Ate Complexes for Catalytic C-C Bond Forming Reaction

Organometallics

Lewis acid

B
|
Al
|
— Zn —
|
Cu —

etc

+

Lewis base

R-Li
R-MgX
R-Na
etc

→

Ate complex

$$\left[\begin{array}{c} R \\ R-B^{-}-R \\ R \end{array} \right] Li^+$$
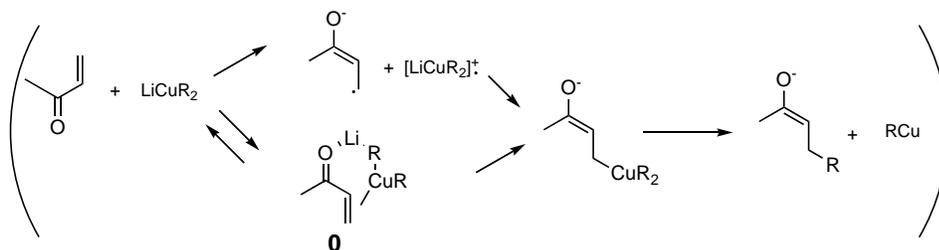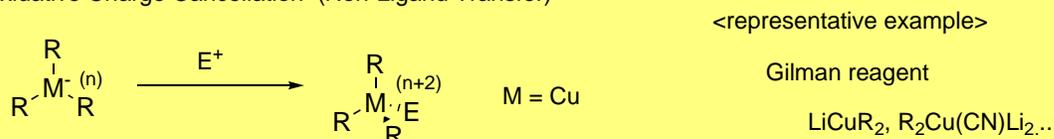
etc

• Central metal is anionic.

→ The reaction proceeds as anionic character is lost.
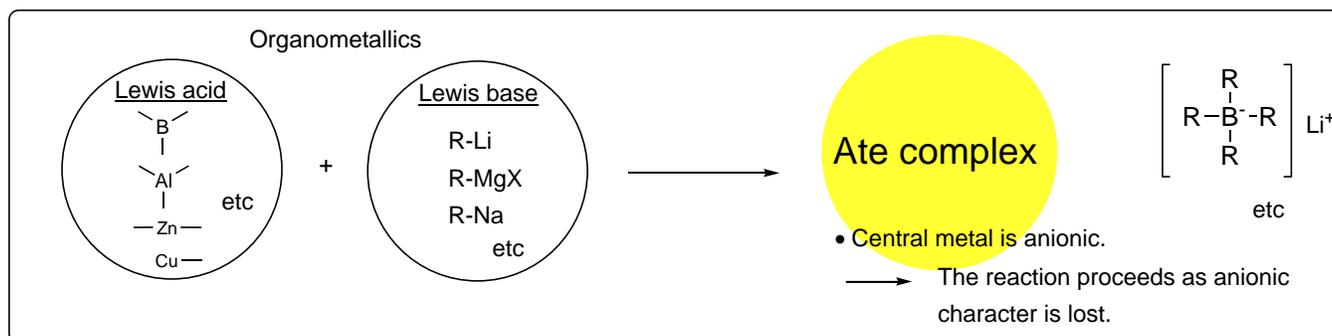
Generalization of Reaction Pathways for Ate Complexes

1) Non-Oxidative Charge Cancellation (Ligand Transfer)

$$\underset{R}{\overset{R}{\underset{R}{M^{-(n)}}}} \longrightarrow \underset{R}{\overset{R}{M^{(n)}}} \quad R^-$$

$M = B, Al, Zn$ etc

<representative example>

$LiAlH_4$, $NaBH_4$...
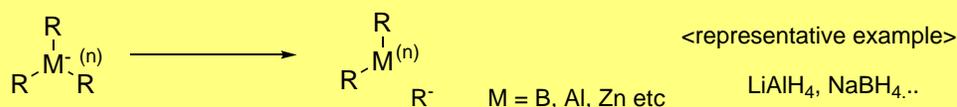
2) Oxidative Charge Cancellation (Non-Ligand Transfer)

$$\underset{R}{\overset{R}{\underset{R}{M^{-(n)}}}} \xrightarrow{E^+} \underset{R}{\overset{R}{\underset{R}{M^{(n+2)}}}} E$$

$M = Cu$

<representative example>

Gilman reagent

$LiCuR_2$, $R_2Cu(CN)Li_2$...

$+$ $LiCuR_2$ ...

0

$+ [LiCuR_2]^{\cdot+}$ ... CuR_2 ... $+$ RCu

- -
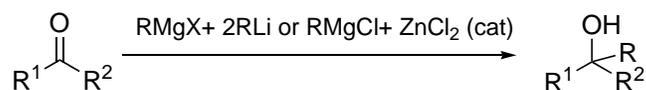
Today's contents

1. Grignard Reaction for the Synthesis of 3°-Alcohol with Ate Complex

   1-0 Introduction about Grignard Reaction of Ketone

   1-1 Grignard Reaction of Ketone with Mg Ate Complex/ Zn Ate Complex (Prof. Ishihara and Dr. Hatano's work)

$$\underset{R^1}{\overset{O}{\underset{R^2}{\|}}} \xrightarrow{RMgX+ 2RLi \text{ or } RMgCl+ ZnCl_2 \text{ (cat)}} \underset{R^1}{\overset{OH}{\underset{R^2}{\overset{|}{\underset{R}{}}}}}$$

   1-2 History About Zn Ate Complex

   1-3 Perspective of Catalytic Synthesis of 3°-alcohol with Grignard Reaction

2. Cross Coupling Reaction of *Alkyl Halide* Catalyzed by Ate Complex

   2-0 Introduction about the Relation between Cross Coupling and Ate Complex

   2-1 Cross Coupling with Ni or Pd Ate Complex (Prof. Kambe and Dr. Terao's work)

$$\text{Alkyl-X} \quad + \quad \text{R-m} \xrightarrow[\diagdown\diagup]{NiCl_2 \text{ (cat)}} \text{Alkyl-R}$$
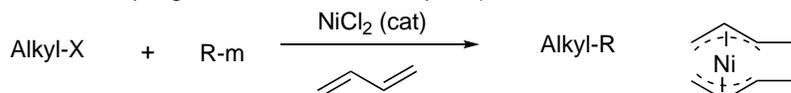
   2-2 Cross Coupling with Cu Ate Complex (Prof. Kambe and Dr. Terao's work)

   Appindix Other Representative Cross Coupling Catalyzed by Ate Complex

1 Grignard Reaction for the Synthesis of 3°-Alcohol with Ate Complex

1-0 Introduction about Grignard Reaction of Ketone
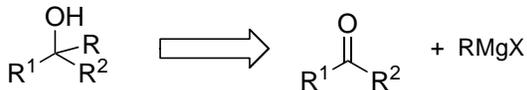
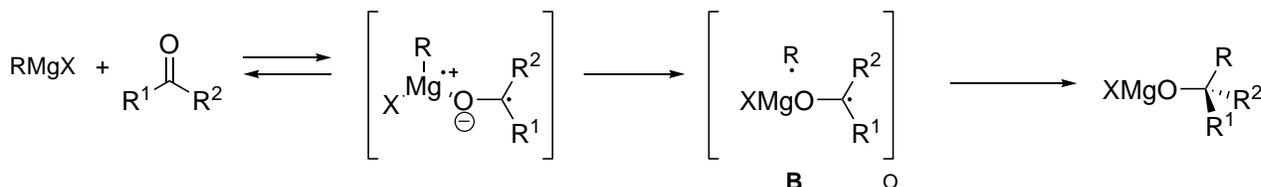~Reaction Mechanism~

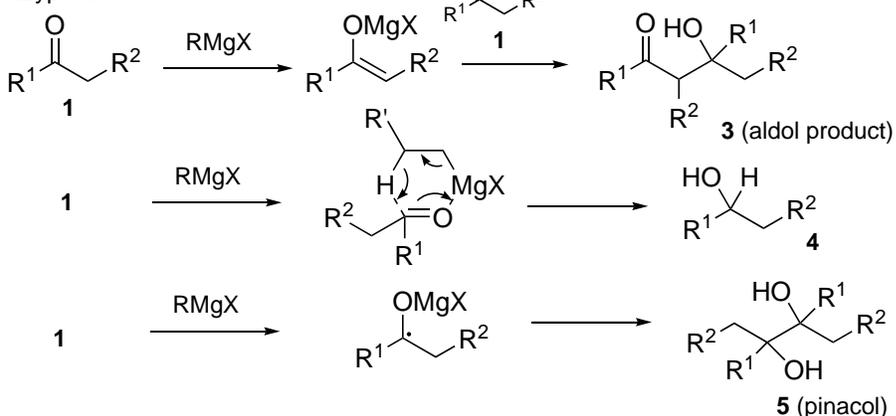1) Concerted reaction mechanism
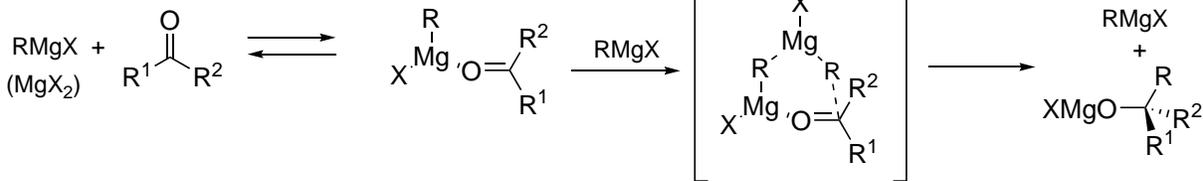
2) Electron-transfer mechanism

<Problem>
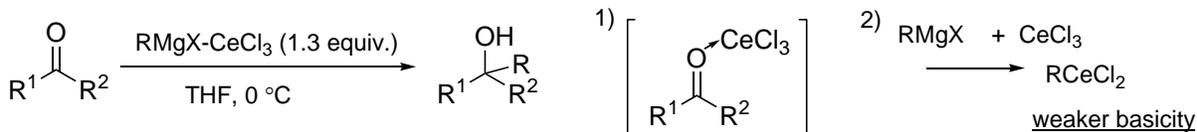- Several byproducts are obtained.

