Organometallic Chemistry — for organic synthesis

Contents

Books

1. Comprehensive Organometallic Chemistry III
   eds. by D. M. P. Mingos and R. H. Crabtree, Elsevier, Oxford, 2007.
   (https://www.sciencedirect.com/science/referenceworks/9780080450476)

2. 第5版 実験化学講座 有機化合物の合成 VI 金属を用いる有機合成
   日本化学会 編, 丸善, 2004. (ISBN4-621-07317-6)

3. 有機金属化学
   山本明夫, 東京化学同人, 2015. (ISBN978-4-8079-0857-8)

4. Organotransition Metal Chemistry: From Bonding to Catalysis
   J. F. Hartwig, University Science Books, Sausalito, 2010. (ISBN978-1-8913-8953-5, 日本語訳あり)

5. Organic Syntheses
   http://www.orgsyn.org/Default.aspx

Abbreviations in Chemical Structures

Me	CH_3-	methyl	Bz	PhC(O)-	benzoyl
Et	$MeCH_2$-	ethyl	Boc	*t*-BuOCO	*tert*-butoxycarbonyl
Pr	$EtCH_2$-	*n*-propyl	Ts	*p*-$TolSO_2$-	p-toluenesulfonyl
Bu	$PrCH_2$-	*n*-butyl	Ms	$MeSO_2$-	methanesulfonyl
Pent	$BuCH_2$-	*n*-pentyl	Tf	CF_3SO_2-	trifluoromethanesulfonyl
Hex	$PentCH_2$-	*n*-hexyl	TMS	Me_3Si-	trimethylsilyl
i-Pr	Me_2CH-	isopropyl	TES	Et_3Si-	triethylsilyl
i-Bu	*i*-PrCH-	isobutyl	TBS	*t*-$BuMe_2Si$-	*tert*-butyldimethylsilyl
s-Bu	EtMeCH-	*sec*-butyl			
t-Bu	Me_3C-	*tert*-butyl			
c-Pent	*c*-C_5H_9-	cyclopentyl			
t-Am	$EtMe_2C$-	*tert*-amyl			
Cy (*c*-Hex)	*c*-C_6H_{11}-	cyclohexyl			
Ph	C_6H_5-	phenyl	pin	-$OCMe_2CMe_2O$-	pinacolate
Bn	$PhCH_2$-	benzyl	cat	1,2-$C_6H_4O_2$	catecholate
o-Tol	2-MeC_6H_4-	2-methylphenyl			
m-Tol	3-MeC_6H_4-	3-methylphenyl	R	any C substituents	
p-Anis	4-$MeOC_6H_4$-	4-methoxyphenyl	Ar	any aromatic substituents	
PMB	*p*-$AnisCH_2$-	4-methoxybenzyl	X	any halogen and related leaving group	
Xyl	5-Me-*m*-Tol-	3,5-dimethylphenyl	M	any metal substituents	
Mes	2,4,6-$Me_3C_6H_2$-	mesityl			
1-(α-)Np	1-$C_{10}H_7$-	1-naphtyl	TMEDA	$Me_2NCH_2CH_2NMe_2$	
2-(β-)Np	2-$C_{10}H_7$-	2-naphtyl	HMPA	$(Me_2N)_3P=O$	
Ac	MeC(O)-	acetyl			

Periodic Table

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	**Ln**	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn

Lanthanoids (Ln)

La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu

1. Main group organometallic chemistry

1-1. Preparations

(0) What is organometallic compounds?

"Organometallic compounds" means the compounds containing one or more carbon–metal (C–M) covalent bonds.

<u>Features and properties</u>
- The organometallic compound has one or more C–M bonds
- It behaves as a carbanion (carbon nucleophiles) to react with electrophilic compounds
- Reactivity of the C–M bond is greatly affected by electronegativity (χ) of the metal atom.
  - Li, Mg *etc.* (small χ) Unstable to water and oxygen
    Not easy to handle in air
    Too reactive.
  - B, Si, Sn *etc.* (large χ) Relatively stable to water and oxygen
    Possible to be purifies with extraction and/or chromatography

(1) Preparation from organic halides and metal (Direct method)

Some main group organometals are prepared from the corresponding organic halides through the reaction with metal elemental substance. This method offers the most fundamental preparation of organometallic compounds.

M = Li *etc.* (alkali metal)

$$R-X \ + \ 2\,M \longrightarrow R-M \ + \ MX$$
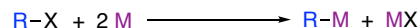
M = Mg *etc.* (alkaline earth metal)

$$R-X \ + \ M \longrightarrow R-MX \qquad (X = I, Br, Cl)$$

<u>Notice</u>
- The reactions are greatly affected by shape of the metal (dispersion, granular, or ingot).
- Reactivity of lithium metal is affected by sodium impurity (<1%). The impurity facilitates the reaction.
- Lithium or magnesium can be activated with a small piece of iodine or dibromoethane.
- Some organozincs, *e.g.* Reformatsky and Simmons–Smith reagents, can be obtained from the reaction of the halide and zinc metal. Zinc–copper couple (alloy) is frequently employed for the preparation.
- Optimal solvent depends on the halide as well as the metal. Therefore, the solvent must be carefully chosen for each combination. Et$_2$O and THF is favorable for the preparation of Grignard reagent and aryllithium. The preparation of alkyllithium is ordinarily carried out in hydrocarbon solvent.
- The organic halide should be carefully and slowly (0.1–3 h) added to the metal suspension to avoid Wurtz reaction.

<u>Half lives of organolithium compounds in ethereal solvents (min)</u>

		–40°C	–20°C	0°C	20°C	35°C
	n-BuLi				9180	1860
in Et$_2$O	*s*-BuLi		1187	139		
	t-BuLi		483	61	complex	
	n-BuLi			1039	107	
in THF	*s*-BuLi		78			
	t-BuLi	338	42			

P. Stanetty, *J. Org. Chem.*, **62**, 1514 (1997).
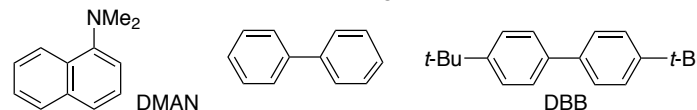
<u>Mechanism</u>
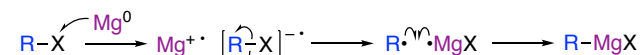
- The generation of Grignard reagent starts from the electron transfer from metal to organic halide.
- The reaction proceeds through the radical species, which must be kept low concentration to avoid its homocoupling.
- In the case of lithium, LiX is generated in the second step. The radical species, R•, reacted with Li atom in place of •MgX.
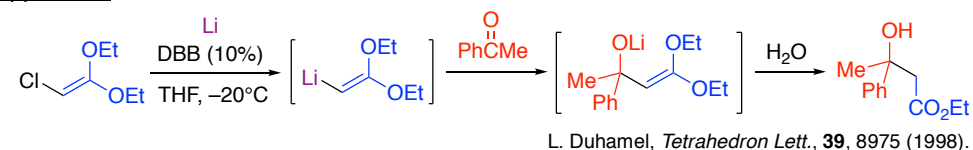
<u>Active metal species</u>
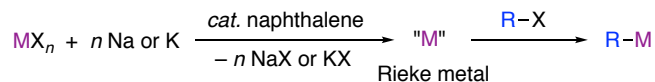### (a) Lithium arenide

lithium naphthalenide (LN)
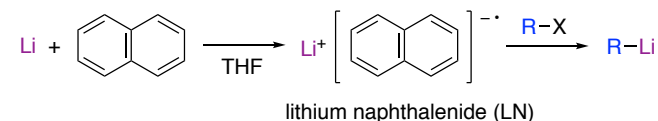
- Lithium give an electron to the LUMO of naphthalene, forming a radical anion, lithium naphthalenide (LN). LN is soluble in THF.
- LN is more reactive to organic halides than common lithium metal. Use of LN allows the preparation of organolithiums at low temperature. The mild condition leads to restriction of the undesired Wurtz reaction.
- A catalytic amount of naphthalene is enough for efficient production of organolithiums.
- Arenes below are also usable for the generation of anion radical in place of naphthalene.

DMAN   DBB

<u>Application</u>

L. Duhamel, *Tetrahedron Lett.*, **39**, 8975 (1998).

(b) Rieke metal

$$MX_n + n \text{ Na or K} \xrightarrow[-\ n \text{ NaX or KX}]{cat. \text{ naphthalene}} \text{"M"} \xrightarrow{R-X} R-M$$

Rieke metal

R. D. Rieke, *Acc. Chem. Res.*, **10**, 301 (1977); *Tetrahedron* **53**, 1925 (1997).

- Metal halides, MXn, are reduced with sodium arenide to fine metal particles, which are named Rieke metal.
- Rieke metal is more reactive than common metal powder.
- Various organometals, *e.g.* Mg, Zn, In, Ca, Cu *etc.*, can be prepared under mild conditions through the reaction of organic halide with Rieke metal.

(c) Knochel's organozinc preparation
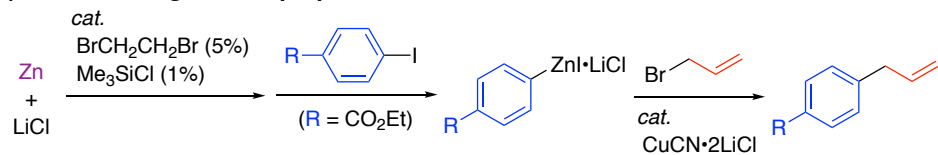
P. Knochel, *Angew. Chem. Int. Ed.*, **45**, 6040 (2006).

- The addition of LiCl remarkably enhance the reactivity of Zn power.
- The zinc is activated by catalytic dibromoethane and TMSCl in the presence of LiCl. The resulting Zn•LiCl readily reacts with various iodo-, bromoarenes, and bromoalkanes.
- This method is applicable for the generation of various functionalized organozincs.

(2) Metal–halogen (M–X) exchange reaction

$$R-X + R'-M \rightleftharpoons R-M + R'-X$$

M = Li, MgX *etc.*
X = I, Br, SeR, TeR *etc.*
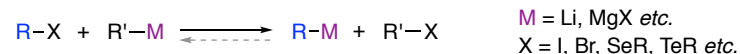
- Metal–halogen (M–X) exchange is useful for preparing organolithiums or Grignard reagents. This method is useful for preparing the organometallic reagents in small scale.
- In this reaction, R'–M and R–M are in equilibrium. The equilibrium is affected by the thermal stability of each carbanion.
- The reaction proceeds to the right, when R'–H is larger in pK_a than R–H.
- Butyllithium or *tert*-butyllithium is frequently employed for the transformation, because it is easily available from reagent company.
- The lithiation proceeds well at lower temperature (–78°C) than the direct method.
- The organolithium obtained from the M–X exchange contains stoichiometric haloalkane R'–X as the by-product. The haloalkane may react with R–M to give R–R' and is sometimes undesirable for the following reaction.
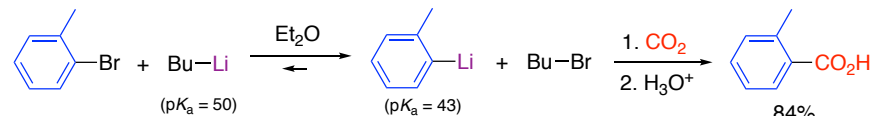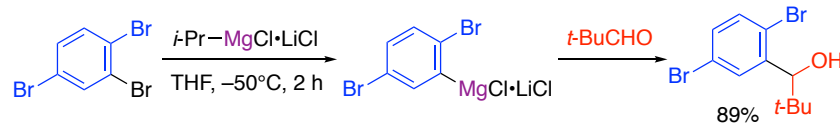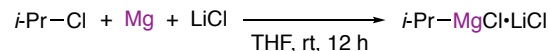

H. Gilman, *J. Am. Chem. Soc.*, **62**, 2327 (1940).
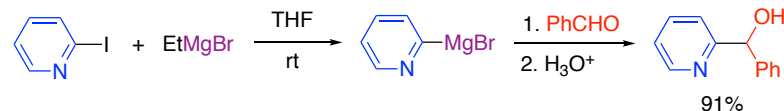
N. Furukawa, *Tetrahedron Lett.*, **28**, 5845 (1987).

