stoichiometric strong base for the efficient formation of the desired product.  The base abstracts a proton from the carbonyl substrate to facilitate the generation of palladium enolate intermediate.
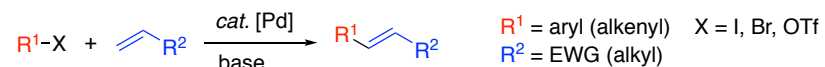
## Mechanism

- A possible pathway is shown in the following graphic.  Relative thermodynamic stabilities of the palladium $C$- and $O$-enolates are affected by the α-substituents of the carbonyl substrate.
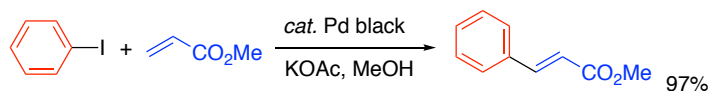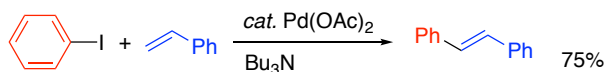


## (8) Mizoroki–Heck reaction
### (a) Typical Mizoroki–Heck reaction



$R^1$–X + (alkene)$R^2$ →[cat. [Pd]][base] $R^1$(alkene)$R^2$

$R^1$ = aryl (alkenyl)    X = I, Br, OTf
$R^2$ = EWG (alkyl)

Review: I. P. Beletskaya, *Chem. Rev.*, **100**, 3009 (2000); S. E. Gibson, *Tetrahedron*, **57**, 7449 (2002).



PhI + $CO_2Me$ →[cat. Pd black][KOAc, MeOH] Ph(alkene)$CO_2Me$   97%

T. Mizoroki, *Bull. Chem. Soc. Jpn.*, **44**, 581 (1971).

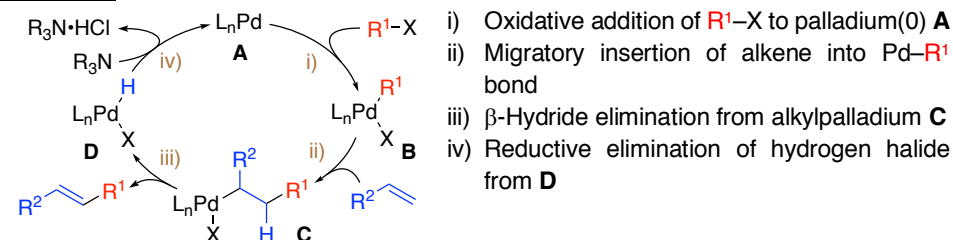PhI + $Ph$ →[cat. Pd(OAc)$_2$][Bu$_3$N] Ph(alkene)Ph   75%

R. F. Heck, *J. Org. Chem.*, **37**, 2320 (1972).

## General

- Mizoroki–Heck reaction is the dehydroarylation of alkenes with haloarenes through palladium catalysis.  One of the hydrogen atoms on the C($sp^2$) is replaced by the aryl group.
- The stoichiometric amount of base is required for neutralizing the hydrogen halide by-product.
- To obtain the Mizoroki–Heck product in high yield, the reaction should be considered from the viewpoint of regio- and stereoselectivities.

## Mechanism



i) Oxidative addition of $R^1$–X to palladium(0) **A**
ii) Migratory insertion of alkene into Pd–$R^1$ bond
iii) β-Hydride elimination from alkylpalladium **C**
iv) Reductive elimination of hydrogen halide from **D**

- In the process from **B** to **C**, the alkene is inserted into **B** to form two possible alkylpalladium species, intermediate **C** and **C'**.  The formation of **C**, which is related to the palladium $C$-enolate, is preferable to that of **C'** when $R^2$ is electron-withdrawing.
- The β-H elimination from **C** leads to the formation of either $E$- or $Z$-product through the conformation **C**($E$) or **C**($Z$).
- Commonly, the $E$-product will be selectively obtained from the reaction, because **C**($Z$) is unfavorable because of the steric repulsion between $R^1$ and $R^2$.
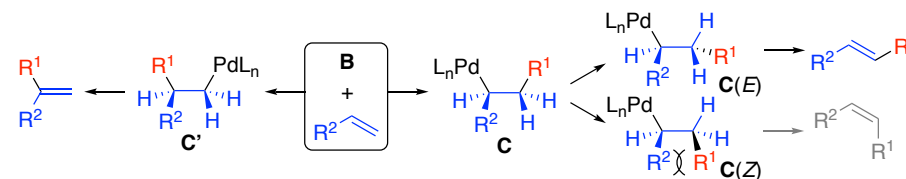


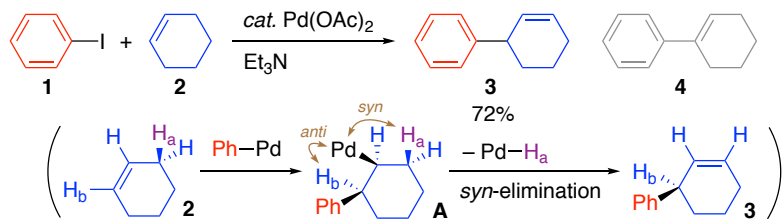## Application



→ lasiodiplodin

M. P. Wentland, *Bioorg. Med. Chem. Lett.*, **10**, 183 (2000).



→ taxol
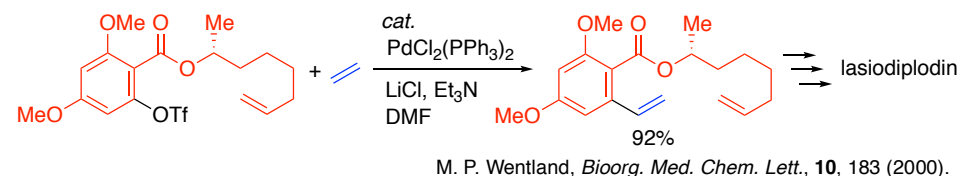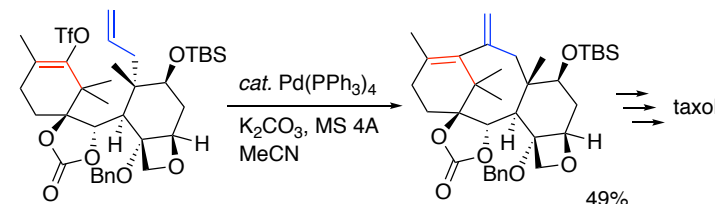
J. J. Masters, (S. J. Danishefsky,) *Angew. Chem. Int. Ed. Engl.*, **34**, 1723 (1995).

## (b) Mozoroki–Heck reaction of cyclic alkenes



R. F. Heck, *J. Org. Chem.*, **43**, 2952 (1978).

- The cyclic alkene is inserted into the Pd–Ph bond to give intermediate **A**. If the reaction followed the typical pathway, $H_b$ would be dissociated through the β-hydride elimination from **A** to yield compound **4**. However, $H_b$ is impossible to participate the following β-elimination because $H_b$ is locates in the *anti*-position of Pd. Therefore, the Pd eliminates from **A** with $H_a$, which is positioned *syn*, to give **3** and Pd–$H_a$.