Grignard reagent
Basicity > Nucleophilicity

<Byproduct>

3 (aldol product)

4

5 (pinacol)

<Classical solution>

Iwamoto *et.al. Tetrahedron Lett.* **1985**, *26*, 4763, *J. Am. Chem. Soc.* **1989**, *111*, 4392-4398

Knochel *et.al. Angew. Chem. Int. Ed.* **2006**, *45*, 497-500

$$LnCl_3 \cdot 6H_2O \xrightarrow[\text{MS 4A}]{2LiCl} LnCl_3 \cdot 2LiCl$$

(Ln = La, Ce, Nd)

- Although the preparation is rather difficult, THF-soluble lanthanide halides can be prepared. (0.3-0.5 M solution in THF)

→ Superior promoters. (Table 1)

Table 1-1

Entry	Grignard reagent 2		Ketone of type 3		Product of type 4		Yield [%] without additives[a]	with CeCl₃[b]	with LnCl₃·2LiCl
1	iPrMgCl	2a		3a		4a	3-5	72 (80)[c]	92[d] 94[e] 92[f]
2	iPrMgCl	2a		3d		4d	3	–	98[d] 95[e] 97[f]
3		2l		3j		4o	17	53	92[g]

[a] Yield of isolated product obtained by the direct reaction of the ketone with the Grignard reagent. [b] Yield of isolated product obtained in the presence of CeCl₃ (1.5 equiv) according to the method of Imamoto. [c] Yield of isolated product obtained in the presence of CeCl₃ (1.0 equiv) according to the method of Dimitrov. [d] Reaction performed with LaCl₃·2LiCl (1.0 equiv). [e] Reaction performed with CeCl₃·2LiCl (1.0 equiv). [f] Reaction performed with NdCl₃·2LiCl (1.0 equiv). [g] The Grignard reagent was first transmetalated by addition of LnCl₃·2LiCl (1.0 equiv) and stirred for 4 h at room temperature before the ketone was added at 0°C. [h] The reaction was performed in the presence of 10 mol% LaCl₃·2LiCl.

(1.0 equiv.)

- Hindered and enolizable ketones are successfully transformed into 3°-alcohol using Knochel modification method.
- Next, catalytic activation would be desired.

Other approach for
nucleophilicity > basicity

→ Ate complex!
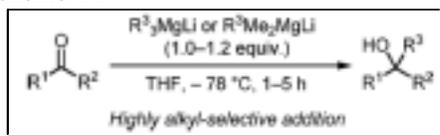
Org. Lett. **2005**, 573-576

Scheme 1-1

Highly alkyl-selective addition

Table 1-2

		HO nBu	O HO	HO H
usual alkylating reagent	^nBuLi	62%	7%	0%
	^nBuMgCl	50%	9%	8%
	nBu_2Mg	48%	27%	20%
Mg ate complex	$^nBu_3MgLi \cdot LiCl$ (**7**)	99%	0%	0%
	$^nBu_3MgLi$ (**8**)	82%	0%	0%
	$^nBu_3MgLi + Bpy$ (**8** Bpy)	96%	0%	0%

<Preparation of Mg ate complex>

1) $R_2Mg + RLi \longrightarrow R_3MgLi$　**8**

2) $RMgX + 2RLi \longrightarrow R_3MgLi + LiX \longrightarrow R_3Mg^- {}^+Li_2X$　**7**

3) $R_2Mg + RLi \longrightarrow R_3MgLi \xrightarrow{Bpy} R_3Mg^- {}^+Li\cdot Bpy$　**8** Bpy
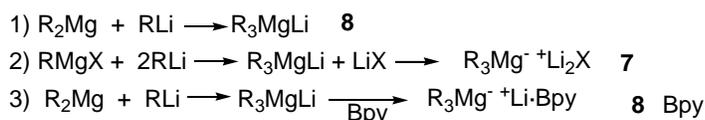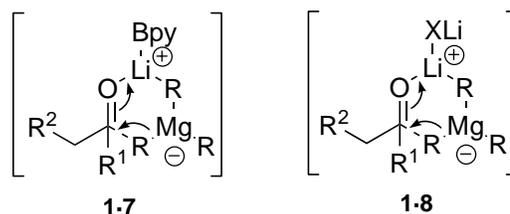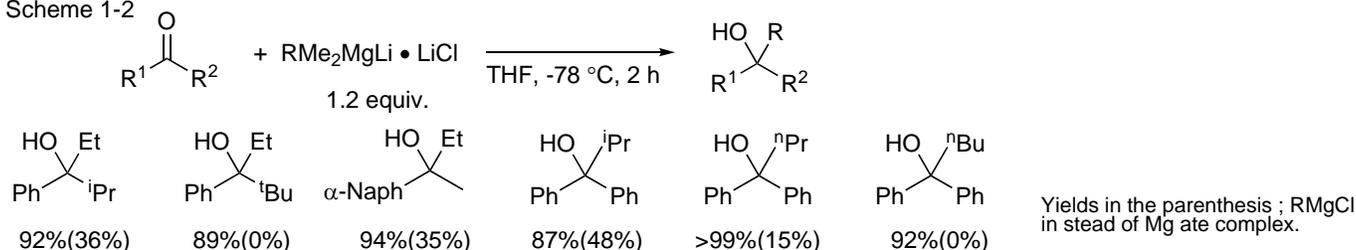
Reactivity; **7** > **8** > **8** Bpy

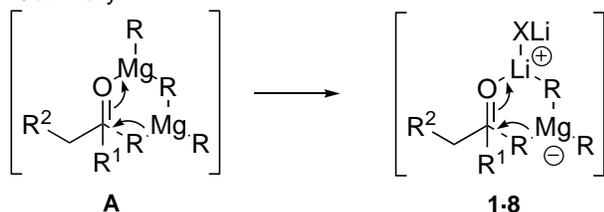Bpy and LiX salt would increase the acidity of Li⁺. (Figure 1-1)

1·7　　　**1·8**

Figure 1-1

♦ Hetero Mg ate complexes ($R^1R^2_2MgLi$, $R^1 \neq R^2$) are also applicable.

　R_2 ; Dummy ligand. Me is best.

Scheme 1-2

HO Et	HO Et	HO Et	HO iPr	HO nPr	HO nBu	
Ph iPr	Ph tBu	α-Naph	Ph Ph	Ph Ph	Ph Ph	Yields in the parenthesis ; RMgCl in stead of Mg ate complex.
92%(36%)	89%(0%)	94%(35%)	87%(48%)	>99%(15%)	92%(0%)	

♦ Summary

A　　　**1·8**

• Mg⁻; anionic → R's nucleophilicity increses.

• Li⁺; More Lewis acidic. → The carbonyl moiety of ketone become more electrophlic.

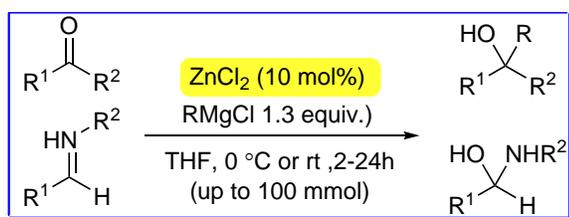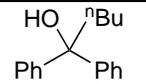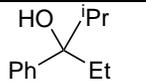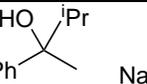*J. Am. Chem. Soc.* **2006**, *126*, 9998-9999

Scheme 1-2 Highly efficient alkylation to ketones/andimines with Grignard reagents catalyzed by $ZnCl_2$

Table 1-3

HO nBu	HO iPr	HO iPr	HO iPr
Ph Ph	Ph Et	Ph	Naph
74%(11%)	95%(56%)	85%(31%)	76%(35%)

HO iPr	HO iPr	HO iPr	Et OH
80%(20%)	91%(40%)	60%(43%)	81%(29%)

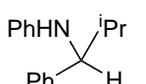| PhHN iPr	PhHN sBu	PhHN	PhHN iPr
Ph H	Ph H	Ph H	Ph H
82%(28%)	88%(44%)	86%(51%)	77%(33%)

Yields in the parenthesis ; RMgCl without ZnCl₂ were used.

<mechanistic insight>
• Zn(OTf)₂ as strong Lewis acid was not effective.

This unique catalytic system should be based on R₃ZnMgCl.

Figure 1-2 Proposed catalytic cycle and transition-state assembly

♦ They said asymmetric alkylation catalyzed by Zn ate complexes might be possible.