Turbo Grignard Reagent (i-PrMgCl•LiCl)

$$i\text{-Pr}-\text{Cl} + \text{Mg} + \text{LiCl} \xrightarrow{\text{THF, rt, 12 h}} i\text{-Pr}-\text{MgCl•LiCl}$$

P. Knochel, *Angew. Chem. Int. Ed.*, **43**, 3333 (2004).

- Turbo Grignard reagent, *i*-PrMgCl•LiCl, is generated from the reaction of *i*-PrCl and magnesium turnings in the presence of anhydrous LiCl.
- *i*-PrMgCl•LiCl exhibits higher reactivity to the X–Mg exchange than classical Grignard reagents. With the reagent, the desired organomagnesiums can be prepared from the corresponding bromoarenes at low temperature (< 0°C).
- This method is applicable for the generation of various Grignard reagents bearing a reactive functional group, such as carboxylate and nitrile.

– 3 –

## (3) Metal–metal (M–M') exchange reaction (transmetalation)

(a) Exchange reaction between organometallic compound and metal halide

$$R-M' \ + \ MX_n \ \longrightarrow \ R-MX_{n-1} \ + \ M'X$$

$MX_n = ZnCl_2, R_3SnCl, R_3SiCl, R_2B(OMe), etc.$
$M' = Li, MgX$

- This reaction is useful for obtaining various organometals, Zn, Al, Sn, Si, B *etc.* from organolithiums or Grignard reagents.
- This reaction is also in equilibrium, but the desired organometal is obtained in high yield when insoluble or thermally stable metal salt is generated as the by-product.
- In the method, various halometals, *e.g.* $ZnCl_2$, Bu_3SnCl, Me_3SiCl, $B(OMe)_3$, work as the metal source. The resulting organometals are frequently used as the nucleophilic substrates in various reactions, such as the palladium-catalyzed cross-couplings.

E. Negishi, *Org. Synth.*, **66**, 67 (1987).

D. Seyferth *J. Am. Chem. Soc.*, **79**, 515 (1957).
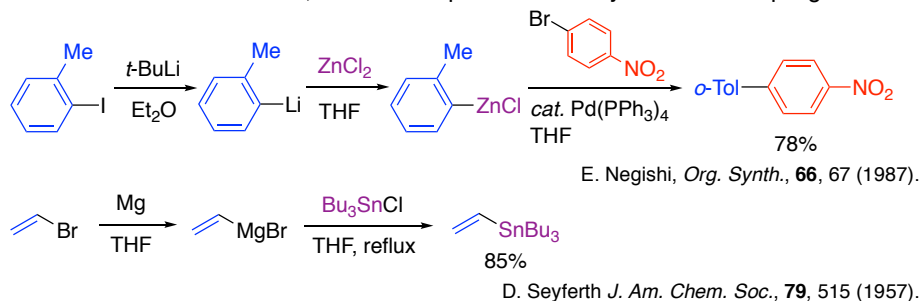
(b) Exchange reaction between two organometallic compounds

$$R-M' \ + \ R'-M \ \rightleftharpoons \ R-M \ + \ R'-M'$$

$M = Na, Li, MgX$ *etc.*
$M' = SnR_3, BR_2$ *etc.*
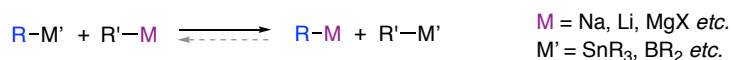
- This method is sometimes useful for generating highly reactive organometallic species, *e.g.* allyllithium, but it is not common.
- This reaction is also in equilibrium. The equilibrium is affected by the thermal stability of each carbanion.
- The reaction proceeds to the right, when R'–H is larger in pK_a than R–H and M is much smaller in electronegativity than M'.

D. Seyferth *J. Org. Chem.*, **26**, 4797 (1961).
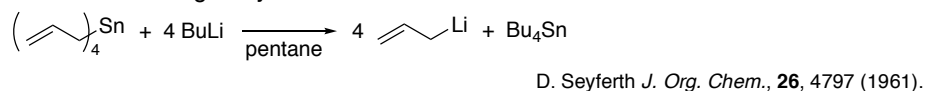
(4) Metal–hydrogen (M–H) exchange reaction (deprotonation)

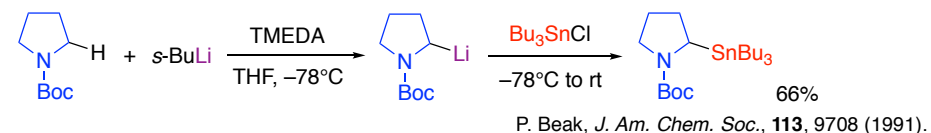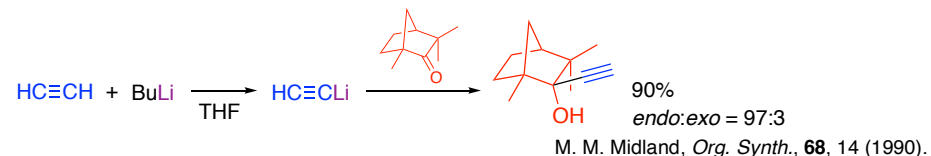$$R-H \ + \ R'-M \ \rightleftharpoons \ R-M \ + \ R'-H$$

- If a substrate has an acidic C–H bond (less than pK_a 40), it will be deprotonated on the carbon with a strong base (*e.g. t*-BuLi) to give the corresponding organometal. This reaction can be classified into an acid–base reaction.
- The deprotonation is in equilibrium. The equilibrium is controlled by the thermodynamic stabilities of the corresponding carbanions, R– and R'–. The reaction proceeds to right, when R'–H is larger in pK_a than R–H.
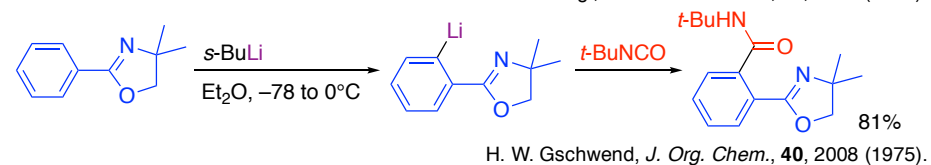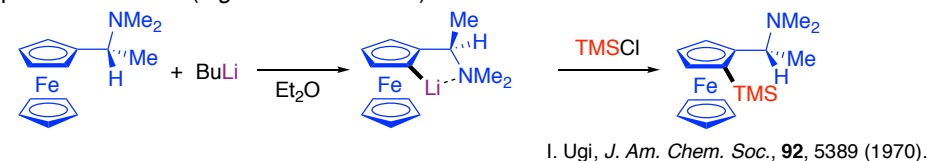
pK_a in hydrocarbons

	Me_3C-H	Me_2CH-H	$MeCH_2-H$	$CH_2=CH-H$	$Ph-H$	$PhCH_2-H$	$HC\equiv C-H$
pK_a	53	51	50	44	43	41	25

- Suitable bases for the M–H exchange reaction:
  (purchasable) BuLi, *s*-BuLi, *t*-BuLi, EtMgBr, *i*-Pr_2NLi (pK_a 38), NaH (pK_a 35) *etc.*
  (preparation for use) Schlosser base, *i*-Pr_2NMgBr, Knochel–Hauser base *etc.*
- This reaction is useful for generating lithium acetylide, heteroaryllithiums, and α-oxa- or aza-alkyllithiums.

M. M. Midland, *Org. Synth.*, **68**, 14 (1990).

E. Jones, *Org. Synth.*, **50**, 104 (1970).
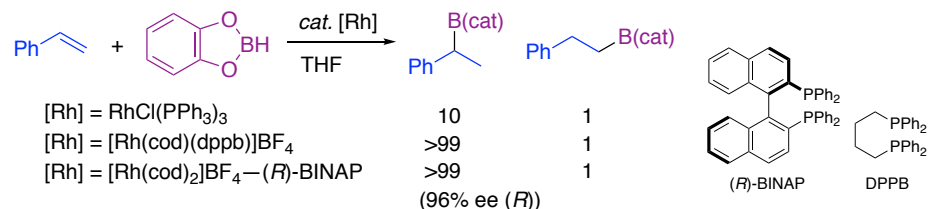

P. Beak, *J. Am. Chem. Soc.*, **113**, 9708 (1991).

- A Lewis basic directing group often facilitates the site-selective M–H exchange on a specific C–H bond (*e.g.* ortho-metalation).

I. Ugi, *J. Am. Chem. Soc.*, **92**, 5389 (1970).

H. W. Gschwend, *J. Org. Chem.*, **40**, 2008 (1975).

Schlosser–Lochmann base

- Schlosser–Lochmann base is prepared by mixing butyllithium (or tert-butyllithium) and potassium *tert*-butoxide in 1:1 ratio. The resulting mixture works as a superbase.

  L. Lochmann, *Tetrahedron Lett.*, 257 (1966); M. Schlosser, *Angew. Chem. Int. Ed. Engl.*, **12**, 508 (1973)

  R. W. Hoffmann, *J. Org. Chem.*, **46**, 1309 (1981); W. R. Roush, *Tetrahedron Lett.*, **29**, 5579 (1988).

Knochel–Hauser base

- Knochel–Hauser base (**1**) is prepared from *i*-PrMgCl·LiCl and 2,2,6,6-tetramethylpiperidine (TMPH).

- The base **1** deprotonates from various arenes bearing a Lewis basic directing group and heteroarenes to give the corresponding Grignard reagents.
- Meanwhile, the M–X exchange reaction scarcely proceeds when **1** is used as the metalation reagent. The magnesium amide has no C–M bond.
- The lithium salt remarkably enhances the reactivity of the magnesium amide as with turbo Grignard reagent.

  P. Knochel, *Angew. Chem. Int. Ed.*, **45**, 2958 (2006).

(5) Hydrometalation

- Hydrometalation is the addition of metal hydride (M–H) across unsaturated bond, *e.g.* alkene or alkynes.
- This reaction is often used for preparing organoboron, organosilane, and organotin compounds *etc.*
- The regio- and stereoselectivity must be controlled to obtain the desired product in high yield. However, the hydrometalation proceeds through syn addition with high regioselectivity. The metal substituent is installed on the less congested site.

(a) Hydroboration

- Borane (BH_3) or dialkylborane readily reacts with alkene or alkyne in the 1,2-addition manner without catalyst to produce the corresponding alkyl or alkenylborane.
- The installed boryl group can be transformed into various functional groups. Furthermore, the resulting organoboranes is usable for Suzuki–Miyaura coupling.

Regioselectivity

- The boryl group is installed at the terminus in the terminal alkene or alkyne substrate (anti-Markovnikov selective).
- The hydroboration of terminal alkynes is accompanied by a small amount of undesired formation of the dihydroboration product.