- This type Mizoroki–Heck reaction is often used in total synthesis of natural products.
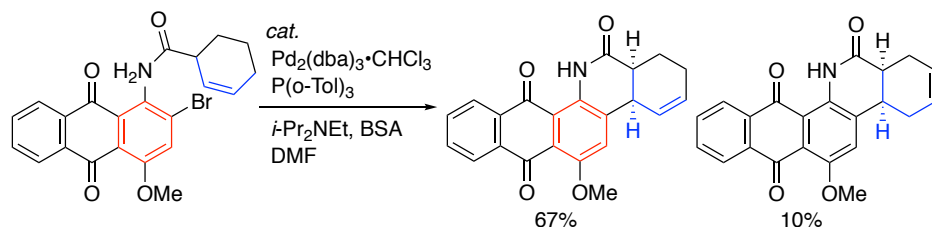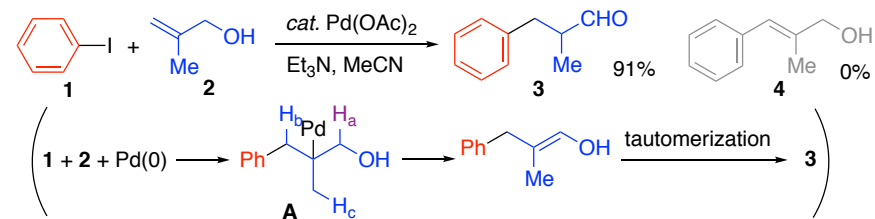


M. Isobe, *Tetrahedron*, **50**, 11143 (1994).

- The regioselectivity can be controlled by choice of catalyst and/or reaction conditions.
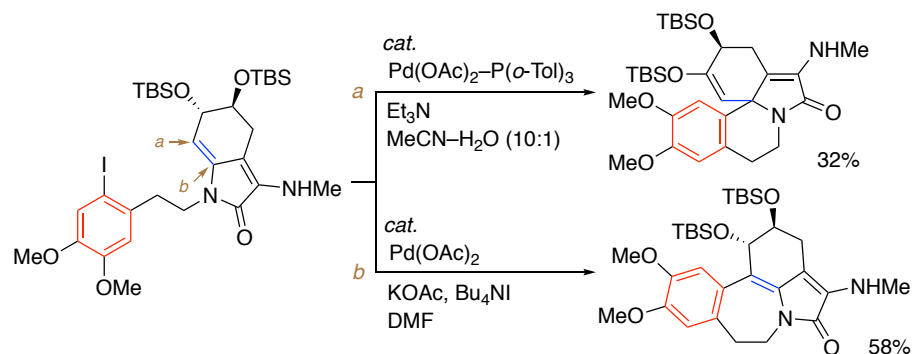


J. H. Rigby, *J. Org. Chem.*, **117**, 7834 (1995).

## (c) Mozoroki–Heck reaction of allylic alcohols



R. F. Heck, *J. Org. Chem.*, **41**, 265 (1976).

- The C–C double bond of **2** is inserted into the Pd–Ph bond to form intermediate **A**, which might lead to the formation of **4** if the reaction followed the typical pathway. However, the β-elimination from **A** takes place with $H_a$ rather than $H_b$ to afford the enol and (hydrido)palladium. The enol rapidly tautomerizes into aldehyde **3**.
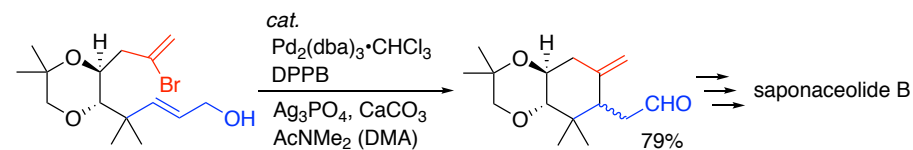


B. M. Trost, *Angew. Chem. Int. Ed.*, **38**, 3662 (1999).

## (d) Cascade Mozoroki–Heck reaction

- Multiple alkenes and alkynes are successively inserted into the Pd–C bond in the intramolecular Mizoroki–Heck reaction. This cascade reaction provides a powerful tool for the construction of complex cyclic structures.



A. de Meijere, *J. Org. Chem.*, **56**, 6488 (1991).
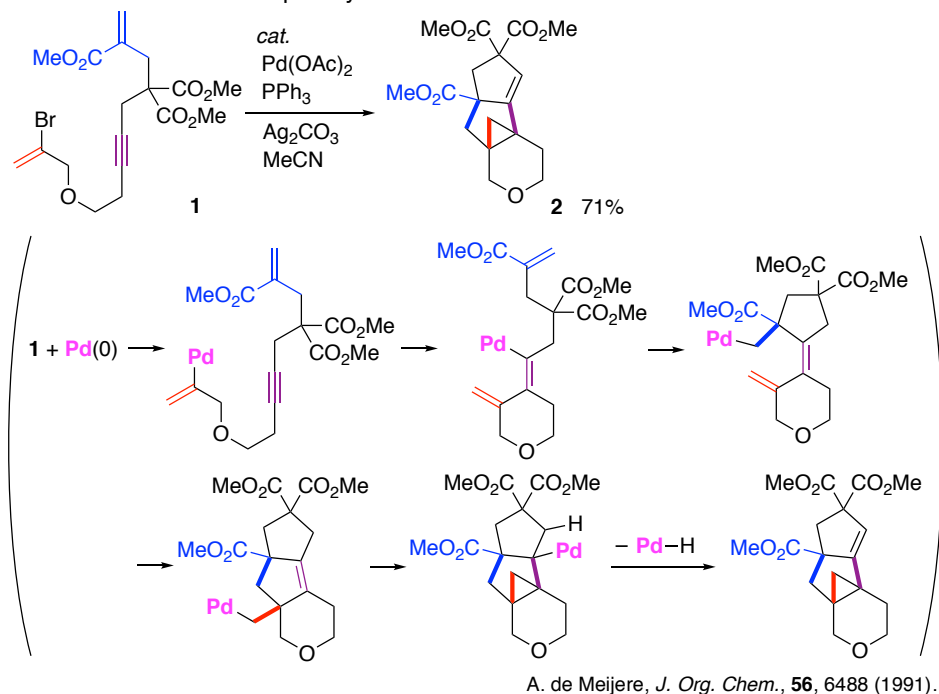
## (9) Toward the success in the cross-coupling reaction



$$R-X + M-R' \xrightarrow{cat.\ Pd} R-R'$$
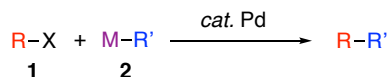
### (a) Combination of substrate

Electrophilic substrate (**1**)

- The relative reactivities of haloarenes follows the trend ArI > ArOTf > ArBr > ArCl, in general.
- Electron-deficient haloarenes are commonly preferable for the cross-coupling to electron-rich ones.
- The electrophilic substrates **1** affect the rate of the oxidative addition, which is the rate-determining step of the cross-coupling reaction in most cases.
- Haloalkanes are not suitable for the electrophilic substrates for the cross-coupling, because the β-hydride elimination from the alkylpalladium intermediate competes with the transmetalation or reductive elimination after the oxidative addition of haloalkane.

Nucleophilic substrate (**2**)

- Electron-rich arylmetals are commonly preferable to electron-deficient ones for the cross-coupling reaction.
- Electron-rich arylmetal and electron-deficient aryl halides is the best substrate combination for the reductive elimination process.
- For the cross-coupling between alkyl and aryl substrates, the alkylmetal rather than than arylmetal should be chosen as the nucleophilic substrate.

### (b) Catalyst
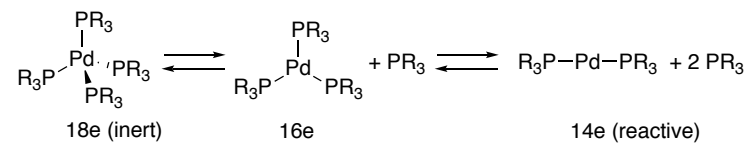
Choice of palladium complex

- Pd(PPh$_3$)$_4$ is widely used as the palladium catalyst for the various cross-coupling reactions using aryl or alkenyl iodides or bromides. The palladium complex is one of reliable catalysts, but is sometimes insufficient in catalytic activity.
- When the coupling reaction is carried out with other ligands than PPh$_3$, the palladium(0) catalyst can be generated *in situ* by mixing Pd$_2$(dba)$_3$ (Pd(dba)$_2$, Pd$_2$(dba)$_3$·C$_6$H$_6$, or Pd$_2$(dba)$_3$·CHCl$_3$) and the ligand.
- In place of Pd$_2$(dba)$_3$, Pd(OAc)$_2$ and PdCl$_2$(MeCN)$_2$ are also usable as the catalyst precursor. However, the palladium(II) complexes require their reduction for working as the catalyst. Grignard reagents, *i*-Bu$_2$AlH, alkyl amines, and phosphines can be used as the reducing agent for the *in-situ* conversion of Pd(II) to Pd(0).