1-2 History About Zn Ate Complex

M. Isobe, T. Goto *et. al. Chem. Lett.* **1977**, 679-682

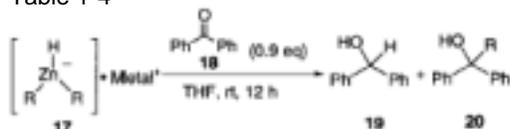• First example trialkylzincate was used in organic chemistry.
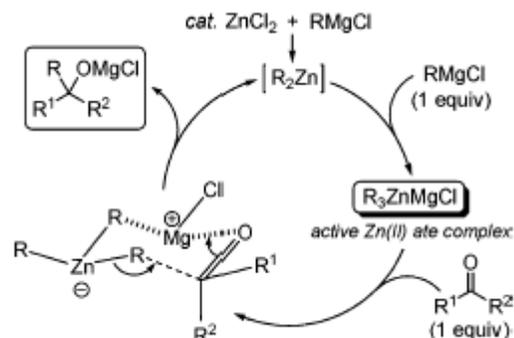
K. Ohshima *et. al. Chem. Ber.* **1986**, *119,* 1581-1593

'Heteroleptic ate complex'
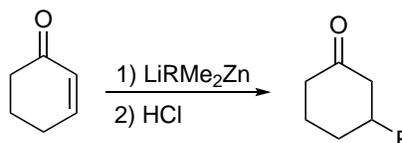
• Me is especially effective as dummy ligand.

M. Uchiyama *et. al. J. Am. Chem. Soc.* **1997**, *119*, 11425
J. Am. Chem. Soc. **1997**, *119*, 12372
, 2002, 122(1), 29-46

<Heteroleptic ate complex for reduction of carbonyl moiety>

Table 1-4

a) Isolated yield.

• Usually, LiH or NaH was used as base.
Basicity > Nucleophilicity
⇩
HMe₂Zn⁻⁺Metal; Basicity < Nucleophilicity

<Proof that Zn ate complex was reactive spiecies.>
two possibilities ; HMe₂Zn⁻ ⁺Metal (Path A)
Lewis Acid + Metal hydride(Path B)
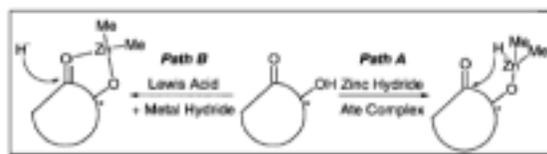
Scheme 1-3
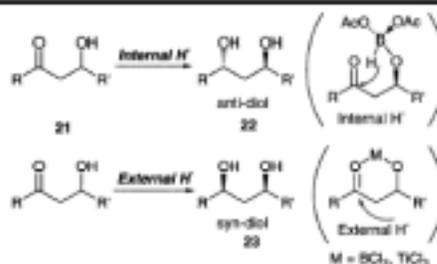
• If Zn hydride ate complex is active spicies, anti-diol **22** should be obtained selectively.
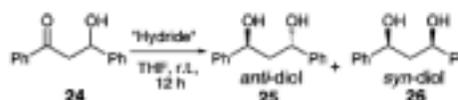
Table 1-5

•Actually, anti-diol **22** was generated mainly. (entry 1,2)

<Possible mechanism>

Scheme 1-4

• Considering this mechanism, Me$_2$Zn should be catalytic.

<Trials with catalytic amount of Me$_2$Zn>

a) The reaction was carried out using metal hydride (20 equiv), Me$_2$Zn (1 equiv; 1mmol), and benzophenone (20 equiv) in THF at room temperature. b) Isolated yield based on the amount of Me$_2$Zn.
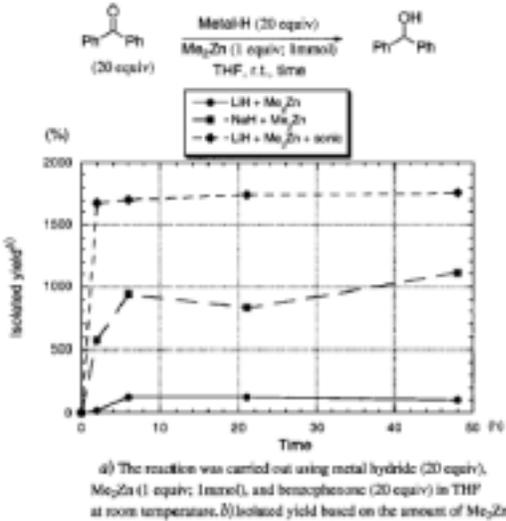
• Actually, Me$_2$Zn works with catalytic amount.(5-10 mol%)

<Substrate generallity>
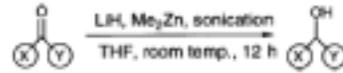
LiH; 3 equiv.
Me$_2$Zn; 30 mol%

• Enolizable aldehydes were successfully reduced. (entry 2,3)

  Carboxylic acids were reduced to aldehyde.(enrty 9,10)

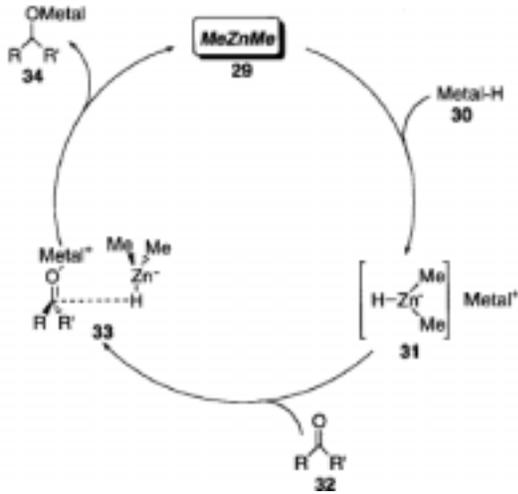| Entry	Substrate	Product	Yield(%)[a]
1			92
2			93[b]
3			94[c]
4			84
5			95[d]
6			46[d]
7			88(96 : 4)[e]
8			94(97 : 3)[f]
9			82[c]
10			68[g]

a) Isolated yield. b) The reaction was carried out at 0°C for 1 h. c) The reaction was carried out using LiH (3.0 equiv) and Me$_2$Zn (30 mol%) at 0°C for 6 h. d) The reaction was carried out using LiH (3.0 equiv) and Me$_2$Zn (30 mol%) at room temperature for 48 h. N-Ethyl-4-chloroaniline was sole product and 4-chloroacetanilide was recovered in 32% yield. e) Value in parentheses are ratio of 1,2-reduction and 1,4-reduction. f) Value in parentheses are ratio of 1-phenethyl alcohol and 2-phenethyl alcohol. g) The reaction was carried out using LiH (3.0 equiv) and Me$_2$Zn (100 mol%) at room temperature for 24 h.

M. Uchiyama *et. al. J. Am. Chem. Soc.* **2004**, *126*, 10897-10903

    1) DFT calculations about the structure of LiZnMe$_3$
    2) Ligand transfer selectivity of heteroleptic zincate Me$_2$Zn(X)Li

1) DFT calculations about the structure of LiZnMe$_3$
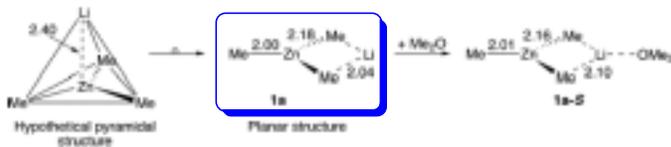
• The gas phase calculations indicated MeLi and Me$_2$Zn react to form a trigonal planer complex with 24.2 kcal/mol exothermically.

Figure 1-3 The comparison between Me$_2$Zn and Me$_3$ZnLi
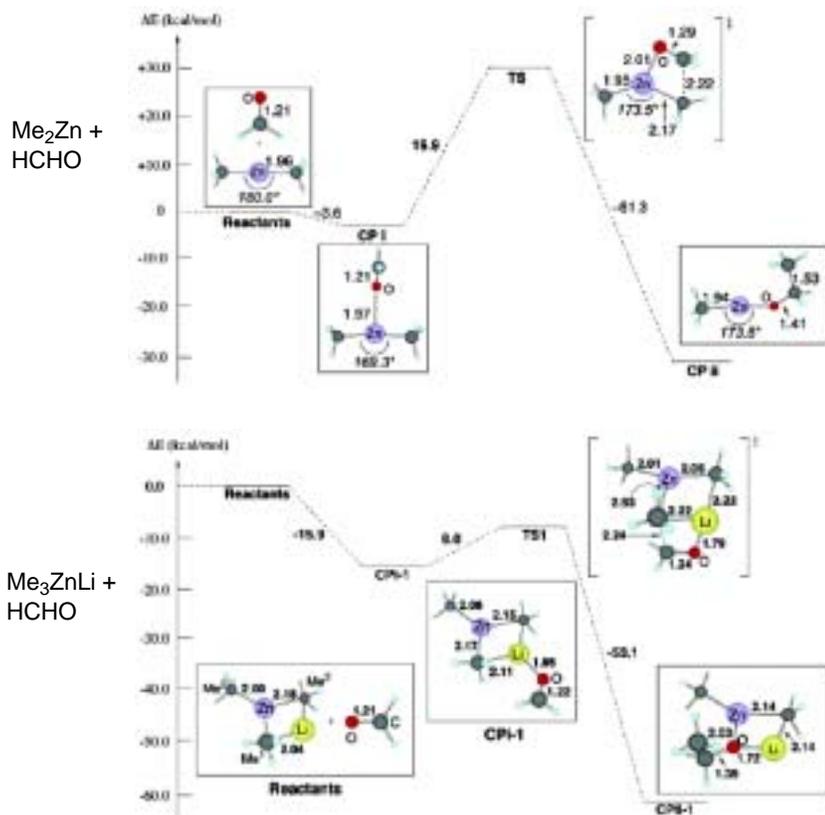
Me$_2$Zn +
HCHO

(A) Energy diagram of the reaction between Me$_2$Zn and HCHO.