R	BH_3	Sia_2BH	9-BBN
Bu	94: 6	99: 1	>99.9:0.1
Ph	80:20	98: 2	98.5:1.5
$MeOCH_2$	81:19	98: 2	98.4:1.6
$AcOCH_2$	65:35	98: 2	97.6:2.4

  H. C. Brown, *J. Am. Chem. Soc.*, **96**, 7765 (1974); *J. Org. Chem.*, **46**, 3978 (1981).

  H. C. Brown, *J. Am. Chem. Soc.*, **101**, 96 (1979).

- Dialkoxyboranes, such as catecholborane and pinacolborane, are less reactive than dialkylboranes. The hydroboration with a dialkoxyborane requires higher temperature or

transition-metal catalyst to give the hydroboration product in high yield.
- The hydroboration of styrene selectively provides 1-boryl-1-phenylethane, Markovnikov product, when it is carried out in the presence of a cationic rhodium complex.
- Chiral alkylborane can be obtained with high enantioselectivity (up to 96% ee) from the rhodium-catalyzed hydroboration when BINAP is used as the chiral ligand.

[Rh] = RhCl(PPh$_3$)$_3$ 10   1
[Rh] = [Rh(cod)(dppb)]BF$_4$ >99   1
[Rh] = [Rh(cod)$_2$]BF$_4$—(R)-BINAP   >99   1
                   (96% ee (R))

(R)-BINAP   DPPB

T. Hayashi, Y. Ito, *J. Am. Chem. Soc.*, **111**, 3426 (1989); *Tetrahedron: Asymmetry*, **2**, 601 (1991).

Stereochemistry
- Commonly, the hydroboration proceeds with syn stereospecificity.
- The hydroboration of 1-substituted cyclic alkenes gives cis-cycloalkylborane product as the sole or major product.
- Terminal alkynes are exclusively converted into *trans*-alkenyl borane through the hydroboration.
- The reaction of internal alkynes also proceeds in syn stereochemistry. In this case, it is difficult to control the regioselectivity.

>99.9%
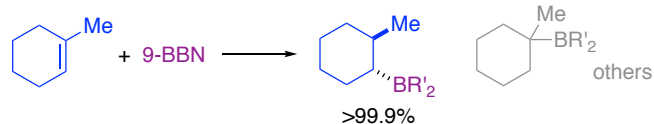
H. C. Brown, *J. Am. Chem. Soc.*, **99**, 3427 (1977).

(b) Hydrostannation
- The Sn–H bond of trialkyltin hydrides can react with C–C double and triple bonds in the presence of a catalyst or radical initiator, while the hydroboration proceeds without catalyst.
- In particular, the hydrostannation of alkynes is often used for the preparation of alkenyltin, which is useful as the substrate for Kosugi–Migita–Stille coupling.
- In the radical hydrostannation of terminal alkynes, the stannyl group is installed on the terminus. The stereoselectivity is affected by the thermodynamic stability of the radical intermediate. Commonly, *trans*-stannylalkenes are preferentially obtained from the radical hydrometalation.
- 2,2'-Azobis(isobutyronitrile) (AIBN) is widely used as the radical initiator for the hydrostannation.

49%
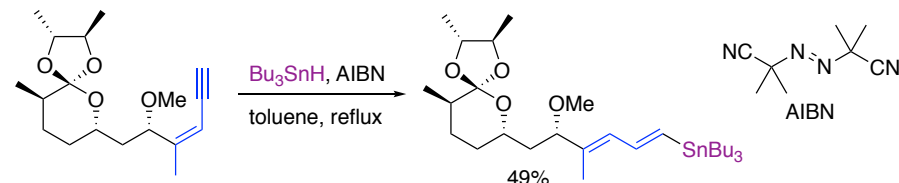
A. B. Smith, III, *J. Am. Chem. Soc.*, **119**, 962 (1997).

- The hydrostannation is facilitated by a catalytic amount of various transition-metal complexes. The regio- and stereoselectivity is affected by the substrate as well as the catalyst.

80%
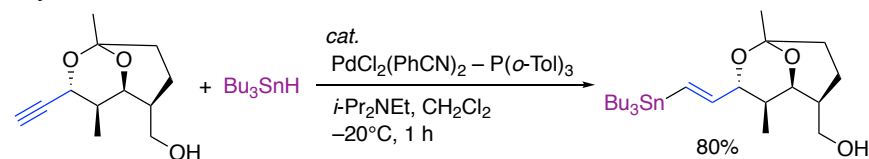
K. C. Nicolaou, *J. Am. Chem. Soc.*, **122**, 3830 (2000).

(c) Hydroalumination
- Dialkylaluminum hydride, *e.g. i*-Bu$_2$AlH (DIBAH), also can be added to C–C double or triple bond with syn stereochemistry to give alkyl- or (E)-alkenylaluminum.
- The hydroalumination is often applied to the selective reduction of alkyne to *cis*-alkene in combination with the following hydrolysis of the alkenylaluminium product.
- The trans-cis isomerization of the alkenylaluminum is often induced by the solvent and/or the functional group around the C–C double bond. In this case, stereochemistry of the product would be controlled by the thermodymanic stability of each isomer.

65%
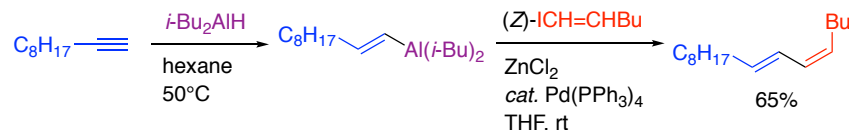
E.-I. Negishi, *Org. Synth.*, **66**, 60 (1988).

84%
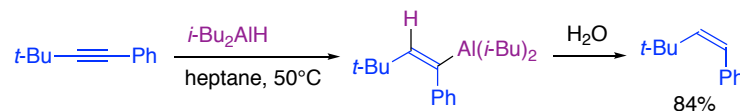
J. J. Eisch, *J. Org. Chem.*, **36**, 3520 (1971).

98%
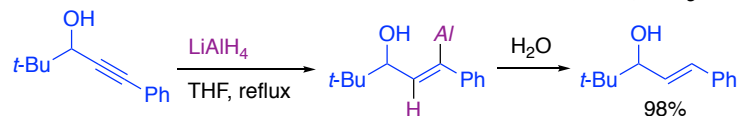
W. T. Borden, *J. Am. Chem. Soc.*, **92**, 4898 (1970).

(d) Hydrozirconation

- Cp$_2$ZrHCl (Schwaltz's reagent), which can be prepared from Cp$_2$ZrCl$_2$ and LiAlH$_4$, also works as the metal hydride reagent for the hydrometalations of alkenes and alkynes.
- The hydrozirconation is superior to the other hydrometalation in the regio- and stereoselectivity.
- In the hydrozirconation of internal alkenes, the installed zirconium atom moves to the terminus of the carbon chain.


S. L. Buchwald, *Org. Synth.*, **71**, 77 (1993).

61%

J. Schwartz, *Org. Synth.*, **71**, 83 (1993).

J. Schwartz, *J. Am. Chem. Soc.*, **96**, 8115 (1974).
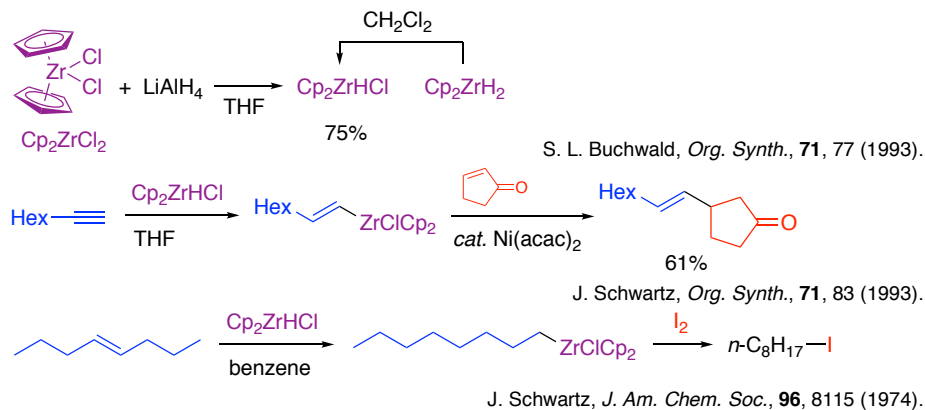
1-2. Reactions

(1) Nucleophilic addition
(a) Ketones and aldehydes
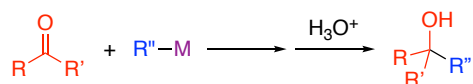
(i) Common organomatals

<u>M = Li, Mg, *etc.*</u>
- The nucleophilic addition proceeds well without any catalyst.
- Some organometallic compounds may work as reducing agents or strong bases rather than nucleophilic carbanions.

8%   11%   78%
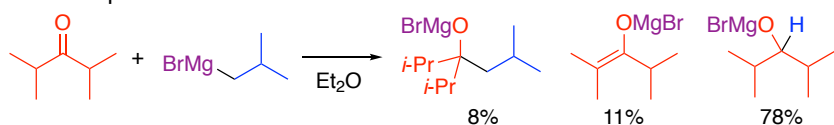
F. C. Whitmore, *J. Am. Chem. Soc.*, **64**, 1239 (1942).

- Mechanism of the reduction with *i*-BuMgBr is as follows:
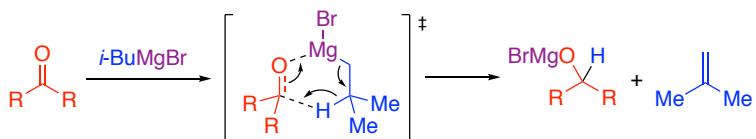
<u>M = CeX$_2$ (?)</u>
- The organocerium can be prepared by mixing anhydrous CeCl$_3$ and organolithium or Grignard reagents in THF. The anhydrous CeCl$_3$ is prepared from CeCl$_3$·7H$_2$O by heating at 100–140°C in vacuo.
- The use of cerium allows the highly enolizable ketones to undergo the nucleophilic addition of organometal reagents in high yields.

without additive   18-36%
with CeCl$_3$ (1:1)   98%
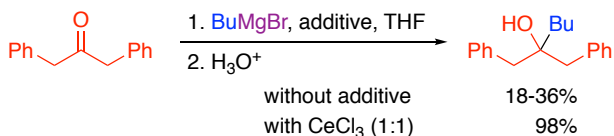
T. Imamoto, *J. Am. Chem. Soc.*, **111**, 4392 (1989); *Org. Synth.*, **76**, 228 (1999).

<u>M = LaCl$_2$·2LiCl (?)</u>
- The side reactions in Grignard reaction are suppressed by conducting it in the presence of LaCl$_3$·2LiCl, which is soluble in THF.
- The THF solution of lanthanide–lithium salt is prepared by mixing LaCl$_3$·6H$_2$O and LiCl in water, drying the mixture in vacuo, and then dissolved the residue in THF.

LnCl$_3$·6H$_2$O + 2 LiCl → LnCl$_3$·2LiCl   (Ln = La, Ce, Nd)
1. mixed in water
2. dried in vacuo
3. dissolved in THF
(0.3-0.5 M solution)

without additive   N.D.   77%
with LaCl$_3$·2LiCl (1 eq)   93%   N.D.
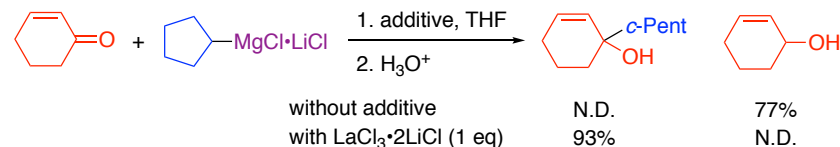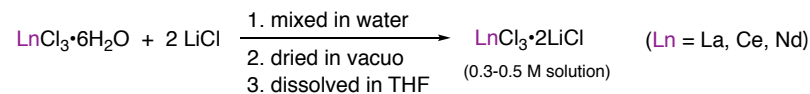
- The combination of Grignard reagent and LaCl$_3$·2LiCl is effective for improving the nucleophilic addition of the organometal to imines. In this case, high yield was achieved with a catalytic amount of the lanthanide salt.