Electronic effect of ligand

- Bulky and electron-donating spectator ligand, such as (*t*-Bu)$_3$P can remarkably improve the activity of the palladium catalyst for cross-coupling reaction.
- With the (*t*-Bu)$_3$P ligand, chloroarenes are acceptable as the electrophilic substrate of the cross-coupling reactions in general use. Furthermore, the ligand enables a remarkable decrease in the catalyst loading.



M. Nishiyama, T. Yamamoto, Y. Koie, *Tetrahedron Lett.*, **39**, 617 (1998); **39**, 2367 (1998).
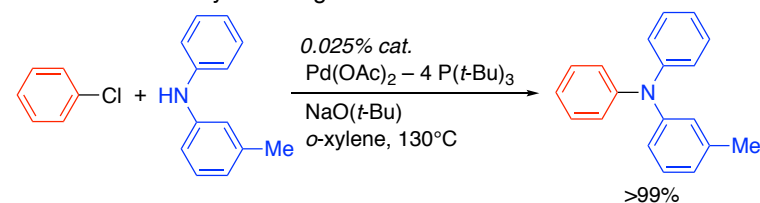
- More electron-donation from the ligand to the metal enhances the rate of the oxidative addition process.
- The bulkiness of ligand is favorable for the reductive elimination process. The reductive elimination releases the steric repulsion between the spectator ligand and the organic substituents on palladium.
- Furthermore, use of the larger spectator ligand is advantageous to the oxidative addition, because its bulkiness assists the generation of coordinatively unsaturated species.

$$\underset{\text{18e (inert)}}{\underset{\text{PR}_3}{\overset{\text{PR}_3}{\underset{\text{R}_3\text{P}}{\text{Pd}}}}}\underset{\text{PR}_3}{\text{PR}_3} \;\rightleftharpoons\; \underset{\text{16e}}{\underset{\text{PR}_3}{\overset{\text{PR}_3}{\underset{\text{R}_3\text{P}}{\text{Pd}}}}}\text{PR}_3 \;+\; \text{PR}_3 \;\rightleftharpoons\; \underset{\text{14e (reactive)}}{\text{R}_3\text{P}-\text{Pd}-\text{PR}_3} \;+\; 2\,\text{PR}_3$$

- Nowadays, various palladium catalysts and bulky electron-donating ligands for the cross-coupling reactions are commercially available.

  see:  https://www.strem.com/catalog/ligands.php

  https://labchem.wako-chem.co.jp/synthesis/organic-synthesis/cross-coupling/

  https://www.tcichemicals.com/eshop/ja/jp/category_index/12639/

  https://products.kanto.co.jp/web/index.cgi?c=t_product_table&pk=143

## 3-3. Olefin metathesis

### (1) General
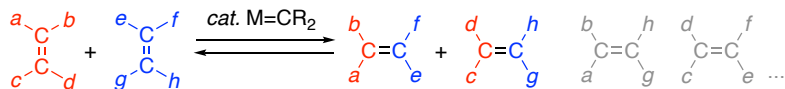


Review: A. Fürstner, *Angew. Chem. Int. Ed.*, **39**, 3012 (2000).

- In the olefin metathesis, the C–C double bond is cleaved to two carbenes and they reconstruct the new C–C double bond.
- The metathesis is catalyzed by metal–carbene complexes, that have a M–C double bond.
- The reaction usually gives an equilibrium mixture of olefins.   Some kind of ingenuity is required for exclusively obtaining the target product in organic synthesis.

Mechanism
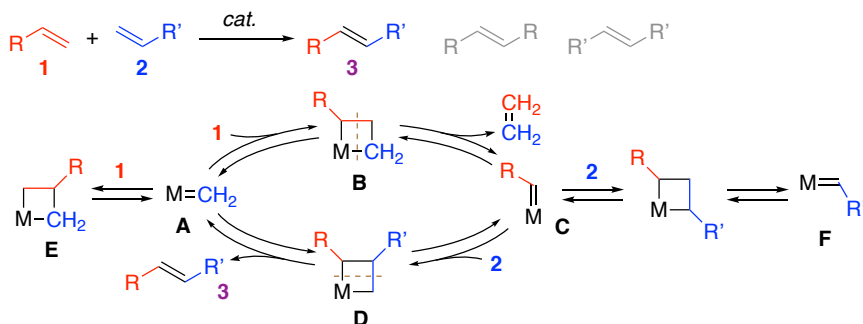


i)   The [2+2] cycloaddition of metal–carbene **A** and olefin **1** gives the metallacyclobutane **B**.   Its retro-cycloaddition leads to form the metal–carbene intermediate **C**.

ii)  The desired product **3** is formed through **D** when **C** reacts with another alkene **2**.
  - The [2+2] cycloaddition of **A** and **1** can form the regioisomeric intermediate **E**.   However, the retro-cycloaddition of **E** gives the starting materials.
  - The metal–carbene **F** would be generated when the reaction of **C** and **2** proceeds with the reversed regioselectivity.   The reaction is accompanied with the formation of **1**.
  - The dimerization of **1** and/or **2** may accompany the cross-metathesis of **1** and **2**.   The dimers are formed through the reactions of **C** and **1** or **F** and **2**.

### (2) Ring-closing metathesis (RCM)
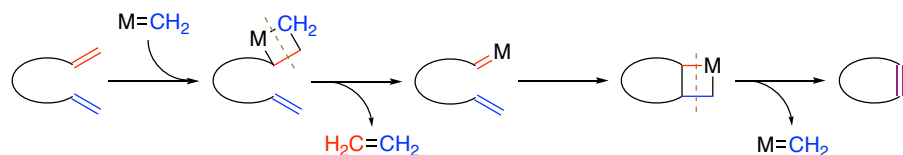


- In the alkene metathesis of $\alpha,\omega$-diene, one of the terminal alkenes intramolecularly reacts with another alkene to provide the cyclic alkene and ethylene.
- The equilibrium of the intramolecular metathesis shifts toward the products.   The cyclic

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alkene is less reactive to the metal–carbene species than the terminal alkenes because of the steric hindrance.   Furthermore, the by-product, gaseous ethylene, is evolved from the reaction mixture.
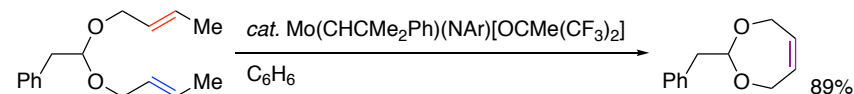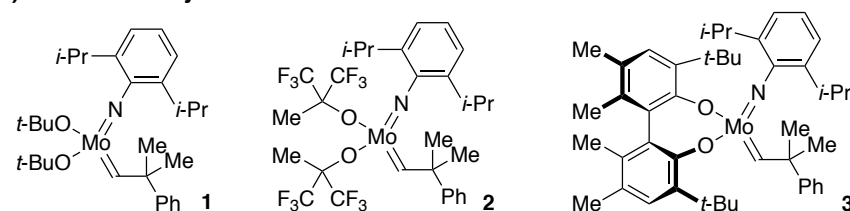


R. H. Grubbs, *J. Am. Chem. Soc.*, **114**, 5426 (1992); **114**, 7324 (1992).
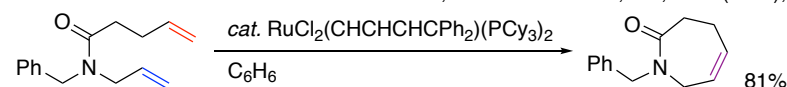


R. H. Grubbs, *J. Am. Chem. Soc.*, **115**, 9856 (1993).

### (3) Catalyst for olefin metathesis in organic synthesis
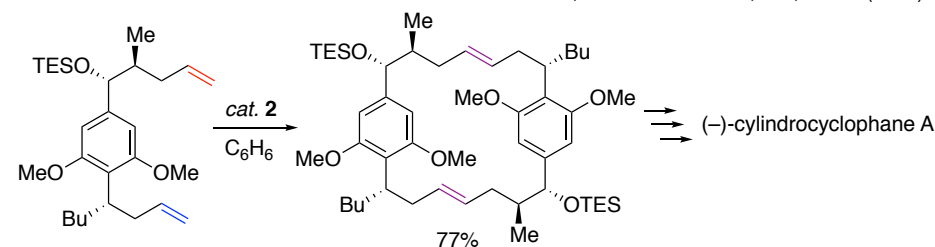#### (a) Schrock catalysts



R. R. Schrock, *Organometallics*, **6**, 1373 (1987); *J. Am. Chem. Soc.*, **112**, 3875 (1990) (for **1**); *J. Am. Chem. Soc.*, **120**, 4014 (1998) (for **3**); V. C. Gibson, *J. Chem. Soc., Chem. Commun.* 1720 (1991) (for **2**).   Reviews: R. R. Schrock, *Tetrahedron*, **55**, 8141 (1999); *Angew. Chem. Int. Ed.*, **42**, 4592 (2003).