• Association complex **CPi** forms without much energy gain (3.6 kcal/mol) and with little change of the geometry.

• C-C formation occurs with activation energy of 19.9 kcal/mol. (← C-Zn > O-Zn)

• The overall gain to form **CPii** is rather small (29.1 kcal/mol).

• This result is consistent with the experimental fact that R$_2$Zn are inert in the carbonyl addition in a nonpolar medium.

Me$_3$ZnLi +
HCHO

(B) Energy diagram of the reaction between Me$_3$ZnLi and HCHO.

• First, Me$_3$ZnLi and HCHO form a Lewis acid/Lewis base complex **CPi-1**.(15.9 kcal/mol)

  (Li coordination for carbonyl moiety)

• Methyl groups bound to the lithium can migrate to carbonyl carbon with a small activation energy.(8.0 kcal/mol from **CPi-1**)

• The stabilization energy of the adduct, Me$_2$Zn(OCH$_2$CH$_3$)Li,**CPii-1** is very large.(-53.1 kcal/mol)
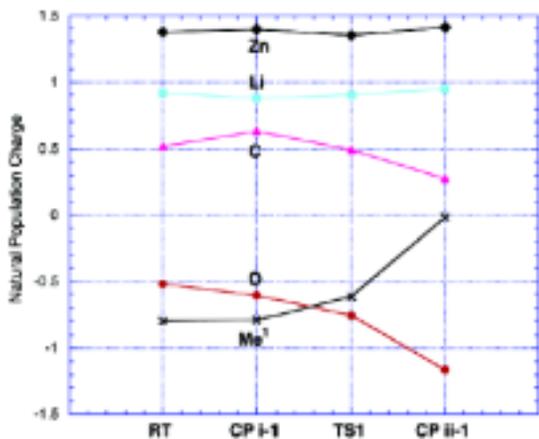
Figure 1-4 Charge change in 1,2-addition of Me$_3$ZnLi to HCHO

• The transfer of the Me group from Me$_3$ZnLi to the carbonyl carbon takes place as a single event.

	negative charge
O of C=O	monotonically increase
Me group	monotonically decrease toward zero.

• The charge of Zn remain especially constant.

  → The absence of any oxidation/reduction process in this reaction.
  ↔ different from the addition of Me$_2$CuLi to an α,β- unstaturated carbonyl compound.(Cu(I) → Cu(III))

2) Ligand transfer selectivity of heteroleptic zincate Me$_2$Zn(X)Li

<Two possible structures of heteroleptic zincate>

X= H

Asymmetric Structure (2a)
E$_{rel}$ = 0.0 kcal/mol
Calcd. 1085 cm^{-1} (δ$_{Zn-H}$)
Experimental value 1055 cm^{-1}

Symmetric Structure (2b)
E$_{rel}$ = 3.4 kcal/mol
Calcd. 1787 cm^{-1} (δ$_{Zn-H}$)

<Ligand-transfer selectivity for Me$_2$Zn(X)Li>
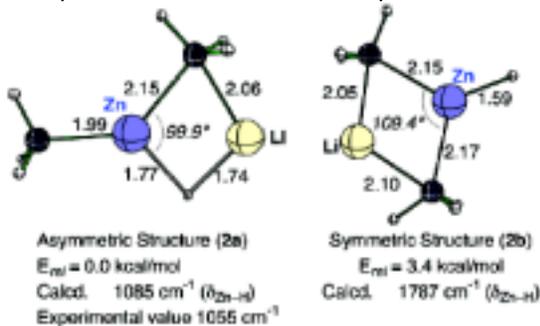
X; H= NR$_2$ > SiR$_3$ > alkyl

	activation energy of **CPi** to **TS1** (kcal/mol)
H	3.1
NR$_2$	2.7
SiR$_3$	6.1
Me	8.0

Figure 1-5 Asymmetric and symmetric structures of Me$_2$ZnHLi

• Zn-H frequency between **2a** and **2b** must be different.
• Experimental data suggest **2a** would be real structure of Me$_2$ZnHLi .
→ Reaction pathway should be similar to that of Me$_3$ZnLi.

1-3 Perspective of Catalytic Synthesis of 3°-alcohol with Grignard Reaction

♦ Asymmetric version.

• Ligand transfer activity of alkyl group is very low.

• Ligand should be designed not to dessociate the chiral ligand.

→ Multidentate ligand is one of the possibility.

• It might be possible to make chiral modification of counter cation(Mg^{2+}, Li^+).
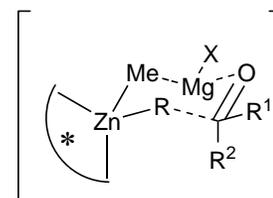
cf. $R_3Mg^-{}^+Li \cdot$Bpy system

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2. Cross Coupling Reaction of *Alkyl* Halide Catalyzed by Ate Complex

2-0 Introduction about the Relation between Cross Coupling and Ate Complex

<Cross coupling reaction>   About cross-coupling reaction → see. Dr. Maki's literature seminer 2006/03/18

R-X + R'-m ⟶ R-R'

<Two reaction pathway>

Path **A**
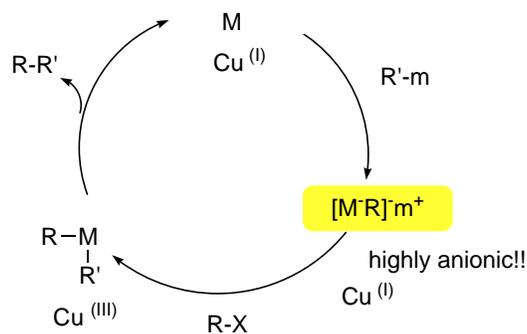
Figure 2-1 Cross-coupling via ate complex
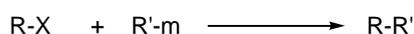
J. K. Kochi, *Synthesis*, **1971**, 303

Alkyl-X + R'MgX $\xrightarrow{\text{Li}_2\text{CuCl}_4}$ Alkyl -R'
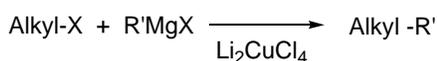
R'MgX; high reactivity
        → low functional group tolerancy.

• Ni or Pd ate complex (Prof. Kambe and Dr. Terao's work)
        → 2-1

Alkyl-X + R-m $\xrightarrow{\text{NiCl}_2\text{ (cat)}}$ Alkyl-R
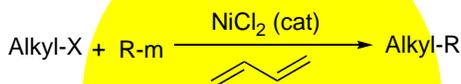
• Cu ate complex (Prof. Kambe and Dr. Terao's work)
        → 2-2

• One-electron donating Co, Fe system. → Appendix

Path **B**
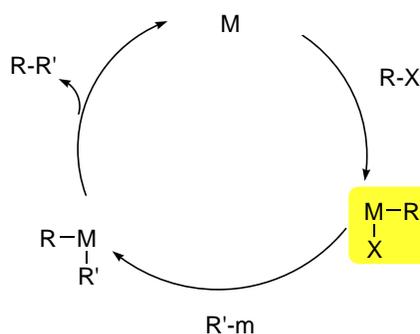
Figure 2-2 Cross-coupling via oxidative addition

J. K. Kochi *et. al. J. Am. Chem. Soc.* **1971**, *93*, 1487

R-X + R'MgX $\xrightarrow{\text{FeCl}_2 \text{ or FeCl}_3}$ R-R'

R = Alkenyl

<Representative cross coupling>
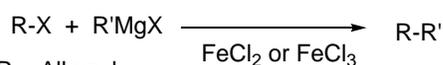
· Kumada-Tamao   MgX
· Negishi   ZnX
· Stille   Sn
· Suzuki-Miyaura   B
· Hiyama   Si
· Sonogashira   R≡C-Cu

Application for R = alkyl

<Problem>

• Oxidative addition is slow.
• Resulted alkyl complex is highly reactive.
  → β- hydride elimination > transmetallation

<Solution>

• Pd + bulky phosphine ligand(PCy$_3$, P^{t}Bu$_2$Me),NHC ligand.