87%
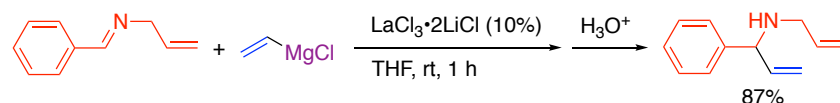
P. Knochel, *Angew. Chem. Int. Ed.*, **45**, 497 (2006).

<u>M = Zn (enantioselective)</u>
- Dialkylzinc also undergoes the nucleophilic addition to aldehydes, but the reaction requires a Lewis acid catalyst for efficient production of the desired secondary alcohol.
- Addition of a catalytic amount of a β-aminoalcohol (DAIB) facilitates the nucleophilic addition of dialkylzinc. The aminoalcohol reacts with dialkylzinc to form the chelate zinc alkoxide **1**. Alkoxide **1** can work as the Lewis acid catalyst for the nucleophilic addition.

(–)-DAIB	yield (%)	ee (%)
0 mol%	0	–
2 mol%	97	98
100 mol%	0	–

(–)-DAIB

1
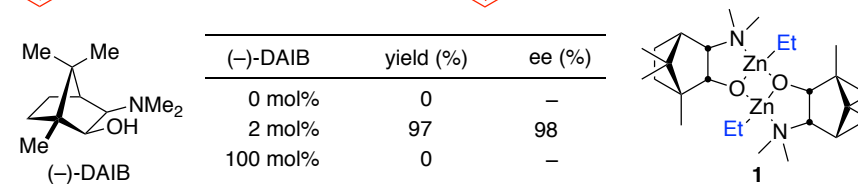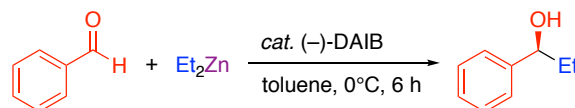
R. Noyori, *J. Am. Chem. Soc.*, **111**, 4028 (1989); *ibid.*, **117**, 4832 (1995).

(ii) Allylmetals

Feature of allylmetals

σ-allylmetal (α-)   π-allylmetal   (ion pair?)   σ-allylmetal (γ-)
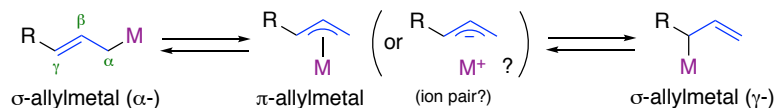
- Most of main group metals form a σ-bond with the allylic carbon to form σ-allylmetal. However, the π-structure (ion pair?) is preferable to the σ-structure in allyllithium or allylpotassium.
- The metal substituent on the allylic position is possible to shift to the γ-position when the M–C bond exhibits some degree of ionic character. In this case, the structure is ambiguous and unstable.
- The rearrangement is hardly observed when the M–C bond has strong covalent character.
- Transition metals can bond to the allyl group through the π-coordination. The d-orbitals on the metal can interact with the π-orbitals of the allyl ligand.

Regioselectivity
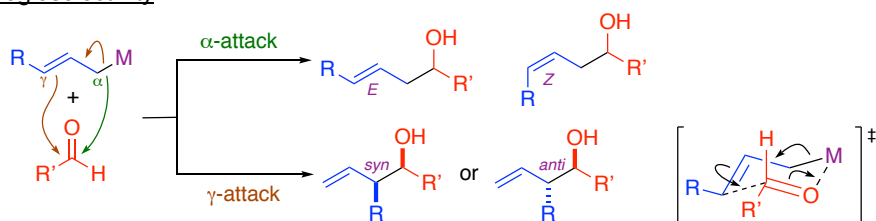
α-attack
γ-attack

- As with other organomatals, the C–M bond in allylmatal can add to the carbonyl C–O double bond. In this case, the α-carbon of allylmetal forms a C–C bond with the carbonyl carbon.
- The γ-carbon of allylmetal is also possible to attack on the carbonyl carbon. The g-attack ordinarily proceeds through the 6-membered ring transition state.
- The regioselectivity (α vs γ) is affected by metal substituent as well as reaction conditions.

α-adduct   γ-adduct
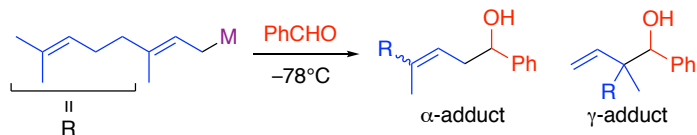
M	α/γ	E/Z (α)
Li	47/53	>99/1
MgCl	<1/99	
CaCl	12/88	98/2
BaCl	92/ 8	98/2
CeCl$_2$	72/28	>99/1

H. Yamamoto, *J. Am. Chem. Soc.*, **113**, 5893 (1991); *ibid.*, **116**, 6130 (1994).

Stereoselectivity

- The nucleophilic addition of γ-substituted allylmetal through the α-attack yields the homoallyl alcohol bearing an internal alkene. In this case, the geometric isomerism must be considered for obtaining the desired product in high yield.
- The homoallyl alcohol having vicinal stereogenic centers is obtained from the nucleophilic addition, when the reaction proceeds through the γ-attack. In this case, the diastereoselectivity must be controlled for obtaining the target product in high yield.
- The homoallyl alcohol having vicinal stereogenic centers is obtained from the nucleophilic addition, when the reaction proceeds through the γ-attack. In this case, the diastereoselectivity must be controlled for obtaining the target product in high yield.
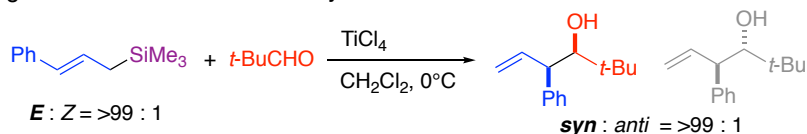
Reaction of allylborane (through cyclic TS)

- In the nucleophilic addition of allylborane, its γ-carbon attacks on the carbonyl carbon.
- The reaction proceeds through the 6-membered ring transition state, in which the carbonyl oxygen is bound to the boron atom and the substituent of aldehyde locates in the equatorial position.
- Therefore, stereochemistry of the product reflects the geometry of the C–C double bond in the γ-substituted allylborane, *e.g.* crotylborane.
- The product is obtained with anti-stereochemistry when (E)-crotylborane is used as the nucleophile.
- The reaction of (Z)-crotylborane selectively provides *syn*-homoallyl alcohol.

E : Z = 93 : 7

anti : *syn* = 94 : 6

E : Z = 5 : >95

anti : *syn* = 4 : 96

R. W. Hoffmann, *J. Org. Chem.*, **46**, 1309 (1981).

– 9 –
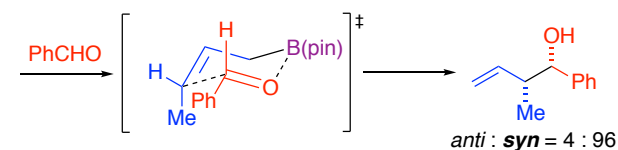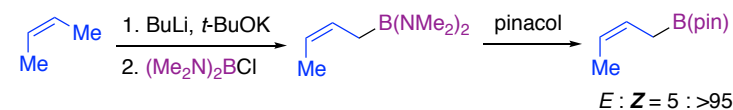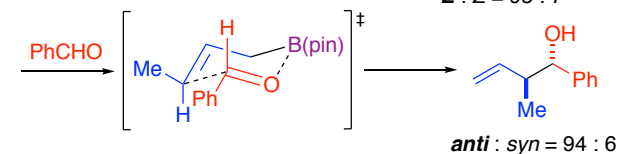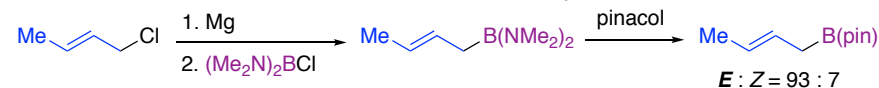
## Reaction of allylsilane (through acyclic TS, Hosomi–Sakurai reaction)

- Commonly, the γ-carbon of allylsilane attacks on the carbonyl carbon.
- In this reaction, a Lewis acid interacts with the carbonyl oxygen to enhance the electrophilicity of the aldehyde.　The oxygen atom cannot be bound to the silicon atom. Therefore, the nucleophilic addition proceeds through the acyclic transition state.
- In the transition state, its stereochemistry is mainly controlled by the steric repulsion between the γ-substituent of allylsilane and the substituent on the carbonyl carbon.
- The nucleophilic addition of γ-substituted allylsilane preferentially yields *syn*-product regardless of the stereochemistry of its C–C double bond.

PhSiMe₃ + *t*-BuCHO　$\xrightarrow[\text{CH}_2\text{Cl}_2,\ 0°\text{C}]{\text{TiCl}_4}$

E : *Z* = >99 : 1

syn : *anti* = >99 : 1

E : *Z* = 6 : 94

syn : *anti* = 75 : 25
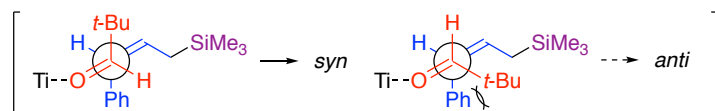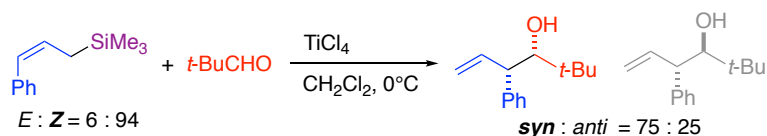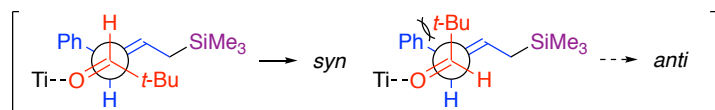
T. Hayashi, M. Kumada, *Tetrahedron Lett.*, **24**, 2865 (1983).

(b) α,β-Unsaturated carbonyl compounds

General

1,2-addition (path a)　　1,4-addition (path b)
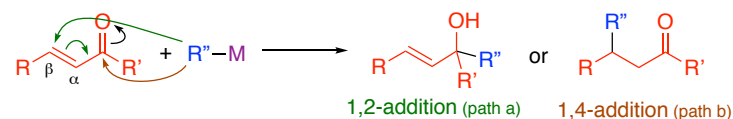
- Two possible reaction pathways, 1,2- and 1,4-additions, must be considered for the reaction of organometals with α,β-unsaturated carbonyl compounds.
- In the 1,2-addition, the nucleophilic organometal attacks the carbonyl carbon to give the corresponding allyl alcohol.
- In the 1,4-addtion (conjugate addition), the nucleophile attacks the β-carbon atom to give the enolate, which leads to the corresponding ketone or aldehyde.
- The chemoselectivity is affected by electron density on each atom, orbital coefficient of LUMO, and steric demand in the α,β-unsaturated carbonyl.　Moreover, the polarizability (hard or soft) of the nucleophile also affects the reaction.　Commonly, the 1,4-addtion is preferable to the 1,2-addition when the nucleophile has large polarizability.

Electron density and LUMO coefficient of acrolein

−0.327　−0.489
−0.427　+0.598

−0.366　**+0.365**
+0.616　−0.533

blue: electron density
red: orbital coefficient of LUMO

(i) α,β-Unsaturated aldehydes

- Organometals mostly reacts with α,β-unsaturated aldehydes through 1,2-addtion.　The nucleophile easily accesses to the carbonyl carbon because of little steric hindrance around the reaction site.
- In some exceptional cases, organometals can react with the β-carbon to lead to selective formation of the 1,4-addition product.