- The molybdenum–carbene catalysts, *e.g.* **1**–**3**, are highly active for various types of olefin metathesis, polymerization and RCM.
- However, the molybdenum complexes are unstable for $O_2$, $H_2O$, and various protic functional groups.   Furthermore, the molybdenum–carbenes readily react with carbonyl groups (see *J. Am. Chem. Soc.*, **115**, 3800 (1993)).
- Catalyst **2** is widely used for RCM in organic synthesis.
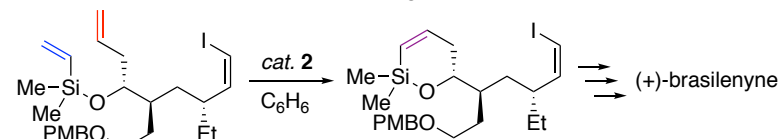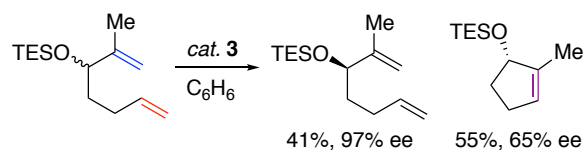


S. E. Denmark, *J. Am. Chem. Soc.*, **126**, 12432 (2004).



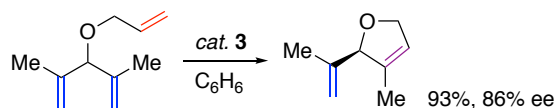A. B. Smith, III, *J. Am. Chem. Soc.*, **122**, 4984 (2000).

- Complex **3** works as a good chiral catalyst for enantioselective olefin metathesis.
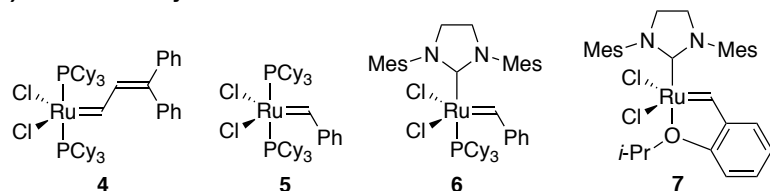
<u>Kinetic resolution of substrate</u>



41%, 97% ee    55%, 65% ee

A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.*, **120**, 4041 (1998).

<u>Enantioselective desymmetrization</u>



93%, 86% ee

A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.*, **120**, 9720 (1998).

**(b) Grubbs catalysts**



**4**    **5**    **6**    **7**

R. H. Grubbs, *J. Am. Chem. Soc.*, **114**, 3974 (1992) (for **4**); *Angew. Chem. Int. Ed. Engl.*, **34**, 2039 (1995) (for **5**); W. A. Herrmann, *Angew. Chem. Int. Ed.*, **37**, 2490, (1998); R. H. Grubbs, *Org. Lett.*, **1**, 953 (1999) (for **6**); A. H. Hoveyda, *J. Am. Chem. Soc.*, **122**, 8168 (2000) (for **7**). Reviews: Reviews: R. H. Grubbs, *Acc. Chem. Res.*, **34**, 18 (2001); *Chem. Rev.*, **110**, 1746 (2010).

- The ruthenium–carbene complexes, in particular **5–7**, are frequently used for the olefin metathesis in organic synthesis.
- The ruthenium complexes are stable and work as the metathesis catalyst in the presence of $O_2$ and $H_2O$. The ruthenium-catalyzed metathesis proceeds even in protic solvent including water.
- The ruthenium catalysis is compatible with a broad range of functionalities, including strongly Lewis basic or protic group.
- Complex **5** is more reactive than **4**.



(+)-nakadomarin A

26%
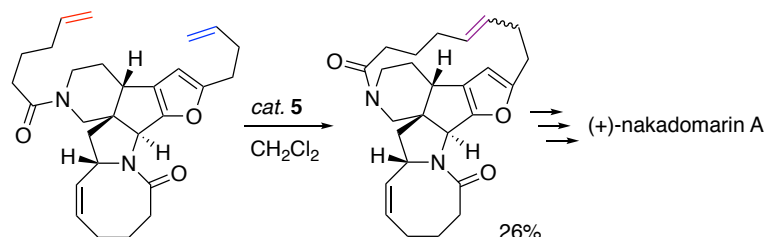
A. Nishida, *J. Am. Chem. Soc.*, **125**, 7484 (2003).



>60%
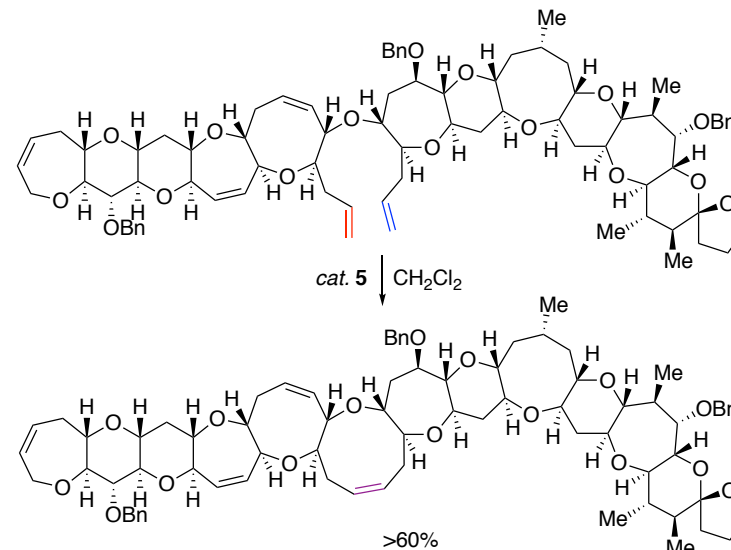
M. Hirama, *Science*, **294**, 1904 (2001).



65%

phorboxazole A
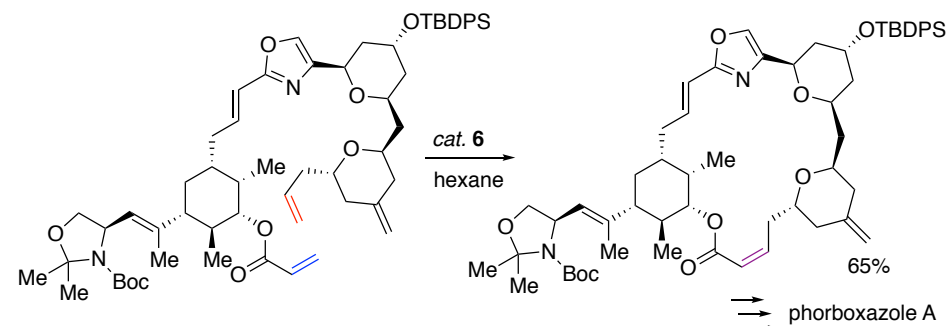
C. J. Forsyth, *Org. Lett.*, **8**, 5223 (2006); *J. Am. Chem. Soc.*, **133**, 1506 (2011).