2-1 Cross Coupling with Ni or Pd Ate Complex
Adv. Synth. Catal. **2004**, *346*, 905-908

Scheme 2-1 Three component reaction of Alkyl halides, butadiene, and Ar-M

X = Cl, Br, I   M = Mg or Zn
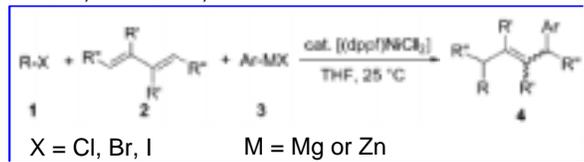
Table 2-1

Run	R-X	R'	R"	As-MX	Isolated yield [%]	[E/Z][a]
1	n-Bu-Br	Me	H	Ph-MgBr	4a; 69	59/41
2	i-Pr-Br	Me	H	Ph-MgBr	4b; 91	67/33
3	t-Bu-Br	Me	H	Ph-MgBr	4c; 74	56/44
4	c-Hex-Br	Ph	H	Ph-MgBr	4d; 73	79/21
5	c-Hex-Br	H	Ph	Ph-MgBr	4e; 60	100/0
6	s-Bu-Cl	Me	H	Ph-MgBr	4f; 63	57/43
7	t-Bu-Cl	Me	H	Ph-MgBr	4c; 81	52/48
8	c-Hex-I	Me	H	Ph-ZnCl	4g; 72	72/28
9	t-Bu-Br	Me	H	p-EtO₂CC₆H₄-ZnI	4h; 69	52/48

Conditions: **1** (1.2 mmol), **2** (1 mmol), **3** (1.5 mmol), [(dppf)NiCl₂] (8 mol %), THF (1.5 mL), 25 °C, 24 h.
[a] Determined by GC.

- Unsubstituted 1,3-butadiene failed to afford the corresponding product.
- 2°,3°-alkyl-Cl was reactive although 1°-alkyl-Cl didn't give the desired product.
- C=CMgBr, PhB(OH)₂ and PhC=CSn(ⁿBu)₃ were ineffective.

<Some control experiments>

Scheme 2-2 The relative reactivities of alkyl halides
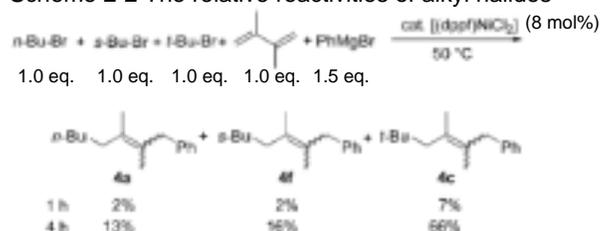

n-Bu-Br + s-Bu-Br + t-Bu-Br + [butadiene] + PhMgBr →[cat. [(dppf)NiCl₂] (8 mol%)][50 °C]
1.0 eq.   1.0 eq.   1.0 eq.   1.0 eq.   1.5 eq.

	4a	4f	4c
1 h	2%	2%	7%
4 h	13%	16%	66%

- the reactivity of R; 1°<2°<3°
  → Alkyl groups are transferred as radical or cationic species.

Scheme 2-3 Reverse combination of the reagent from Table 1 Run 2

Ph-Br + [diene] + i-Pr-MgBr →[[(dppf)NiCl₂] (8 mol %)][THF, 25 °C, 24 h]

5   Ph-i-Pr + Ph-H + Ph-n-Pr + **4b**
        27%   3%   2%   4b, 2%
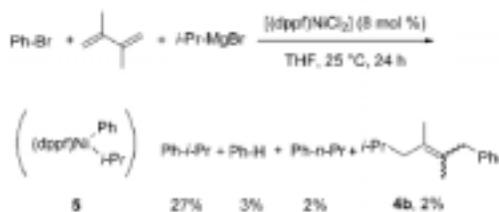
- Cumene was the major product via an intermediate **5**.
→ The present three component reaction may not proceed through **5**.

Scheme 2-4 control experiment 3

run 1   1 mmol   1 mmol   2 mmol   1 mmol
run 2   (3 mmol)

	4f	recovered	Ph-Ph
run 1	4f, 0%	>99% recovered	0.97 mmol
run 2	(41%)	(54% recovered)	(1.00 mmol)
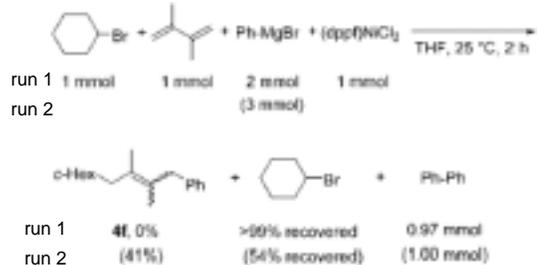
- In run 1, the major product was Ph-Ph (reductive coupling).
Alkyl-Br was recovered completely.
- In run 2, three component coupling product was afforded in 41% yield.
→ Excess PhMgBr promoted the C-Br bond cleavage.

Scheme 2-5 A plausible reaction pathway
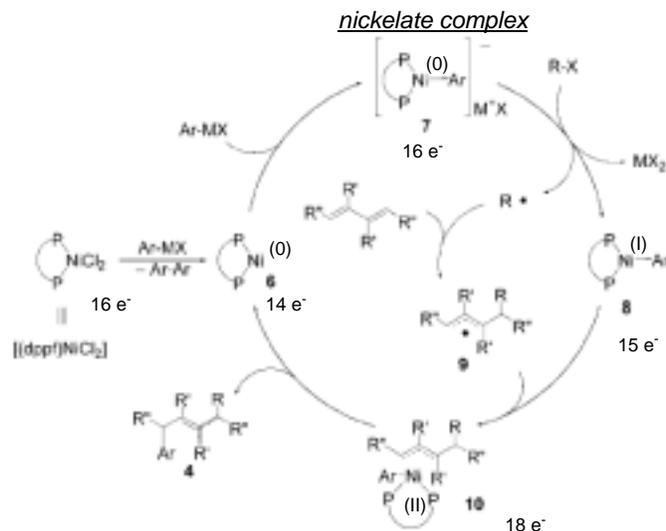
nickelate complex

- The nickelate complex **7** would act as an active electron transfer reagent.
→ The generation of an alkyl radical and arylnickel(I) complex **8**.

Scheme 2-6 Ni-catalyzed cross-coupling with 1,3-butadiene

Table 2-3 Substrate generality

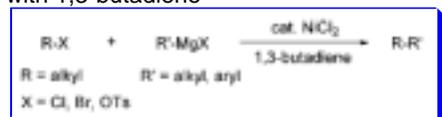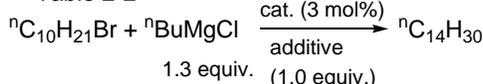| entry	R-X	R'-MgX[c] (equiv. to R-X)	NiCl$_2$ (mol %)	1,3-butadiene (mol %)[a]	temp. (°C)	time (h)	product	yield (%)[b]
1	^{n}C$_{10}$H$_{21}$-Br	^{n}Bu-MgCl (1.3)	1	10 (3.07 M)	0	0.5	^{n}C$_{14}$H$_{30}$	100
2	Br-〈Ar〉-Br	^{n}Bu-MgCl (1.3)	1	10 (3.07 M)	0	0.5	Br-〈Ar〉-^{n}Bu	100
3	Ph-OTs	Et-MgBr (1.3)	3	30 (0.23 M)	0	3	Ph-Et	87
4	^{n}Bu-OTs	^{n}Bu-MgCl (1.3)	3	100 (3.69 M)	0	3	^{n}C$_8$H$_{18}$	100
5	Et-OTs	Ph-MgBr (1.3)	3	100 (3.77 M)	0	6	Et-Ph	56
6	^{n}Oct-Br	Ph-MgBr (1.3)	3	30 (0.23 M)	25	3	^{n}Oct-Ph	90
7	^{n}Oct-Br	⟩-MgCl (3.0)	3	30 (0.07 M)	0	0.5	^{n}Oct-⟨	72
8	^{n}Oct-Cl	^{n}Bu-MgCl (2.6)	3	50 (0.23 M)	25	20	^{n}C$_{12}$H$_{26}$	96

[a] Based on R-X concentration in parentheses. [b] Determined by GC.

Table 2-2

^{n}C$_{10}$H$_{21}$Br + ^{n}BuMgCl $\xrightarrow[\text{additive}]{\text{cat. (3 mol%)}}$ ^{n}C$_{14}$H$_{30}$

1.3 equiv. (1.0 equiv.)

entry	catalyst	additive	n-C$_{14}$H$_{30}$	decane	decenes[b]
1	NiCl$_2$		92	<1	2
2	NiCl$_2$	none	2	49	27
3	Ni(acac)$_2$		90	<1	2
4	Ni(COD)$_2$		92	<1	3
5	PdCl$_2$		38	1	3
6	NiCl$_2$		99	<1	0
7	NiCl$_2$		5	14	9
8	NiCl$_2$	COD[c]	10	15	30
9	NiCl$_2$	Ph—≡≡—Et	3	7	23
10	NiCl$_2$	3-CF$_3$-styrene	15	25	14

[a] Conditions: n-C$_{10}$H$_{21}$Br (2 mmol), catalyst (3 mol %), n-BuMgCl (1.3 equiv, 0.9 M), additive (1 equiv, 0.7 M); 25 °C; 3 h. [b] A mixture of 1-decene and 2-decene. [c] 1,5-Cyclooctadiene.

• entry 1; Optimized results
• entry 2; Br on Ar ring remained intact.
• entry 8; X=Cl is OK.

<control experiment>

1) NiBr$_2$ + ^{n}Oct-MgCl $\xrightarrow{\text{25 °C, 15 min}}$ 1-octene + octane + hexadecane

2 equiv. 45%   43%   0%

$\left(\text{NiBr}_2 + ^n\text{Oct-MgCl} \longrightarrow ^n\text{Oct-Ni-Br}\right)$

• The present coupling reaction does not involve oxidative addition of alkyl halides to Ni(0).

n-DecylBr + Ni(COD)2 $\xrightarrow[\text{THF, 0 °C}]{\text{1,3-butadiene}}$ n-DecylBr
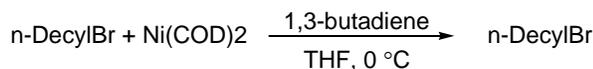
• Oxidative addition didn't occur.