MeCHO + R–M　　1,2-addition　　1,4-addition

R−M	1,2- : 1,4-
BuLi	>99 : 1
MeMgBr	>99 : 1
Bu₂CuLi + TMSCl	1 : >99

(1,4-addition) J. F. Normant, *Tetrahedron*, **36**, 2305 (1980).

$\xrightarrow[\text{Et}_2\text{O}]{\text{BF}_3 \cdot \text{OEt}_2}$

46%
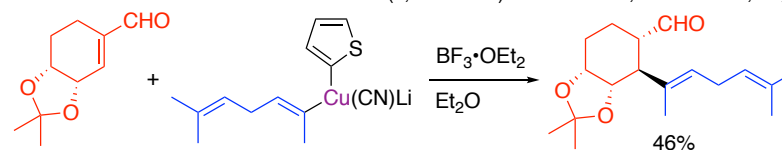
E. J. Sorensen, *Angew. Chem. Int. Ed.*, **38**, 971 (1999).

(ii) α,β-Unsaturated ketones

- In the case of organolithium, the 1,2-addition is commonly preferable to the 1,4-addition. Size of the substituent on carbonyl carbon affects the chemoselectivity.
- In the case of Grignard reagent, the chemoselectivity depends on the substrate combination of organometals and enones.　In general, the 1,2-addition is preferable to the 1,4-addtion, when the organometal can interact to the enone with small or no steric repulsion.
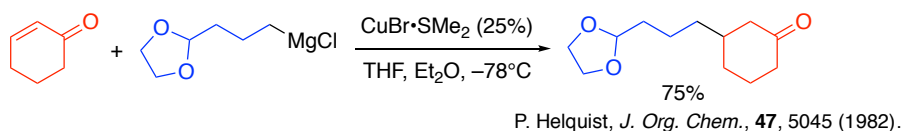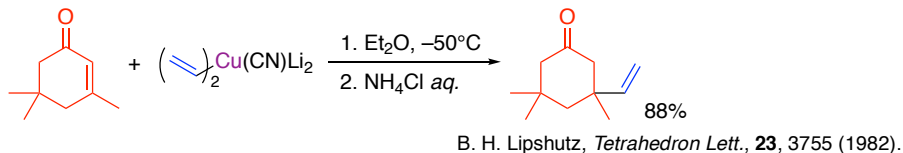

1,2-addition　　　1,4-addition

M	1,2- : 1,4-
Li	85 : 15
Li + CeCl$_3$	98 : 2
MgBr	<1 : 99
MgBr + CeCl$_3$	91 : 9

T. Imamoto, *J. Am. Chem. Soc.*, **111**, 4392 (1989).

1,2-addition　　　1,4-addition
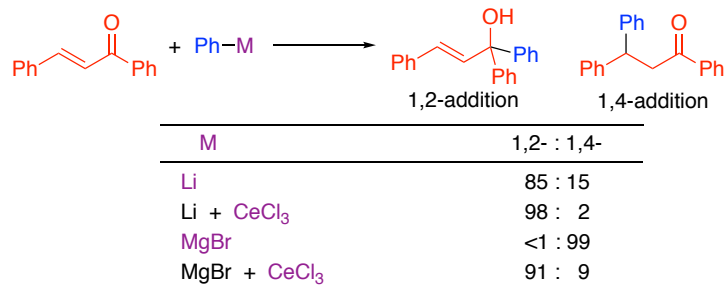
M	1,2- : 1,4-
Li	>99 : 1
K	38 : 62
MgCl	95 : 5
CaCl	72 : 28
BaCl	< 1 : 99
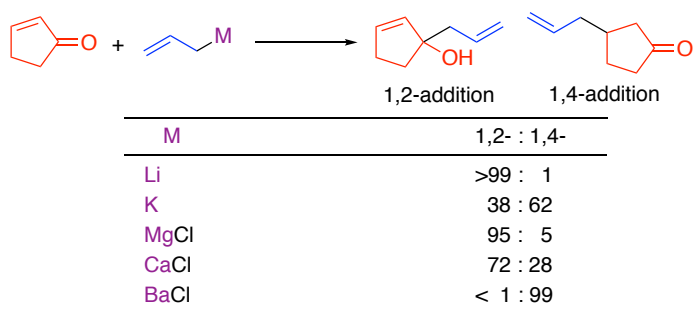
H. Yamamoto, *J. Am. Chem. Soc.*, **116**, 6130 (1994).

- Use of organocerium reagents, which are generated by mixing Grignard reagent (or R–Li) and CeCl$_3$, facilitate the selective 1,2-addition.
- Organocuprates is suitable as the organometallic reagent for the conjugate addition to enones.　Grignard reagent selectively attacks on the β-carbon of enone in the presence of catalytic amount of a copper(I) salt, CuBr•SMe$_2$ and CuI *etc*.

88%

B. H. Lipshutz, *Tetrahedron Lett.*, **23**, 3755 (1982).

75%

P. Helquist, *J. Org. Chem.*, **47**, 5045 (1982).

(iii) Three-component coupling
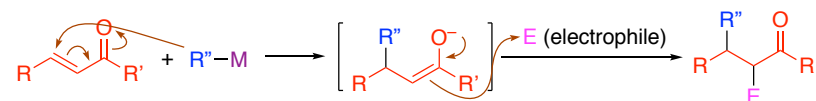
- The conjugate addition of organometal to enone directly affords the enolate.　The resulting enolate can react with electrophiles, *e.g.* haloalkanes and aldehydes.
- This type of reactions is called 'three-component coupling', because the target product is obtained from three compounds, organometal, enone, and electrophile.
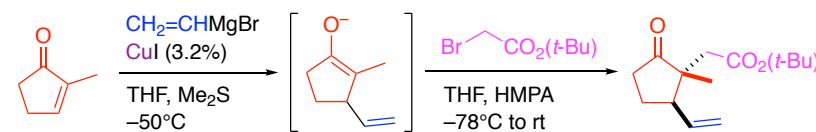
Y. Ito, M. Nakatsuka, T. Saegusa, *J. Am. Chem. Soc.*, **104**, 7609 (1982).

64%, 91% ee
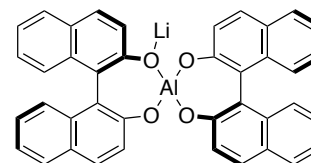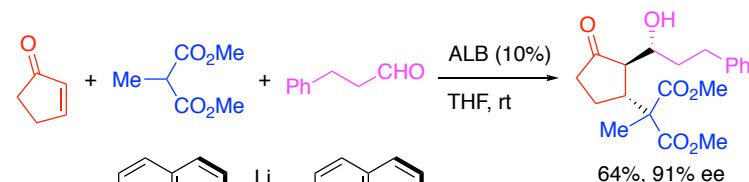
ALB

M. Shibasaki, *Angew. Chem. Int. Ed.*, **35**, 104 (1996).

(c) Carboxylic acid and its derivatives

<u>General</u>
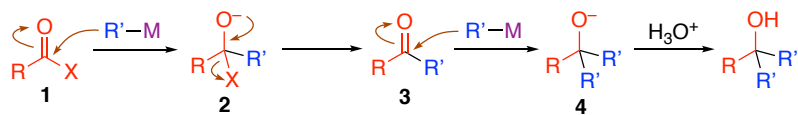
X = OR'' (ester), Cl (acyl halide), OH (carboxylic acid)

- Organometal attacks on the carbonyl carbon to give ketal analogue **2**.   The intermediate **2** usually decomposes into ketone **3** under the reaction condition.   The ketone **3** easily undergoes the nucleophilic attack of the organometal, because ketone is more reactive than the carboxylic acid or its ester.   The nucleophilic attack leads to the formation of the *tert*-alkoxide **4**.
- To achieve the selective formation of ketone **3**, the substrate **1** should be more reactive to the organometallic reagent than ketone.   In general, acyl halide and anhydride are more reactive than ketone.   In this case, the reaction condition should be carefully set to avoid the overreaction.
- Alternatively, the intermediate **2** should be designed to remain intact under the reaction conditions.   The intermediate is readily converted to **3** under aqueous acidic condition, in which the organometallic reagent rapidly decomposes.
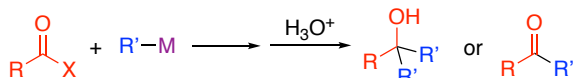
X	M	product	
OR	Li	◎	×
	MgX	◎	×
OH (OLi)	Li	×	○
Cl	Li	○	○
	MgX	○	○○○
	Cu (cuprate)	×	◎

(i) Carboxylates
- Commonly, carboxylates react with two molar equivalents of organometal (R'–Li or R'–MgX) to give the corresponding *tert*-alcohol.
- In some specific cases, the reaction can selectively provide the ketone product in high yield.

93%
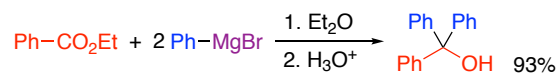
W. E. Bachmann, *Org. Synth.*, **23**, 98 (1943).

86%
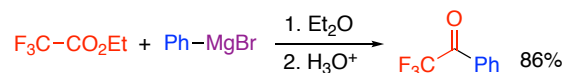
X. Creary, *J. Org. Chem.*, **52**, 5026 (1987).

(ii) Carboxylic acids
- Carboxylic acid is immediately neutralized with organometal to form the metal carboxylate salt, which is ordinarily too inactive to undergo the nucleophilic addition.
- Organolithium can react with the metal carboxylate salt to give bisalkoxide **1**.   The intermediate **1** remains intact in the absence of acidic proton because OLi cannot function as the leaving group well.

91%
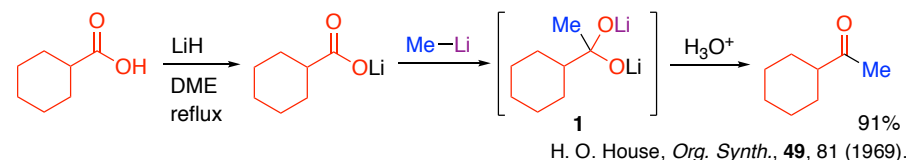
H. O. House, *Org. Synth.*, **49**, 81 (1969).

(iii) Acyl halides and acid anhydrides
- Acyl halide also reacts with two molar equivalents of organometal (R'–Li or R'–MgX) to give the corresponding *tert*-alcohol.
- Ketones are obtained in high yields from the nucleophilic addition by carefully controlling temperature and/or stoichiometry of organometallic reagent.
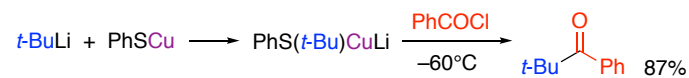

81%
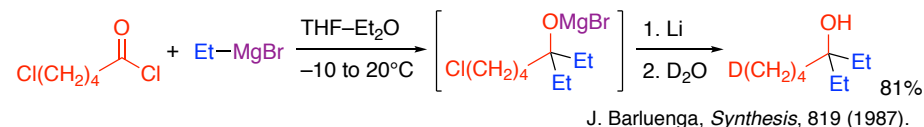
J. Barluenga, *Synthesis*, 819 (1987).
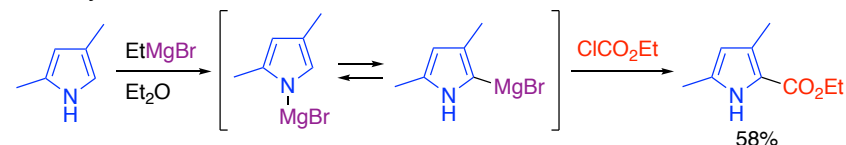

90%
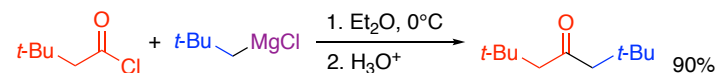
J. Ciabattoni, *Org. Synth.*, **54**, 97 (1974).