**(4) Selective cross metathesis**

- Generally, the intermolecular metathesis of equimolar two alkenes provides the mixture of their cross-coupling product and dimers with statistical ratio, 2:1:1. The product ratio is controlled by the thermodynamic stability of each alkene.
- However, successful cross metatheses have been often seen in total syntheses of natural products.
- To obtain the desired product in high yield, one of the alkene substrates is used in an excess amount to the other.
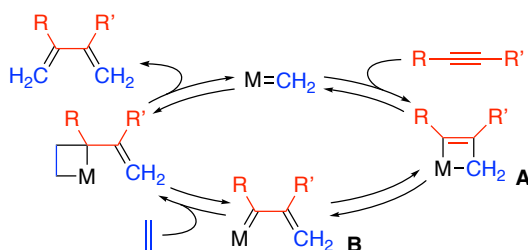
79%

T. J. Donohoe, *J. Am. Chem. Soc.*, **128**, 13704 (2006).

(+)-*cis*-sylvaticin
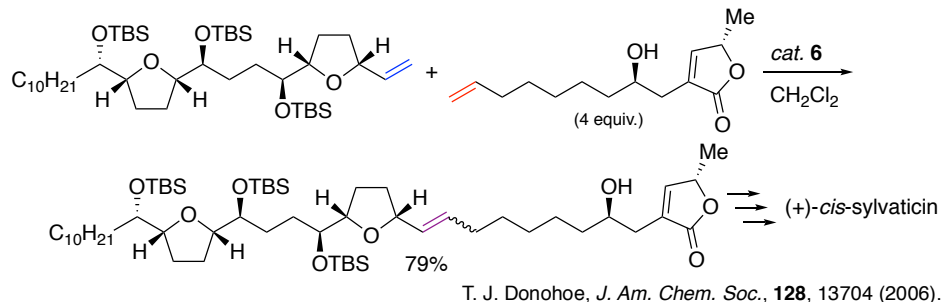
## (5) Ene–yne metathesis
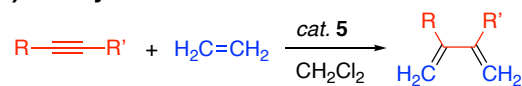


M. Mori, *J. Am. Chem. Soc.*, **119**, 12388 (1997).

- Carbon–carbon triple bond can undergo the metathesis in a similar manner to alkenes. The metathesis between alkyne and alkene provides 1,3-diene.

Mechanism



i) The carbene–ruthenium complex reacts with the alkyne substrate to form metallacyclobutene **A** (not -butane).

ii) As with metallacyclobutane, **A** undergoes the ring-opening reaction in a similar manner to the retro [2+2] cycloaddition to form **B**. In the intermediate **B**, the C–C double bond in **A** remains as a C–C single bond.

iii) The M–C double bond in **B** reacts with the remaining alkene through metallacyclobutane intermediate to give 1,3-diene product.

- The ene-yne metathesis is applicable to α,ω-enyne substrate.



50%
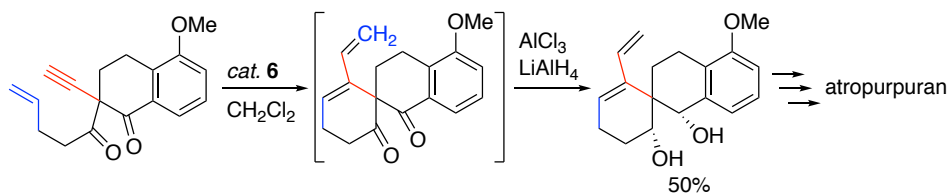
J. Xu, *J. Am. Chem. Soc.*, **141**, 3435 (2019).

## (6) Cascade metathesis

- Olefin metathesis is possible to successively take place in a single molecule that has more than three C–C unsaturated bonds in well-designed positions.
- The cascade metathesis often offers a powerful and elegant strategy for constructing complicated condensed ring systems.
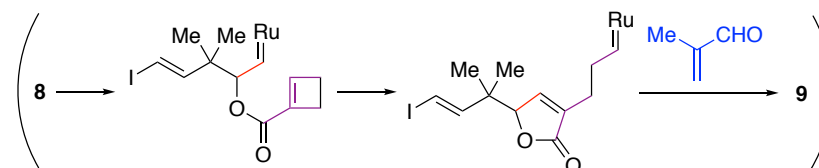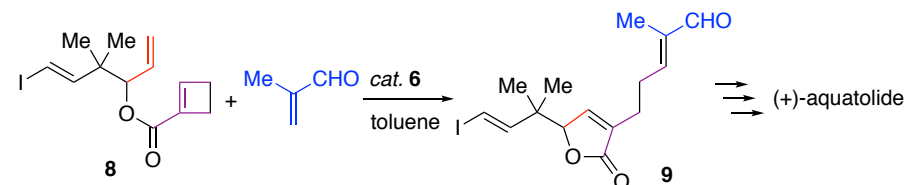


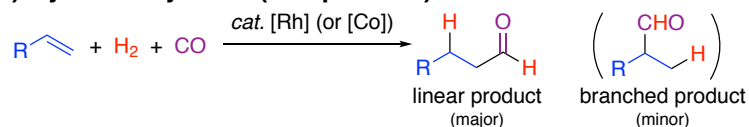K.-i. Takao, *Angew. Chem. Int. Ed.*, **58**, 9851 (2019).
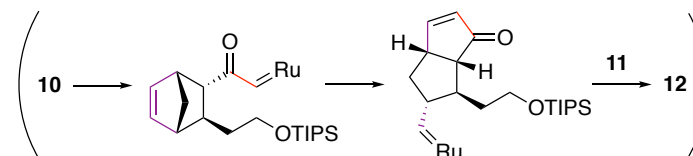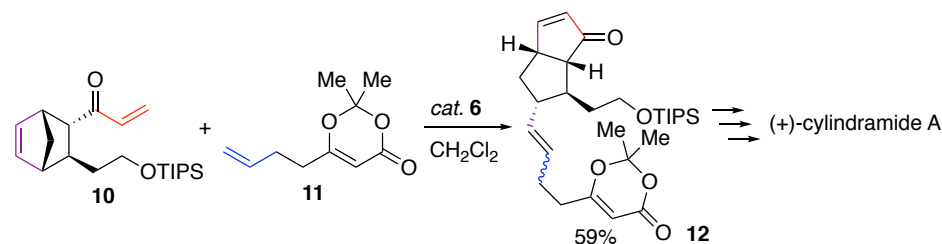


A. J. Phillips, *J. Am. Chem. Soc.*, **128**, 1094 (2006).

I. Hanna, *Org. Lett.*, **6**, 1817 (2004).
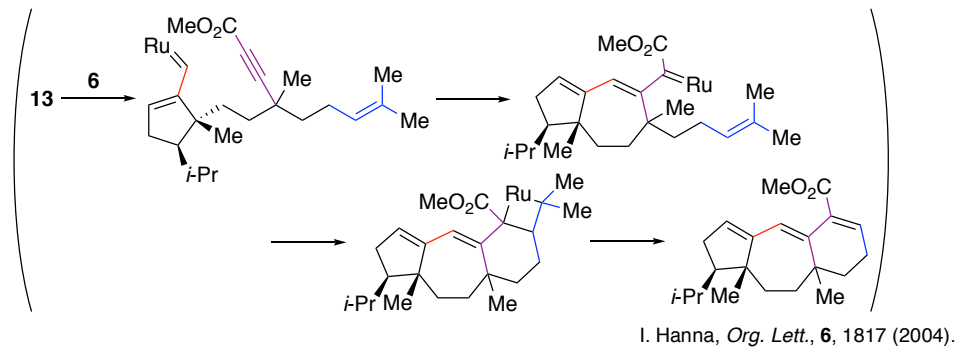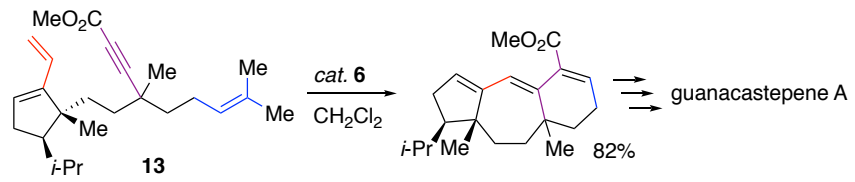
## 3-4. Homogeneous metal catalysis in the petrochemical industry

### (1) Hydroformylation (oxo process)



Review: A. Börner, *Chem. Rev.*, **112**, 5675 (2012).