• When Ni complex bearing phosphine ligands, such as NiCl$_2$(PPh$_3$)$_2$, NiCl$_2$(dppp), were used, the yield was 45% and 22%, respectively.
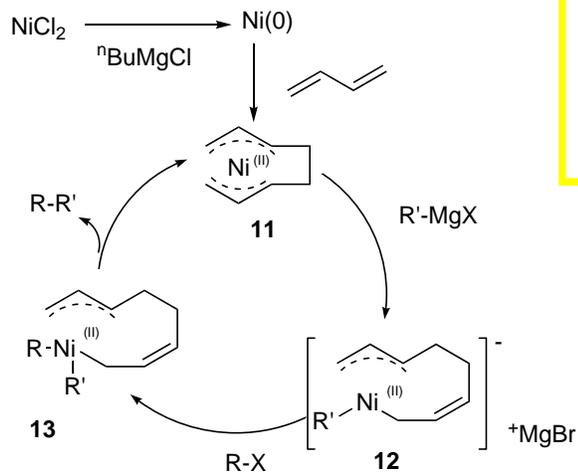• Unsubstituted 1,3-butadiene shows the highest activity.(entry 6-10)

2)

A radical pathway would be ruled out.

NiCl$_2$ $\xrightarrow{^n\text{BuMgCl}}$ Ni(0)

R-R'

R'-MgX

11

R–Ni$^{(II)}$ / R'

13

$[$R'–Ni$^{(II)}]^-$ $^+$MgBr

12

R-X

Figure 2-3 A plausible reaction pathway
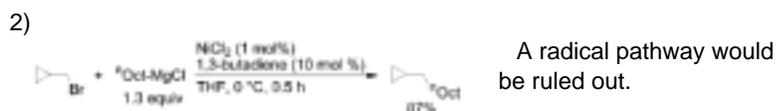
Ni(0) reacts with 2 equiv. of 1,3-butadiene to afford bis-π-allyl Ni complex. (oxidative cycloaddition)

→ Less reactive to R-X but readily reacts with R'-MgX to form **12**.

The complexation for **12** might enhance nucleophilicity of Ni toward R-X.

The central metal (Ni) in this catalyst system is always ...

d^8, 16e$^-$, plane structure.

♦ The difference between the condition of 3-component reaction and this cross coupling

+ the presence/absence of phosphine ligand.
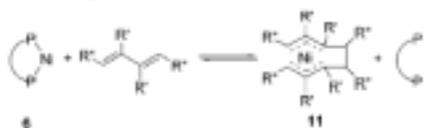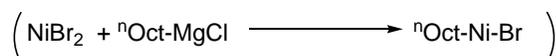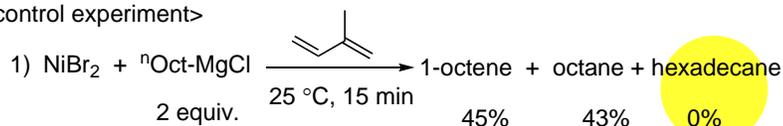+ whether butadiene is substituted or not.

Scheme 2-6

Bidentate dppf ligand is bound strongly on Ni.
→ the supression of the formation of bis-allylnickel complex **11**.
  When substituents were introduced on butadiene skeleton, formation of **11** became thermodynamically less favorable.

Angew. Chem. Int. Ed. **2004**, *43*, 6180-6182

R'MgX; high reactivity
$\rightarrow$ low functional group tolerancy.

$\downarrow$

R'$_2$Zn

$$^{n}C_{10}H_{21}\text{-Br} + Et_2Zn \xrightarrow[\substack{\text{THF/NMP= 2/1,} \\ 25\ ^\circ\text{C, 48 h}}]{\text{cat. (3 mol\%)}} \text{dodecane}$$
2 equiv.

Table 2-4

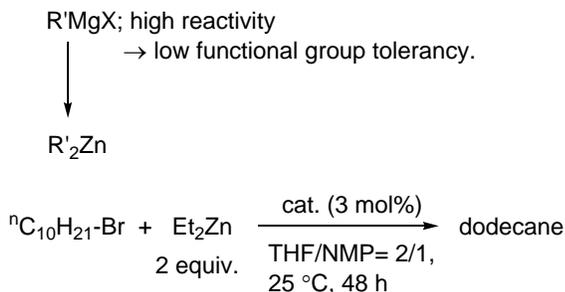| Entry	Catalyst	Additive (equiv)	t [h]	Dodecane	Decane	Decenes[c]
1	NiCl$_2$	C$_4$H$_6$ (1)	48	<1	23	<1
2	NiCl$_2$	C$_4$H$_6$ (1), MgBr$_2$ (3)	48	45	20	11
3	NiCl$_2$	none	48	0	5	<1
4	NiCl$_2$	MgBr$_2$ (3)	48	2	49	46
5	NiCl$_2$	C$_4$H$_6$ (1), Bu$_4$NBr (3)	48	<1	45	3
6	NiCl$_2$	C$_4$H$_6$ (1), Bu$_4$NI (3)	48	3	69	23
7	NiCl$_2$	C$_4$H$_6$ (1), LiBr (3)	48	16	7	0
8	NiCl$_2$	C$_4$H$_6$ (2), MgBr$_2$ (3)	48	68	14	9
9	NiCl$_2$	C$_4$H$_6$ (4), MgBr$_2$ (3)	48	73	2	2
10	[Ni(acac)$_2$]	C$_4$H$_6$ (4), MgBr$_2$ (3)	48	84	3	3
11	[NiCl$_2$(PPh$_3$)$_2$]	C$_4$H$_6$ (4), MgBr$_2$ (3)	48	40	2	<1
12	[NiCl$_2$(dppp)]	C$_4$H$_6$ (4), MgBr$_2$ (3)	48	31	3	0
13	PdCl$_2$	C$_4$H$_6$ (4), MgBr$_2$ (3)	48	5	55	3
14	[Ni(acac)$_2$]	isoprene (4), MgBr$_2$ (3)	48	37	5	3
15	[Ni(acac)$_2$]	p-fluorostyrene (4), MgBr$_2$ (3)	48	7	<1	23
16	[Ni(acac)$_2$]	2a (2), MgBr$_2$ (3)	48	>99	0	0
17	NiCl$_2$	2a (2), MgBr$_2$ (3)	48	>99	0	0
18[d,e]	[Ni(acac)$_2$]	2a (0.09), MgBr$_2$ (3)	1	>99	0	0
19[d]	[Ni(acac)$_2$]	2b (0.09), MgBr$_2$ (3)	1	>99	0	0

[a] Conditions unless otherwise stated: n-Decyl bromide (1 mmol), catalyst (3 mol%), additive [equivalents based on the substrate], diethylzinc (2 equiv, 1 M in hexane), mixed solution of THF [8 mL] and NMP [4 mL], 25 °C, 48 h. [b] Determined by GC analysis. [c] A mixture of 1-decene and 2-decenes. [d] n-Decyl bromide (1 mmol), diethylzinc (1.3 equiv, 1 M in hexane), mixed solution of THF [8.4 mL] and NMP [4.2 mL], 25 °C, 1 h. [e] The yields were decreased to 41 and 11% when the amount of MgBr$_2$ was decreased to 1.3 and 0.65 equivalents, respectively.

(structure) COOMe / COOMe **2a**   (structure) N–Ph **2b**

The addition of MgBr$_2$ increased the dodecane although side reactions could not be suppressed.(entry 2)
When tetraene **2a** was used in stead of 1,3-butadiene, this cross-coupling proceeded completely.(entry 16-19)
entry 18; the optimized condition.
Et$_2$Zn 1.3 equiv.,9 mol% of **2a**.

Table 2-5 Functional group tolerancy

Entry	RX	R'$_2$Zn	Product	Yield [%][a]
1	NC~~~Br	nOct$_2$Zn	NC~~~nOct	96
2	nBu~~~Br (ketone)	nOct$_2$Zn	nBu~~~nOct (ketone)	87
3	Et$_2$N~~~(amide)	(Ph~~~)$_2$Zn	Et$_2$N~~~Ph	91
4	EtOOC~~~Br	nPr$_2$Zn	EtOOC~~~	87
5	(cyclohexyl Br)	iPr$_2$Zn		79[c]
6	nPrBr	Ph$_2$Zn	Ph	86[c]
7	~~~OTs	Et$_2$Zn	~~~	83[c]

[a] Conditions: RX (1 mmol), R'$_2$Zn (1.3 equiv), NiCl$_2$ (3 mol%), 2a (9 mol%), MgBr$_2$ (3 mmol), mixed solution of THF [8.4 mL] and NMP [4.2 mL], 25 °C, 1 h. [b] Yield of isolated product. [c] GC yield.