- Organocuprate also reacts with acyl halide to give the ketone product in high yield.

87%

G. H. Posner, *Org. Synth.*, **55**, 122 (1976).

- Alkyl chloroformate is often used as the electrophilic substrate for the direct synthesis of carboxylates.


58%

H. Fisher, *Org. Synth.*, **17**, 48 (1937).

(iii) Carboxamides

- Organolithium or Grignard reagent can react with carboxamides to give the corresponding ketones. However, carboxamide functionality is often insufficient in electrophilicity for the nucleophilic addition.
- The reaction of N,N-dimethylformamide or N-formylpiperidine with organometals is useful for preparing aldehydes.

G. A. Olah, *Angew. Chem., Int. Ed. Engl.*, **20**, 878 (1981); *Org. Synth.* **64**, 114 (1986).
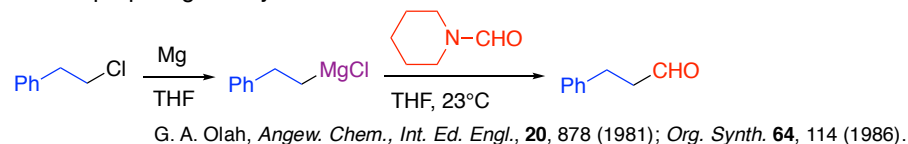
- To avoid the overreaction, N-methoxy-N-methylamide (Weinreb amide) is frequently used as the electrophilic substrate for the ketone synthesis.
- The methoxy oxygen interacts with the lithium or magnesium atom to form a chelate structure in the aminal-like intermediate. The chelation restricts the decomposition of the intermediate to the ketone in the reaction mixture.
- Weinreb amide is readily prepared by treating the corresponding carboxylate with aluminium amide, which was generated *in situ* from N-methoxy-N-methylammonium chloride and trimethylaluminum.

S. M. Weinreb, *Tetrahedron Lett.*, **22**, 3815 (1981).
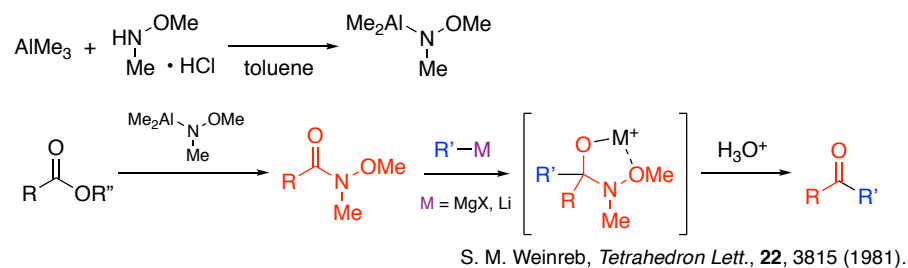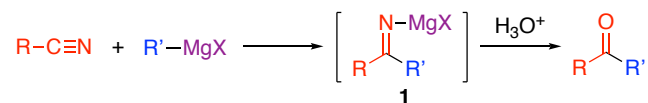
(d) Nitriles

- Nitriles undergo the nucleophilic attack of Grignard reagent to give intermediate **1**, which is readily hydrolyzed with aqueous acid to give ketones.
- The intermediate **1** is stable to the organometal at ambient temperature.

R. B. Moffett, *Org. Synth.*, **21**, 79 (1941).
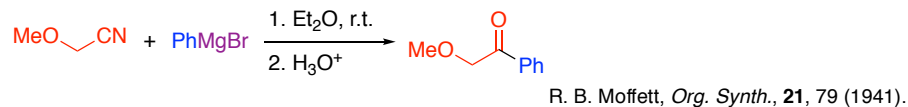
(2) Nucleophilic substitution of haloalkanes

(a) Wurtz reaction

$$2\ R\text{–}Br \xrightarrow{\text{Na}} R\text{–}R$$
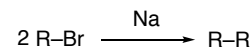
- Alkyl and aryl halides is dimerized in the presence of sodium metal.
- Sodium reduces the halide to give the carboradical. The radical randomly couples with the halide or another radical species.
- This reaction is not suitable for the cross-coupling reaction between two organohalides.
- However, this method is applicable to the cross-coupling reaction between aryl and alkyl halides (Wurtz–Fittig reaction).
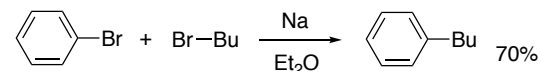
R. R. Read, *Org. Synth.*, **25**, 11 (1945).

(b) Organocuprate
### (i) Lithium diorganocuprate (Gilman reagent)
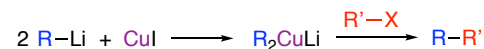
H. Gilman, *J. Org. Chem.*, **17**, 1630 (1952); E. J. Corey, *J. Am. Chem. Soc.*, **89**, 3911 (1967).
(review) G. H. Posner, *Org. React.*, **22**, 253 (1975).

- Diorganocuprate (Gilman reagent) is generated by mixing copper(I) iodide and 2 molar equivalents of organolithium, magnesium, or zinc. The cuprate is soluble in ethereal solvent.
- Gilman reagent reacts with primary or secondary alkyl halides to form the new C–C bond. The C–C bond formation proceeds through the S_N2-pathway or the oxidative addition followed by reductive elimination.
- The organocuprates are unstable for heat. Therefore, the nucleophilic substitution is usually carried out at low temperature (< 0°C).
- Gilman reagent has two same alkyl substituents on its copper, but only one of them can participate in the target reaction.

Reactivity (for substitution)
- R on copper: alkyl (primary > secondary > tertiary) > alkenyl, aryl > alkynyl
- R' on electrophile: allyl, benzyl > alkyl (primary > secondary >> tertiary) > alkenyl, aryl
- X on electrophile: tosylate, epoxide > iodide > bromide >> chloride > acetate
- Functional group compatibility: ketones, carboxylates, nitriles
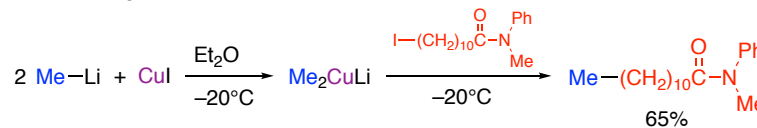
G. H. Posner, *Org. React.*, **22**, 253 (1975).

(ii) Higher order cyanocuprate (Lipshutz cuprate)

$$2 \ R-Li \ + \ CuCN \longrightarrow R_2Cu(CN)Li_2$$
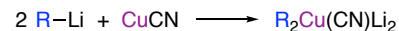
B. H. Lipshutz, *J. Am. Chem. Soc.*, **103**, 7672 (1981).

- Copper(I) cyanide is believed to react with the two molar equivalents of organolithium without elimination of cyanide from copper.   The resulting diorganocyanocuprate is called 'higher order cyano cuprate.'
- The higher order cyanocuprate is more reactive than Gilman reagent.
- Lipshutz cuprate also has two same alkyl substituents, but only one of them participate in the nucleophilic substitution.
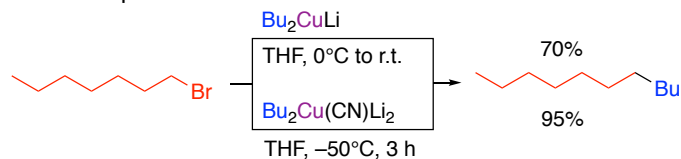
H. O. Hause, *J. Am. Chem. Soc.*, **91**, 4871 (1969); B. H. Lipshutz, *J. Org. Chem.*, **48**, 3334 (1983).

(iii) Mixed ligand cyanocuprate
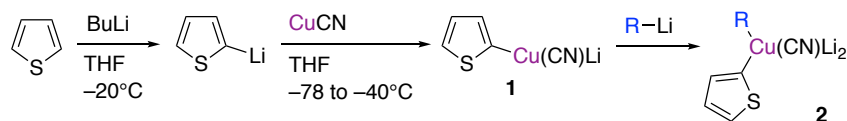
B. H. Lipshutz, *J. Organomet. Chem.*, **285**, 437 (1985); B. H. Lipshutz, *Tetrahedron Lett.*, **28**, 945 (1987).

- Lithium 2-thienyl(cyano)cuprate(I) (**1**), which is prepared from 2-thienyllithium and copper(I) cyanide, is storable over 2 months and commercially available.
- The lower order cuprate **1** reacts with equimolar organolithium or Grignard reagent to give the higher order mixed ligand cyanocuprate.
- Commonly, the 2-thienyl substituent is inert as compared to the latter-installed substituent R.   Therefore, R selectively reacts with various electrophile.   The thienyl group functions as the dummy ligand.
- Alkynyl and other 5-membered heteroaryl groups similarly work as the dummy ligands.
- The cuprate **1** is very useful for organic synthesis, when the organolithium is prepared through multistep synthesis.
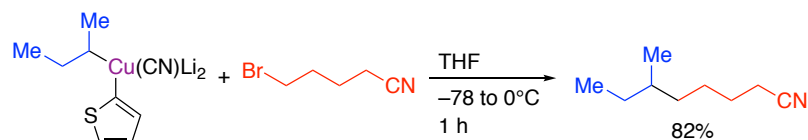
B. H. Lipshutz, *J. Organomet. Chem.*, **285**, 437 (1985).

(vi) Substitution of allylic electrophiles with organocuprate

- In the reaction of organocuprates with allylic electrophiles, the nucleophilic species commonly attacks on the γ-carbon.   The reaction proceeds in the S$_N$2' manner.
- Acetoxy, hydroxyl, and other groups is usable for the leaving group of the allylic substrate.
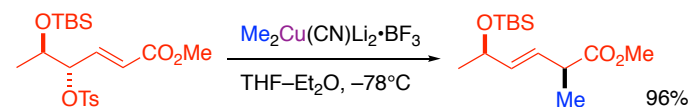
Y. Yamamoto, *J. Am. Chem. Soc.*, **108**, 7420 (1986).

- Propargyl electrophiles also react with organocuprates in the S$_N$2' manner to give the allene products.
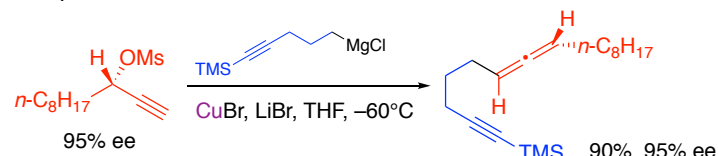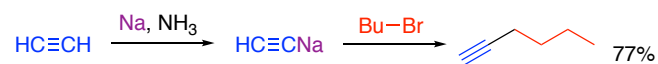

K. M. Brummnond, *J. Org. Chem.*, **67**, 5156 (2002).

(c) Grignard reagent and related organometals
(i) Without catalyst

- Commonly, no S$_N$2 substitution is observed in the mixture of Grignard reagents and haloalkanes without any transition-metal compound.   However, alkynyl metals can work as the nucleophiles in the S$_N$2 reaction of haloalkanes.

K. N. Cambell, *Org. Synth.*, **30**, 15 (1950).

- Some reactive haloalkanes (*e.g.* allyl halides) or alkyl sulfonates undergo the nucleophilic attack of the organomagnesium.
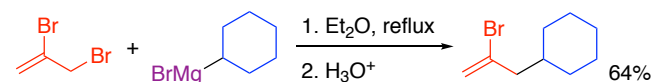

R. Lespieau, *Org. Synth.*, **6**, 20 (1926).

(ii) With copper catalyst
- As with the 1,4-addition, the substitution of haloalkanes with Grignard reagents is catalyzed by some copper salts, CuI, Li$_2$CuCl$_4$, and CuBr·SMe$_2$ etc. In the copper catalysis, organocuprate species would be generated from the organomagnesium and copper(I).