- Syngas, which is a mixture of hydrogen and carbon monoxide, reacts with alkenes in the presence of a transition-metal catalyst to give aldehydes as the major product.
- Through the reaction, a hydrogen atom and formyl (CHO) groups add across the carbon–carbon double bond.
- The hydroformylation used to be carried out with a cobalt catalyst.　Nowadays, rhodium is commonly used as the catalyst for the reaction.　The use of rhodium leads to improvement of the linear/branch ratio.
- RhH(CO)(PPh$_3$)$_3$ or in-situ-generated complex from Rh(CO)$_2$(acac) and phosphorus ligand (*e.g.* P(OPh)$_3$ *etc.*) is commonly used as a catalyst in organic synthesis.

Mechanism
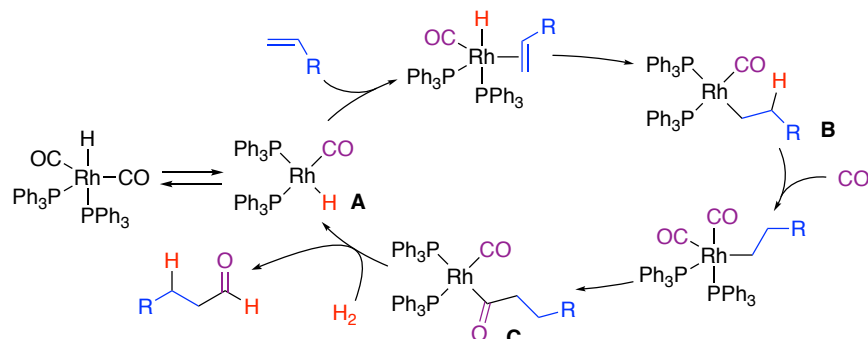


i)　The C–C double bond is inserted into the C–Rh bond in **A** to form alkylrhodium **B**.

ii)　A carbon monoxide is inserted into the C–Rh bond in **B** to form acylrhodium **C**.

iii)　The intermediate **C** reacts with H$_2$ to give the desired aldehyde and regenerate **A** through two possible pathways.
- Oxidative addition of H$_2$ followed by the reductive elimination of the acyl group and the hydride from rhodium
- σ-Bond metathesis between the acyl C–Rh and H–H bond

Applications
- Rhodium-catalyzed hydroformylation of terminal alkenes is used for the mass production of 1-butanol and 2-ethylhexanol.
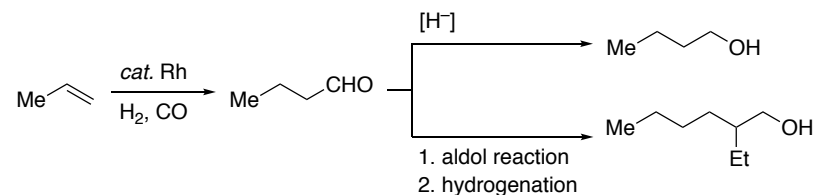


- In total synthesis of natural products
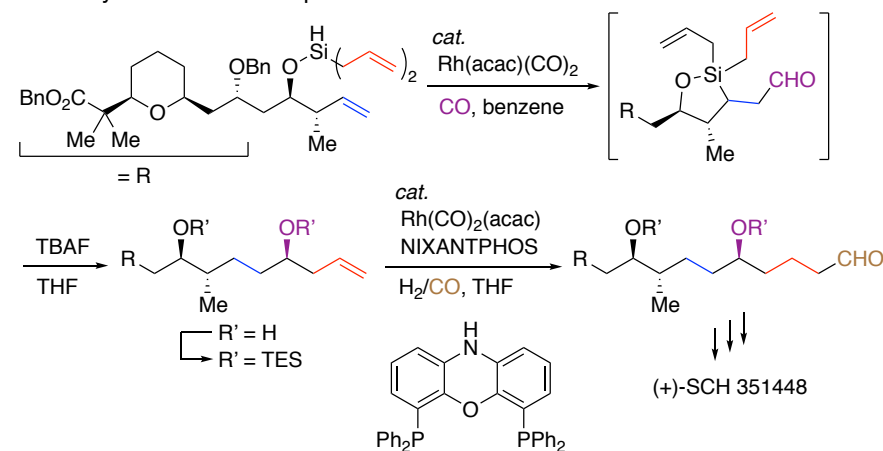


J. L. Leighton, *Org. Lett.*, **7**, 3809 (2005).

- Enantioselective hydroformylation



H. Takaya, *J. Am. Chem. Soc.*, **113**, 7033 (1993).

## (2) Wacker process

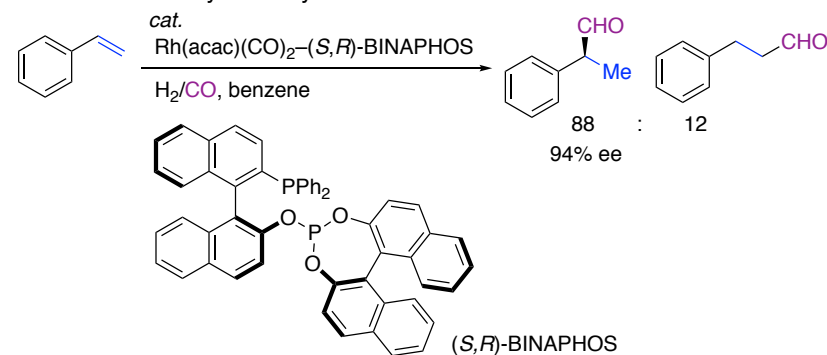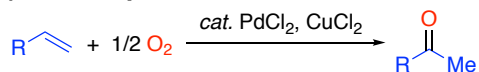$$R\diagdown\diagup + 1/2\ O_2 \xrightarrow{\text{cat. PdCl}_2,\ \text{CuCl}_2} \underset{R}{\overset{O}{\diagdown}}Me$$

Essay: R. Jira, *Angew. Chem. Int. Ed.*, **48**, 9034 (2009).   Review: J. Tsuji, *Synthesis*, 369 (1984).

- Wacker oxidation is the transformation of terminal alkenes into methyl ketones through a palladium catalysis.
- The oxidative reaction is applied to the mass production of acetaldehyde from ethylene (Wacker process).
- In classic Wacker reaction, $O_2$ gas and copper(II) chloride is employed as the oxidant and co-catalyst, respectively.
- Copper(II) salt and benzoquinone are usable as the oxidant in the absence of copper co-catalyst.
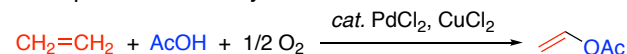
### Mechanism
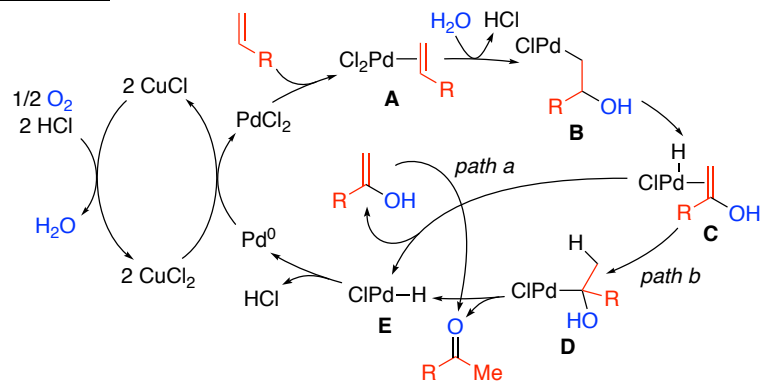