This catalyst system tolerates unsaturated heteroatom functional groups, such as nitriles, ketones, amides, esters.(enrty 1-4)

Table 2-6 Effects of additives

$$n\text{C}_9\text{H}_{19}\text{-F} + n\text{C}_2\text{H}_5\text{-MgBr} \xrightarrow[\text{THF (1.5 mL), RT, 6 h}]{3\ \text{mol \% [Ni(acac)}_2]} \text{Dodecane}$$
2 mmol   3 mmol

Entry	[Ni(acac)$_2$] [mol%]	Additive [mol%]	Yield [%]
1	3	1,3-butadiene (10)	11
2	3	1,3-butadiene (100)	58
3	3	1,3-butadiene (200)	65
4	3	1,3-butadiene (300)	67
5	0.6	2b (15)	94

Alkyl-F was reacted in this reaction system.
Tetraene **2b** as additives; the yield was improved dramatically.(entry 5)

In the case of 1,3- butadiene

Ni(0) center will react with more than 2 equiv. of 1,3-butadiene .

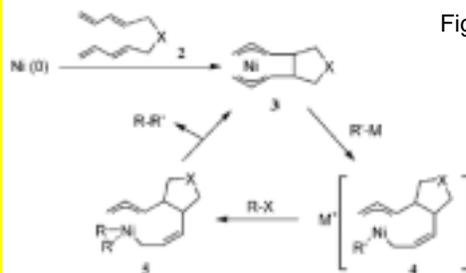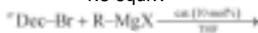$\rightarrow$ Complexes composed of C12-butadiene-oligomer units might be genarated.

Figure 2-4
Selective and efficient formation of **3** from Ni(0) and **2** would facilitate the generation of **4**.
$\rightarrow$ accelerate the nucleophlic addition that leads to **5**.

Chem. Commun. **2007**, 825-827

<the use of η^3-allylnickel and η^3-allylpalladium complexes as catalyst>

Scheme 2-7

1) To prove the intermediary of bis(η^3-allyl)nickel complexes.
2) Whether the ethylene tether between two ligand is essential or not.

Table 2-7

1.3 equiv.

$$^nDec–Br + R–MgX \xrightarrow[THF]{cat.(10 mol\%)}$$

^nDec-R + decane + decenes

Entry	R	Cat.	T/°C	Yield[a] (%)		
1	Bu	PdCl₂	0	3	54	26
2	Bu	(PPh₃)₂PdCl₂	0	2	1	1
3[b]	Bu	(C₃H₅PdCl)₂	0	10	26	23
4	Bu	(C₃H₅)₂Pd	0	58	13	12
5	Me	PdCl₂	0	9	26	26
6	Me	(PPh₃)₂PdCl₂	0	9	1	1
7[b]	Me	(C₃H₅PdCl)₂	0	83	6	6
8	Me	(C₃H₅)₂Pd	0	90	3	1
9	Bu	NiCl₂	−30	5	33	18
10	Bu	(PPh₃)₂NiCl₂	−30	1	3	1
11[b]	Bu	(C₃H₅NiCl)₂	−30	7	33	24
12	Bu	(C₃H₅)₂Ni	−30	94	4	2
13	Me	NiCl₂	−30	1	8	14
14	Me	(PPh₃)₂NiCl₂	−30	3	4	4
15[b]	Me	(C₃H₅NiCl)₂	−30	92	2	3
16	Me	(C₃H₅)₂Ni	−30	98	0	2

[a] Determined by GC. [b] 5 mol% of catalyst was used.

Pd or Ni complexes without η³-allyl ligands were ineffective.(entry 1,2,5,6,9,10,13,14)
Mono(η³-allyl)metal complexes afforded a successful result when MeMgBr was employed but not in the case of ⁿBuMgCl. (entry 3,7,11,15)

Table 2-8

$$AlkyI–X + R–MgX \xrightarrow[-30\,°C, 3\,h, THF]{2a (10 mol\%)} AlkyI–R$$

1.3 equiv

entry	Alkyl-X	R-MgX	Yield[a] (%)
1	ⁿOct-OTs	Et-MgBr	78
2	ⁿOct-OTs	Ph-MgBr	87
3	[Br]	ⁿBu-MgCl	41
4	[cyclopropyl-Br]	ⁿOct-MgCl	86 (81)
5	[Ar-Br, OTs]	Et-MgBr	76 (70)
6[b]	ⁿDec-Br	Me₃SiCH₂-MgCl	70 (65)

[a] Determined by GC. Isolated yield is in parenthesis. [b] Reaction was carried out at −20 °C for 20 h.
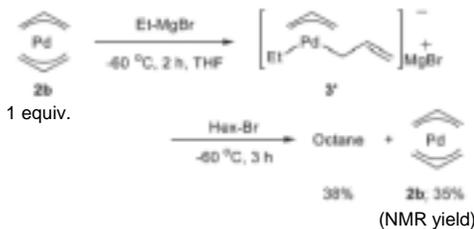
entry 3; 1-decene was obtained as a sole product.
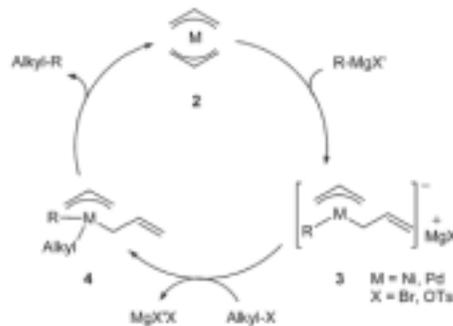
entry 4

→ These results ruled out a radical pathway.
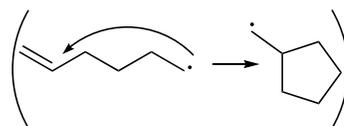
entry 5; Br on Ar ring was intact.

Scheme 2-8 control experiment

2b
1 equiv.

38%   2b; 35%
(NMR yield)

Nearly equal amounts of octane and bis(η³-allyl)Pd complexes.
Possible products, 1-pentane or 1-nonane by reductive elimination of an allyl group were not formed.
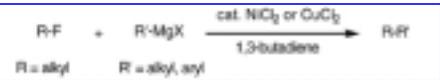→ Reductive elimination proceeds preferentially with alkyl group than allyl group.

Scheme 2-9 a plausible reaction pathway

3   M = Ni, Pd
X = Br, OTs

2-2 Cu-catalyzed cross-coupling reaction

J. Am. Chem. Soc. **2003**, *125*, 5646-5647

Scheme 2-10

$$R–F + R'–MgX \xrightarrow[1,3-butadiene]{cat. NiCl_2 or CuCl_2} R–R'$$

R = alkyl   R' = alkyl, aryl

Table 2-9   Cross-Coupling Reaction of ⁿC₈H₁₇-F with ⁿC₂H₅-MgBr[a]

			product yield (%)[b]		
entry	catalyst	additive (mol %)	undecane	octane	octene[c]
1	NiCl₂	none	0	0	0
2	(PPh₃)₂NiCl₂	none	0	0	0
3	(dppp)NiCl₂	none	0	0	0
4	NiCl₂	1,3-butadiene (10)	9	1	0
5	NiCl₂	1,3-butadiene (50)	44	2	1
6	NiCl₂	1,3-butadiene (70)	50	2	2
7	NiCl₂	1,3-butadiene (100)	64	4	2
8	NiCl₂	1,3-butadiene (200)	67	3	1
9	NiCl₂	isoprene (100)	47	0	0
10	NiCl₂	2,3-methyl-1,3-butadiene (100)	0	0	0
11	NiCl₂	1,5-cyclooctadiene (100)	0	0	0
12	NiCl₂	diphenylacetylene (100)	0	0	0
13	(PPh₃)₂NiCl₂	1,3-butadiene (100)	8	3	2
14	(dppp)NiCl₂	1,3-butadiene (100)	57	3	2
15	FeCl₂	1,3-butadiene (100)	0	0	0
16	CuCl₂	1,3-butadiene (100)	0	0	0
17	PdCl₂	1,3-butadiene (100)	23	1	4
18	CuCl₂	1,3-butadiene (100)	97	0	0
19	CuCl	1,3-butadiene (100)	94	0	0
20	Li₂CuCl₄	1,3-butadiene (100)	30	0	0

[a] Conditions: ⁿOct-F (2 mmol), 3 mol % catalyst, additive (mol % based on the substrate), and ⁿEt-MgBr (2 equiv, 1 M), in THF, 25 °C, 3 h. [b] Determined by GC. [c] A mixture of 1-octene and 2-octenes.

Table 2-10

$$^nOct-F + R-MgX \xrightarrow[THF]{CuCl_2 (3 mol \%)} {}^nOct-R$$

2 mmol   2.6 mmol

entry	R-MgX	additive (0.2 mmol)	temp (°C)	time (h)	GC yield (%)
1	ⁿC₂H₅-MgBr	1,3-butadiene	25	6	94
2		isoprene	25	6	34
3		none	25	6	20
4		1,3-butadiene	−20	6	38
5		none	−20	6	36
6		none	−20	48	68
7		none	−40	6	3

In entry 4,5 ; at -20 °C, the reaction proceeded slowly without significant loss of catalytic activity in the absence of 1,3-butadiene.

→ 1,3-butadiene plays impotant roles in stabilizing an active species.

$$^nOct-X + R-MgBr \xrightarrow{CuCl_2 (3 mol \%)} {}^nOct-R$$

X	ⁿC₁₁H₂₃ (R = ⁿPr)[a]
F	94% (entry 1)
Cl	3%
Br	87%

[a] Butadiene was added, 25 °C.

Scheme 2-10

the reactivity of R-X;
Cl< F< Br
(the reason is not clear yet.)