92%

B. Breit, *Angew. Chem. Int. Ed.*, **44**, 5267 (2005).
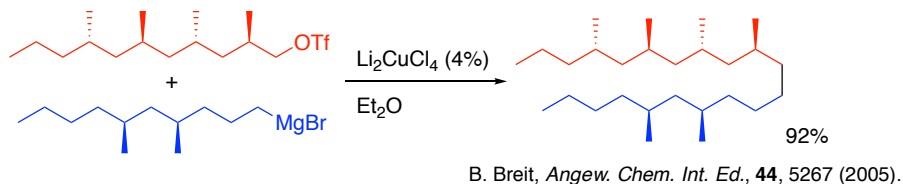
(3) Nucleophilic ring-opening reaction of epoxides

M = Li, Na, Mg, Cu etc.
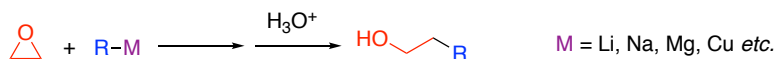
(a) Grignard reagent and organolithium
- Epoxides are sufficiently electrophilic to be attacked by the organolithiums and magnesiums, although these organometals cannot work as the nucleophiles to ordinary haloalkanes in general.
- This reaction with ethylene oxide is useful for the two-carbon homologation of primary alcohols.

E. E. Dreger, *Org. Synth.*, **6**, 54 (1926).
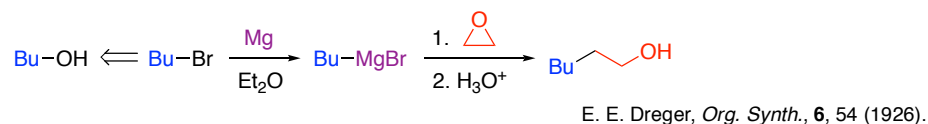
- However, the ring-opening reaction of substituted epoxides is often accompanied by the undesired side reactions, *e.g.* M–H exchange reaction, formation of halohydrins. The side reaction is often supressed by addition of Lewis acid, such as BF$_3$·Et$_2$O.
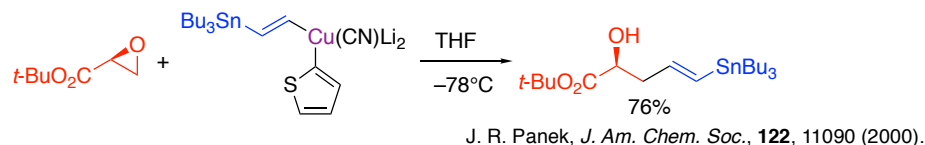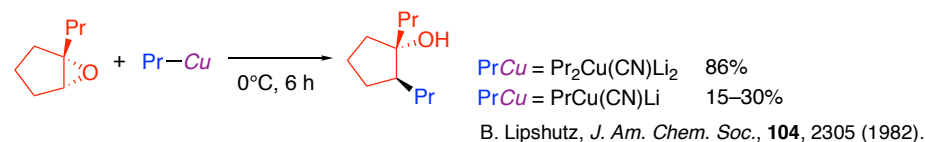

B. Ganem, *J. Am. Chem. Soc.*, **106**, 3693 (1984).
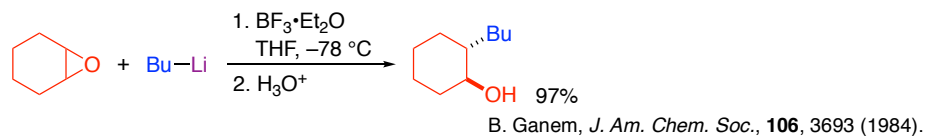
- Use of copper catalyst leads to the remarkable improvement of the ring-opening reaction of epoxides with Grignard reagents.

T. Oh, *Org. Synth.*, **76**, 101 (1999).
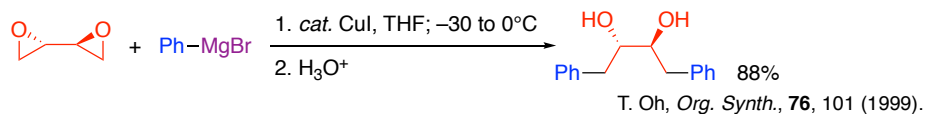
(b) Higher order cyanocuprate
- Higher order cyanocuprates are preferred for the ring-opening reaction of substituted epoxides to avoid the above side reactions.
- For the reaction of epoxide, higher order cyanocuprate is preferable to lower one.
- The organometallic species preferentially attacks on the less hindered carbon atom to give the more congested alcohol as the major product.


PrCu = Pr$_2$Cu(CN)Li$_2$ 86%
PrCu = PrCu(CN)Li   15–30%

B. Lipshutz, *J. Am. Chem. Soc.*, **104**, 2305 (1982).

76%

J. R. Panek, *J. Am. Chem. Soc.*, **122**, 11090 (2000).

(4) Halogenations
(a) Grignard reagent and organolithium

R–M + [X$^+$] ⟶ R–X   M = Li, MgX, ZnX etc.

- The metal substituent in reactive organometallic species is replaced by halogen atom with halogen cation or its equivalent.
- Some excellent halogen sources are known for the iodination or bromination.
- From the viewpoint of organic synthesis, this reaction is useful for the synthesis of organic halides by a combination of M–H exchange reaction.

For iodination: I$_2$, ICH$_2$CH$_2$I
For bromination: Br$_2$, BrCH$_2$CH$_2$Br, BrCCl$_2$CCl$_2$Br, BrCN
For chlorination: NCS (*N*-chlorosuccinimide)

51%

R. C. Ronald, *J. Org. Chem.*, **47**, 2541 (1982).
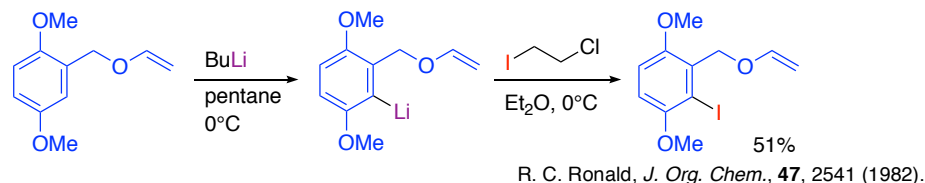
(b) Organoborane, organostannne etc.

- These oraganometallic compounds can be transformed into the corresponding organic bromides or iodides by treatment with Br_2 or I_2.
- Stereochemistry of the transformation depends on the reaction conditions.
- This transformation is useful for the stereoselective synthesis of haloalkenes in combination with the hydrometalation of terminal alkynes.

(i) Organoboranes

- Both geometric isomers of haloalkenes can be obtained from the (E)-alkenylboron compounds, which are readily obtained from the hydroboration of terminal alkynes, by appropriate choice of reaction parameters.
- Selective formation of (Z)-Iodoalkenes is accomplished by treating the alkenyl borane with iodine in the absence of the base. This transformation starts from the anti-addition of iodine across the C–C double bond. The iodo and boron substituents are eliminated from the resulting intermediate to give the iodoalkene with Z configuration.
- (E)-Alkenylboronic acids are selectively transformed into (E)-iodoalkenes, when the organoboranes are reacted with iodine after treatment with a base (e.g. OH^-). The base may activate the boron substituent through the formation of borate.
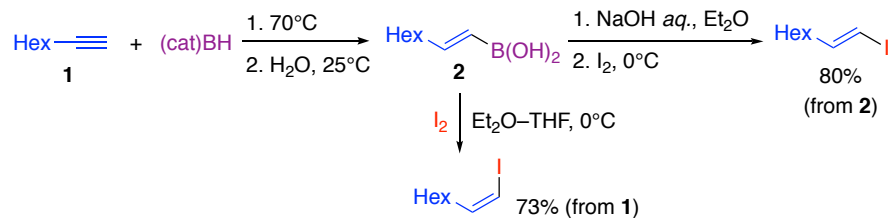
H. C. Brown, *J. Org. Chem.*, **54**, 6068 (1989); *ibid.*, **54**, 6075 (1989).

- This methodology, treatment with a base and then I_2, is applicable to the conversion of alkylboranes to iodoalkane. The stereochemistry of this transformation is inversion.
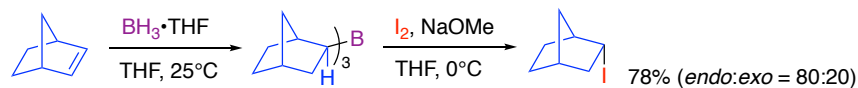
H. C. Brown, *J. Am. Chem. Soc.*, **98**, 1290 (1976).

(ii) Organostannanes

- The combination of hydrostannation and treatment with I_2 is frequently used for the transformation of terminal alkynes into *trans*-iodoalkenes.
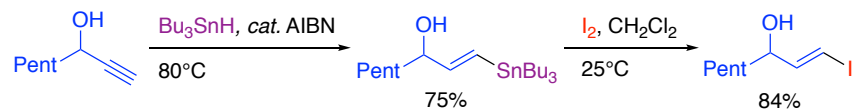

M. E. Jung, *Tetrahedron Lett.*, **23**, 3851 (1982).

(iii) Miscellaneous

- The silyl group in organosilicate ($RSiF_4^-$) can be replaced by halogen atom. This transformation is effective for the preparation of optically active haloalkanes by combination with enantioselective hydrosilylation of alkenes.
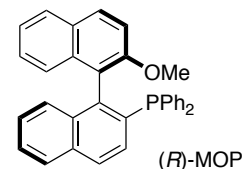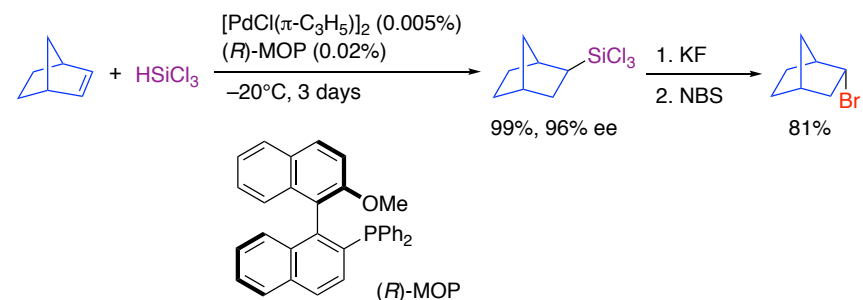
K. Tamao, M. Kumada, *J. Am. Chem. Soc.*, **102**, 3267 (1980); T. Hayashi, *Tetrahedron Lett.*, **33**, 7185 (1992).