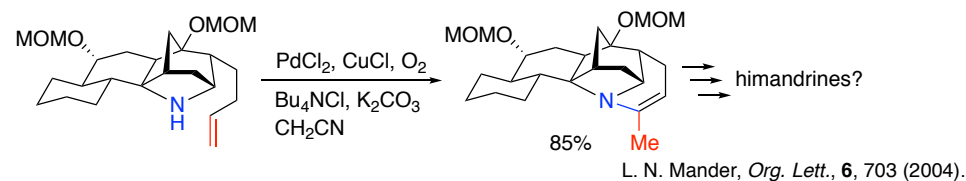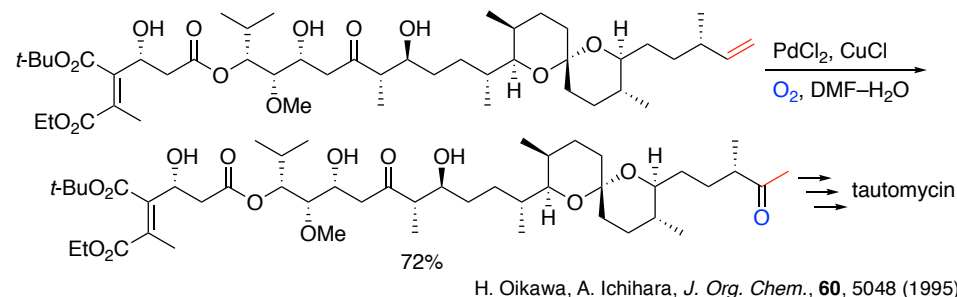Review: J. A. Keith, *Angew. Chem. Int. Ed.*, **48**, 9038 (2009).

i)   Alkene substrate coordinates to $PdCl_2$ to form intermediate **A**.   The pallaldium(II) withdraws the p-electron to enhance the electrophilicity of the C–C double bond.

ii)  Nucleophilic $H_2O$ attacks on the alkene ligand on palladium to form **B**.   The regioselectivity follows Markovnikov rule.

iii) The β-hydride elimination from **B** leads to the formation of the vinyl alcohol, which rapidly tautomerizes to methyl ketone (path a).

J. Smidt, *Angew. Chem. Int. Ed. Engl.*, **1**, 80 (1962); P. M. Henry, *J. Am. Chem. Soc.*, **86**, 3246 (1964).

iv)  The vinyl alcohol intermediate is inserted into the Pd–H bond in **C** to form **D**.   The resulting alkyl ligand is transformed into the ketone product through the β-hydride elimination from **D** with the proton of the hydroxy group (path b).

J. E. Bäckvall, *J. Am. Chem. Soc.*, **101**, 2411 (1979); M. S. Sigman, *J. Am. Chem. Soc.*, **127**, 2796 (2005).
W. A. Goddard, III, *J. Am. Chem. Soc.*, **128**, 3132 (2006).

v)   The reductive elimination of HCl from **E** gives the palladium(0) species.

vi)  The palladium(0) is oxidized to $PdCl_2$ with 2 equivalents of $CuCl_2$.

vii) The resulting CuCl is oxidized with $O_2$ and HCl to $CuCl_2$.

## Applications

- Mass production of vinyl acetate

$$CH_2{=}CH_2 + AcOH + 1/2\ O_2 \xrightarrow{\text{cat. PdCl}_2,\ \text{CuCl}_2} \diagup\!\!\diagdown OAc$$

- Application of Wacker oxidation toward total synthesis of natural products



H. Oikawa, A. Ichihara, *J. Org. Chem.*, **60**, 5048 (1995).



L. N. Mander, *Org. Lett.*, **6**, 703 (2004).

- The palladium-catalyzed oxidation can be expandable to dialkoxylation.



M. S. Sigman, *J. Am. Chem. Soc.*, **128**, 1460 (2006); *J. Org. Chem.* **76**, 9210 (2011).
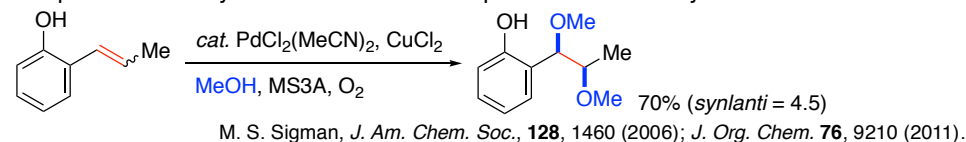
- Enantioselective Wacker-type cyclization



Y. Uozumi, T. Hayashi, *J. Am. Chem. Soc.*, **119**, 5063 (1997).
See: T. Hosokawa, S.-i. Murahashi, *J. Am. Chem. Soc.*, **103**, 2318 (1981).
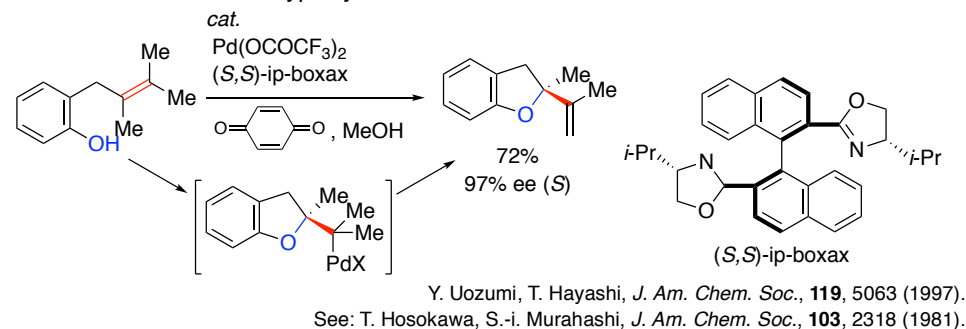
## (3) Monsant process (Cativa process)

$$MeOH + CO \xrightarrow{cat.\ Rh,\ HI} Me\text{-}C(=O)\text{-}OH$$
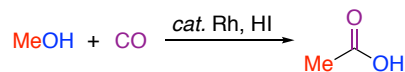
J. F. Roth, *Chem. Commun.*, 1578 (1968); G. J. Sunley, *Catalysis Today*, **58**, 293 (2000).

- Acetic acid used to be produced from methanol and carbon monoxide through a rhodium and hydrogen iodide catalyst.   The process is called Monsant process.
- Monsant process was remarkably improved by replacing the rhodium by iridium.   The acetic acid production with iridium catalyst is named Cativa process, which is very similar in mechanism to Monsant process.

Mechanism



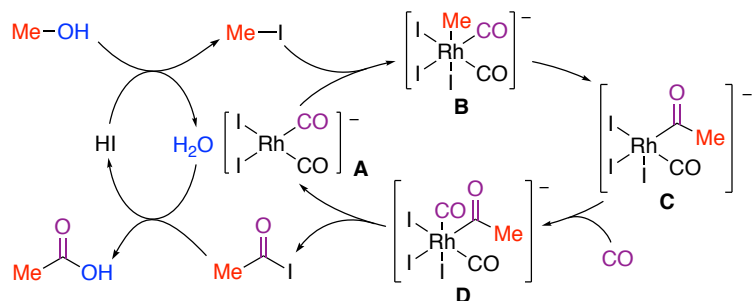i)   Hydrogen iodide protonates the oxygen atom of methanol to form its oxonium.   The protonation enhances the reactivity.   The protonated methanol reacts with iodide anion to form iodomethane through $S_N2$ pathway.
ii)   Oxidative addition of the iodomethane to rhodium(I) **A** leads to the formation of methylrhodium(III) **B**.
iii)   A carbonyl ligand on the rhodium inserts into the Rh–C bond to form acylrhodium(III) **C**. The resulting vacant coordination site on rhodium is saturated with carbon monoxide.
iv)   The reductive elimination of acyl and iodide ligand from **D** gives acetyl iodide and **A**.
v)   The acyl iodide is rapidly hydrolyzed to acetic acid with the water, which is generated from step i).