R-Cl was almost unreactive in this catalyst system.

$$^nC_8H_{17}-MgBr + {}^nC_8H_{17}-F + {}^nC_8H_{17}-Cl = {}^nC_{16}H_{33} + {}^nC_8H_{17}-Br$$

1.5 equiv   1.5 equiv   1.5 equiv   THF, 25 °C, 30 min

	ⁿC₁₆H₃₄ + ⁿC₈H₁₈ + ⁿC₈H₁₆
NiCl₂ (3 mol %), 1,3-butadiene (100 mol %)	8% 0% 39%
CuCl₂ (3 mol %), 1,3-butadiene (10 mol %)	16% 0% 40%

Scheme 2-11
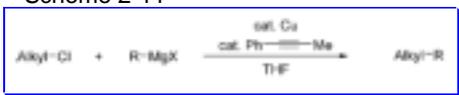
R-Cl
  wide availability
  low cost

Table 2-11

R	3% NiCl₂ 55% THF, 25 °C, 20 h	2% CuCl₂ 10% Ph——Me THF, reflux, 6 h
nBu	96%	>99%
sBu	1%	95%
tBu	0%	>99%
Ph	4%	82%

Scheme 2-12 competitive experiments

	nBu-nOct	nBu-nNon	nBu-nDec
with nDec-Br	2%	0%	98%
without nDec-Br	95%	5%	—
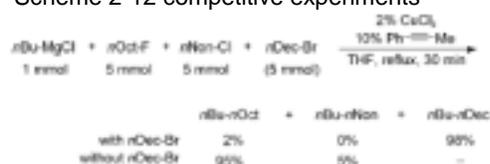
the reactivity of R-X; Cl< F< Br

Scheme 2-13 site-selective sequential cross-coupling
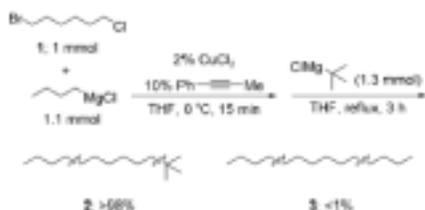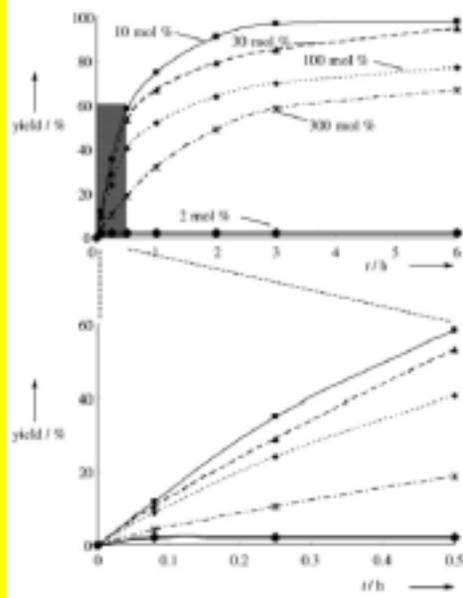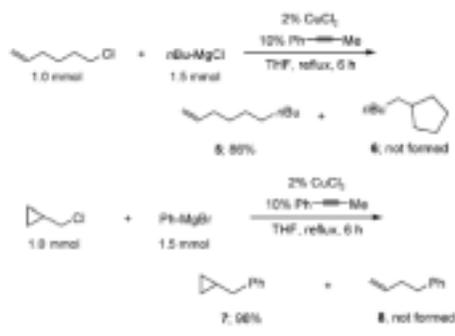

Figure 2-4 Time course of Cu-catalyzed cross-coupling reaction using different amounts of 1-phenylpropyne in THF under reflux.

As the amount of additive was increased, the reaction rate at early stage decreased.
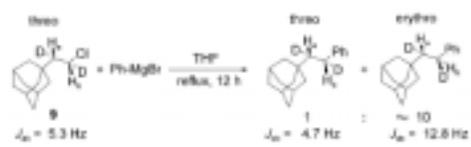 When only 2 mol% of the additive was employed, the catalyst rapidly lost its activity and reaction stopped.
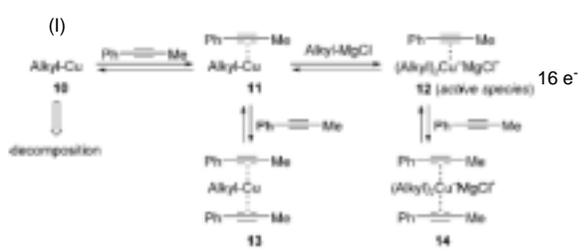
Scheme 2-14

These results would rule out a radical mechanism.

Scheme 2-15 the stereochemistry

The present reaction for primary-alkyl chlorides proceeds principally by an S_N2 mechanism.

Scheme 2-16 A plausible pathway

1-phenylpropyne would stabilize the alkyl-copper complex to form the alkyne-alkyl-copper complex **11**.
  Increasing alkynes shifts the equilibrium toward the formation of the complexes **13** or **14**, which might be the resting states of the catalyst.

K. Ohshima *et. al.* *J.Am. Chem. Soc.* **2001**, *123*, 5374-5375

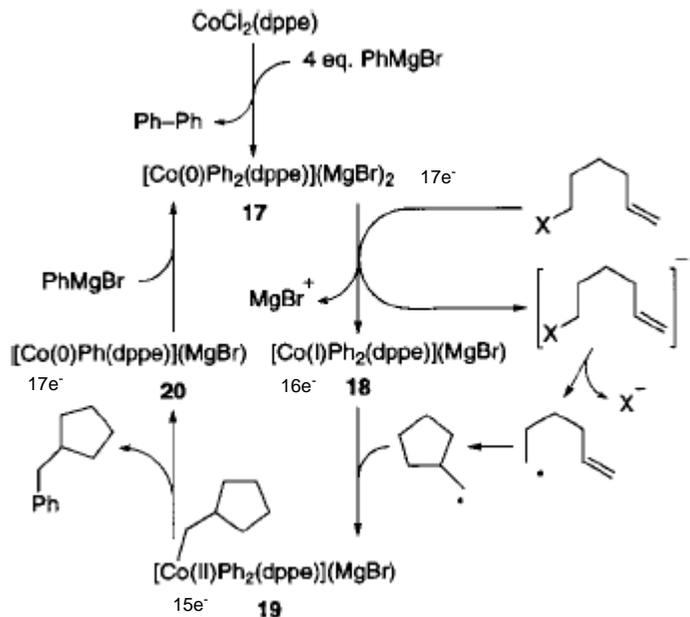<Cobalt-Catalyzed Tamdem Radical Cyclization and
Cross-Coupling Reaction>

Scheme 2-16 A draft mechanism

Table 2-12 Co-catalyzed phenylative radical cyclization

substrate	X	R^1	R^2	R^3	R^4	R^5	product	yield[b]
1a	Br	n-C$_4$H$_9$	H	H	n-C$_5$H$_{11}$	H	**2**	80% (55/45)
1b	I	n-C$_4$H$_9$	H	H	n-C$_5$H$_{11}$	H	**2**	78% (55/45)
1c	Cl	n-C$_4$H$_9$	H	H	n-C$_5$H$_{11}$	H	**2**	N.R.
1d	Br	(CH$_2$)$_3$	H	n-C$_5$H$_{11}$		H	**3**	71% (51/49)
1e	Br	(CH$_2$)$_3$	Me	Me		H	**4**	84% (62/38)
1f	I	(CH$_2$)$_3$	Me	Me		H	**4**	84% (60/40)
1g	Br	(CH$_2$)$_3$	H	H		Me	**5**	51% (single)
1h	I	(CH$_2$)$_3$	H	H		H	**6**	22% (91/9)

[a] Substrate (0.5 mmol), CoCl$_2$(dppe) (0.05 mmol), PhMgBr (1.1
mmol), and THF (1 mL) were employed. [b] Isolated yield. Diastereomer
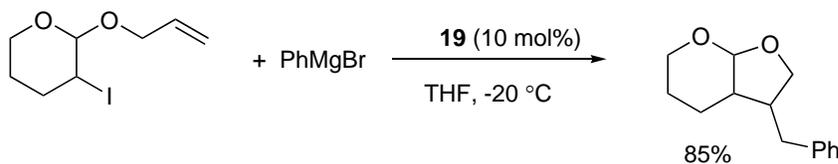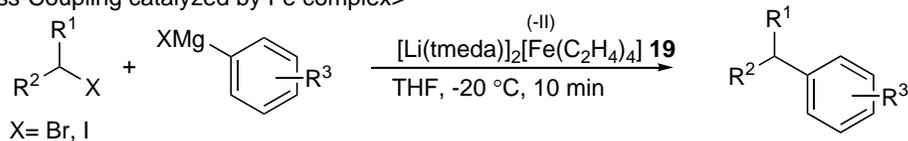ratios are in parentheses.

An active spicies would be the 17-electron-ate complex **17**.
A single electron transfer from **17** to a substrate to yield an anion
radical of the substrate and Co(I) complex **18**.

They also investigated the allylation, alkynylation with Co ate complex.

A. Furstner *et. al.* *Angew. Chem. Int. Ed.* **2004**, *43*, 3955-3957

<Cross-Coupling catalyzed by Fe complex>

A consise mechanistic
interpretation is not yet possible.
2-iodoacetal derivative undergoes
ring-closure prior to cross-coupling
seems to indicate a radical
intermediates.
→ This reaction pathway might be like
scheme 2-16.