- Hydrozirconation and hydroalumination are often used for the transformation of alkynes to iodoalkenes.
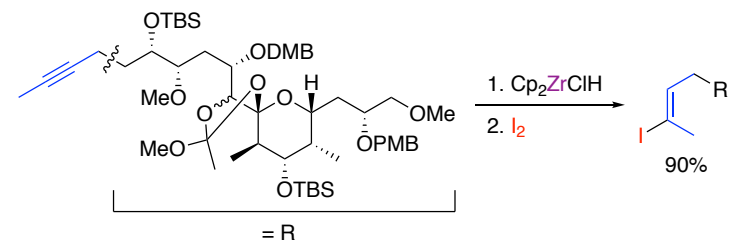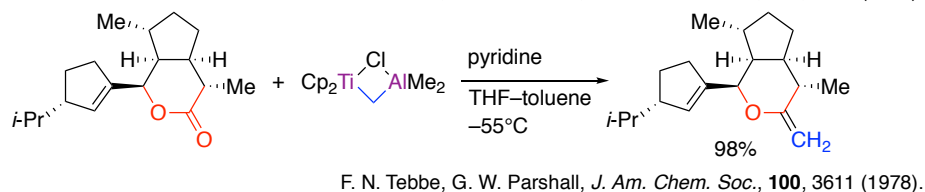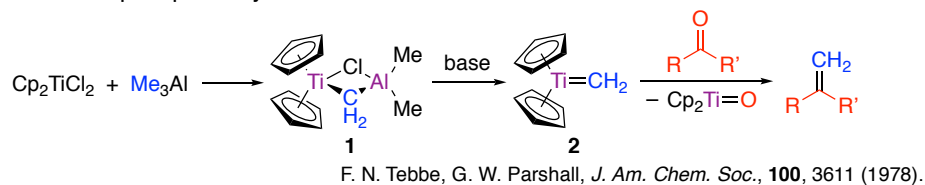

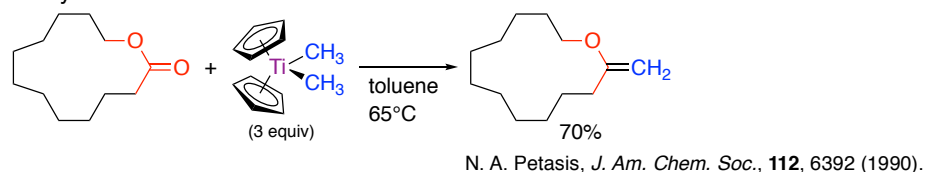K. C. Nicolaou, *Angew. Chem. Int. Ed.*, **40**, 3854 (2001).

(5) Olefinations

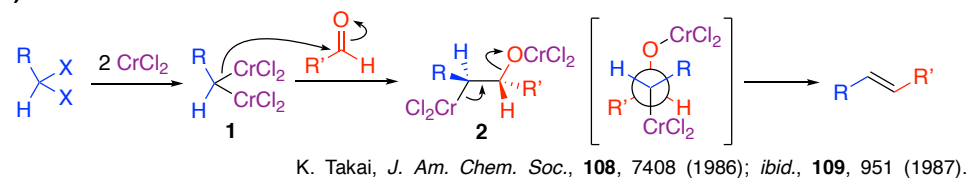## (a) Tebbe and Petasis reagents

- Tebbe reagent **1** reacts with various carbonyl functionalities, including carboxylates and carboxamides, to give the exo-methylene products in high yields.   This reagent is very useful for the synthesis of enol ethers and enamines.
- The titanium reagent **1** is generated by mixing titanocene dichloride and 2 equivalents of trimethylaluminum.
- Titanium carbene species **2** is generated by treating **1** with pyridines.   The Intermediate **2** acts like a phosphorus ylide to react with a C–O double bond.


F. N. Tebbe, G. W. Parshall, *J. Am. Chem. Soc.*, **100**, 3611 (1978).

98%

F. N. Tebbe, G. W. Parshall, *J. Am. Chem. Soc.*, **100**, 3611 (1978).

- Dimethyl titanocene, Petasis reagent, is also useful for the methylenylation of various carbonyl functionalities.

70%

N. A. Petasis, *J. Am. Chem. Soc.*, **112**, 6392 (1990).

(b) Takai reaction

K. Takai, *J. Am. Chem. Soc.*, **108**, 7408 (1986); *ibid.*, **109**, 951 (1987).
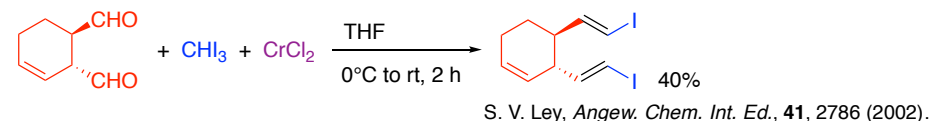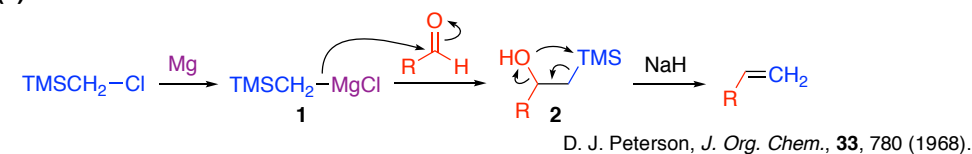
- Aldehydes react with *gem*-dihaloalkanes and anhydrous chromium(II) chloride to form new C–C double bonds.   The reaction selectively yields the alkenes with trans geometry.
- The *gem*-dihaloalkane was reduced with two $CrCl_2$ to give *gem*-metal species **1**.   The nucleophilic addition of **1** to aldehyde gives β-oxychromium intermediate **2**.   The desired (*E*)-alkenes forms through the β-elimination of $CrCl_2$ and $OCrCl_2$ from **2**.
- Formation of **2** proceeds with high stereoselectivity to avoid the steric repulsion between R and R'.   The following β-elimination from **2** is *anti*-specific.

29%

F. R. Kinder, S. Wattanasin, R. W. Versace, *J. Org. Chem.*, **66**, 2118 (2001).
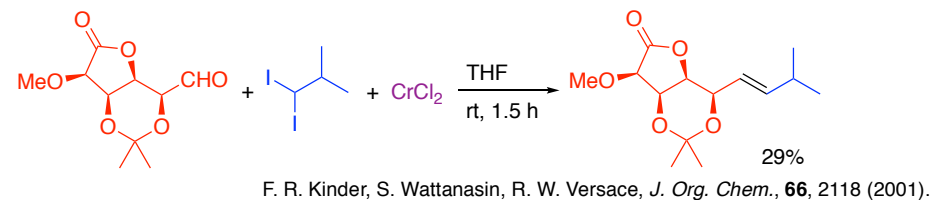
- This method is very useful for the preparation of *trans*-haloalkenes.   Iodoform or bromoform is frequently used as the substrate for Takai reaction.

40%

S. V. Ley, *Angew. Chem. Int. Ed.*, **41**, 2786 (2002).

(c) Peterson olefination


D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968).

- α-Silyl organolithium or magnesium **1** is usable as an alternative of the corresponding Wittig ylide.   Carbonyl compounds bearing an acidic a-proton can be transformed to the alkenes through Peterson reaction, which is the olefination of carbonyl with α-silyl organometallic compound.
- The nucleophilic addition of **1** to aldehyde affords the β-hydroxysilane **2**.   The following β-elimination of Si–OH from **2** leads to the formation of a C–C double bond.
- The β-elimination from **2** proceeds with *syn*-stereochemistry, when **2** is treated with a strong base.   The resulting alkoxide attacks on the silicon atom to facilitate the elimination.
- Under acidic conditions, the β-elimination proceeds through E2-mechanism.

– 17 –
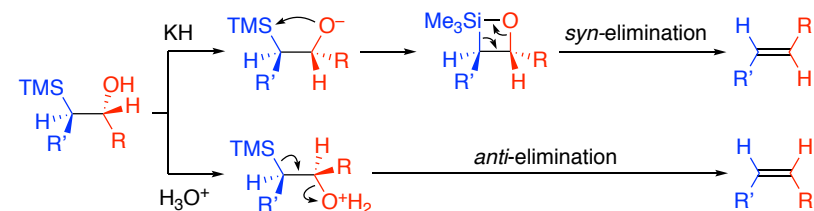
(6) Miscellaneous
(a) Insertion of carbon monoxide
(i) Organolithium

$$Bu-Li + CO \xrightarrow{-110°C} \left[\underset{\textbf{1}}{Bu-\overset{O}{\overset{\|}{C}}-Li} \right]$$
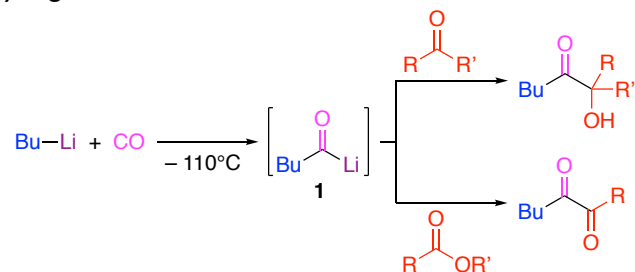
D. Seyferth, *J. Org. Chem.*, **48**, 1144 (1983); *Tetrahedron Lett.*, **24**, 4907 (1983).

- Organolithium reacts with carbon monoxide to give the acyllithium species **1**, which behaves as an acyl anion, which is potentially useful for organic synthesis.
- The nucleophilic addition of **1** to various carbonyl groups leads to the formation of α-hydroxyketones or 1,2-diketones.
- Cabanion **1** should be very unstable because of its self-condensation. Carbonyl group of one acyllithium **1** undergoes the nucleophilic attack of another **1**. Therefore, the solution of **1** must be kept at very low temperature.

(ii) Organoboron
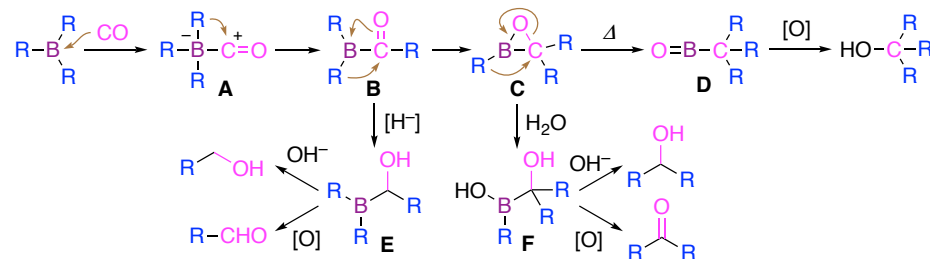
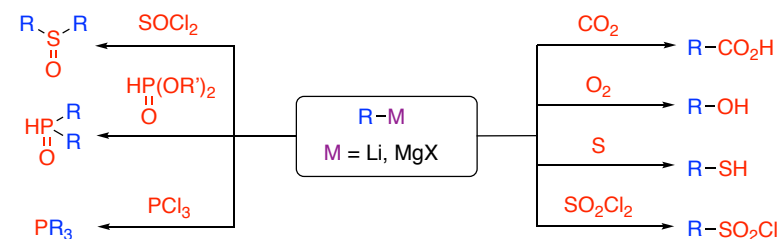H. C. Brown, *Acc. Chem. Res.*, **2**, 65 (1969).

- Carbon monoxide, which is Lewis basic, is bound to Lewis acidic boron atom in R_3B to form boron–carbon monoxide complex **A**. The alkyl groups R in **A** migrate to the carbon atom in CO stepwise.
- Only one R moves from boron to carbon when the trialkylborane reacts with CO in the presence of an appropriate hydride reducing agent, *e.g.* $LiAlH(OMe)_3$. The reaction selectively provides α-hydroxyalkylborane **E** because the C–O double bond in **B** is rapidly reduced with the reducing agent. The intermediate **E** is converted to the primary alcohol through alkaline protonation. Meanwhile, the aldehyde is obtained from the treatment of **E** with H_2O_2 under an alkaline condition.
- Two R substituents migrate to the carbon atom in the presence of water to form boraepoxide **C**. The water molecule attacks on the boron in **C**, leading to the selective formation of intermediate **F** or its cyclic dimer. Aqueous alkaline solution transforms **F**

into the secondary alcohol, while the oxidative treatment gave the ketone.
- At high temperature (*e.g.* 150°C) in ethylene glycol, all Rs migrate on the CO moiety to give the *tert*-alkylborane **D**. The oxidation of **D** with H_2O_2 gave the tertiary alcohol product.

(b) Installing functional groups
(i) Organolithium and magnesium

(ii) Organoboron