## (4) Coordination polymerization of alkenes

$$H_2C=CH_2 \xrightarrow{M-R} -\!\!\left(CH_2CH_2\right)_n\!\!-$$

M = metal atom
R = methyl or alkyl
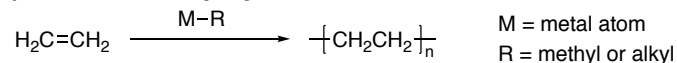
### (a) Ziegler–Natta catalyst

K. Ziegler, *Angew. Chem.*, **67**, 426 (1955); L. L. Böhm, *Angew. Chem. Int. Ed.*, **42**, 5010 (2003).

- A mixture of $TiCl_4$ and $AlEt_3$ allows ethylene to polymerize to high-density polyethylene.
- For polymerization of propylene, $TiCl_3$ is preferred to $TiCl_4$.
- The polymerization is induced by the alkyltitanium species, which is generated through the transmetalation between $AlEt_3$ and $TiCl_4$.

Mechanism



□ : vacant site
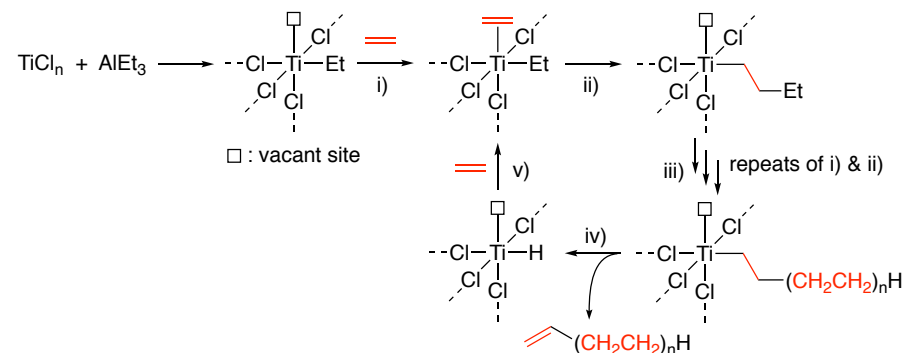
i)   An ethylene molecule occupies the vacant coordination site on the titanium atom in the ethyltitanium species.
ii)   The ethylene ligand inserts into the Ti–C bond to give butyltitanium.
iii)   The coordination and insertion of ethylene is successively repeated to form the long alkyl chain on the titanium.
iv)   The β-hydride elimination of the alkyl chain provides polyethylene and hydridotitanium species.   The polyethylene has a C–C double bond at its terminus.
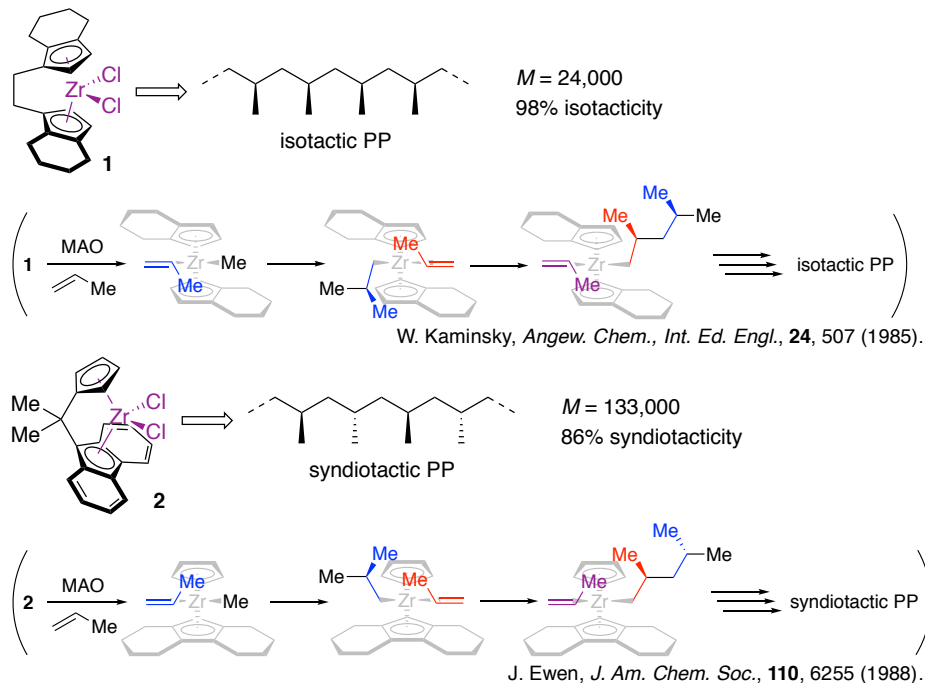v)   Ethylene inserts into the Ti–H bond to regenerate ethyltitanium species.

### (b) Kaminsky catalyst (metallocene catalyst)



$$\left(AlMe_3 + H_2O \longrightarrow \left[\begin{array}{c}Me\\Al\\O\end{array}\right]_n MAO\right)$$

(2:1 to 5:1)
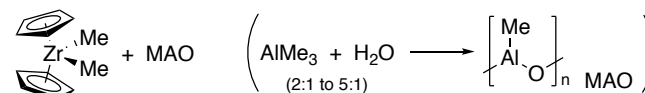
H. Sinn, *Angew. Chem., Int. Ed. Engl.*, **15**, 630 (1976); W. Kaminsky, *ibid.*, **19**, 590 (1980).
Review: W. Kaminsky, *J. Chem. Soc., Dalton Trans.*, 1413 (1998).

- Dimethylzirconocene ($Cp_2ZrMe_2$) works as the excellent catalyst for the polymerization of ethylene in the presence of methylalumoxane (MAO), which is generated from trimethylaluminum and a small amount of water.
- Zirconocene dichloride ($Cp_2ZrCl_2$) is also used as the catalyst precursor.
- Reaction of the zirconocene and MAO would generate cationic methylzirconium species ($Cp_2ZrMe^+$), which would be active for the polymerization.

- Kaminsky catalyst is useful for the polymerization of 1-alkenes, such as propylene. Its stereoselexivity (tacticity) is controlled by means of well-designed cyclopentadienyl ligand.
- Use of complex **1** leads to the formation of isotactic polypropylene (PP). Meanwhile, syndiotactic polypropylene is obtained from the polymerization with complex **2**. These catalysts were designed for the stereoselective polymerizations according to the steric repulsion between the modified cyclopentadienyl ligands and the methyl group of the monomer. But...



isotactic PP

$M$ = 24,000
98% isotacticity



W. Kaminsky, *Angew. Chem., Int. Ed. Engl.*, **24**, 507 (1985).



syndiotactic PP

$M$ = 133,000
86% syndiotacticity



J. Ewen, *J. Am. Chem. Soc.*, **110**, 6255 (1988).

## (c) Brookhart catalyst



M. Brookhart, *J. Am. Chem. Soc.*, **117**, 6414 (1995). Review: C. Chen, *Polym. Chem.*, **10**, 2354 (2019).
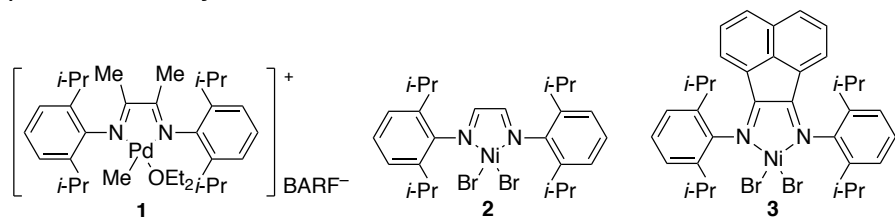
- Alkenes are inserted into late-transition-metal–carbon, *e.g.* Pd–C or Ni–C, bond. However, the resulting alkyl ligand on the late transition-metal readily decomposes into the corresponding alkene through its β-hydride elimination. Therefore, the late transition-metal complex had been believed to be wrong for the polymerization catalyst.

- Nevertheless, the palladium and nickel complexes **1**–**3** are known to function as good or excellent catalysts for the polymerization of terminal alkenes. The nickel complexes **2** and **3** require the activation with MAO for working as the polymerizing the alkenes.
- The *o*-isopropyl groups in diimine ligand cover the vacant coordination site, which causes the β-agostic interaction of the long alkyl chain. Therefore, the steric hindrance of the isopropyl group restricts the undesirable β-hydride elimination.