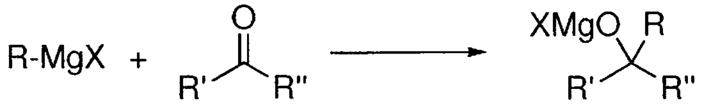
litarature seminar (1st) / 26 Jan 2005

Grignard reaction: efforts toward mechanism

Shun Sakuraba (B4)

1 Introduction

As everybody knows...

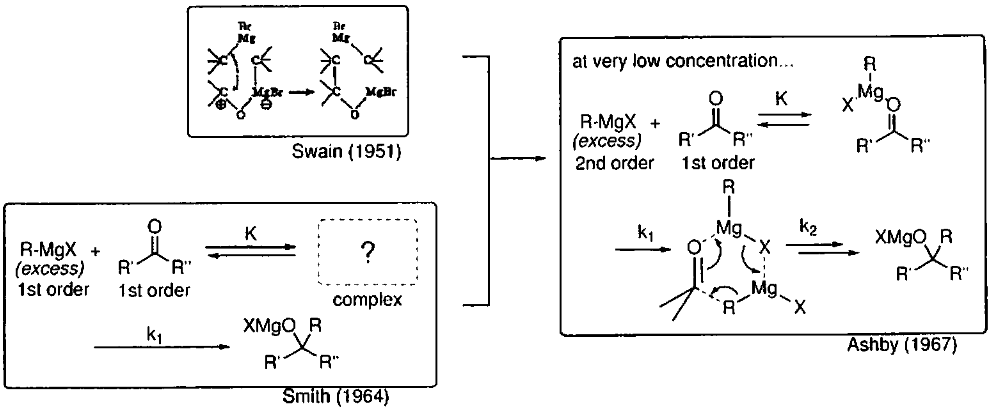


X = Cl, Br, I

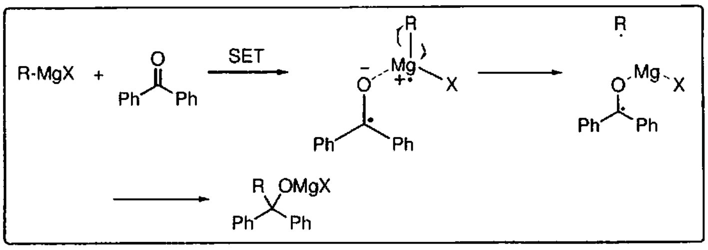
Original report: Grignard, V. (1900)

Reaction Mechanism: various mechanism reported

- Polar Mechanism was long believed, as "standard" explanation of Grignard reaction.
  two molecules involved Swain C. G. and Boyles H. B.; *JACS* **1951**, *73*, 871.
  "first order" kinetics Smith S. G.; *JACS* **1964**, *80*, 2751.
  "Pesudo-first order" kinetics Ashby E. C.; *JACS* **1967**, *89*, 1965.

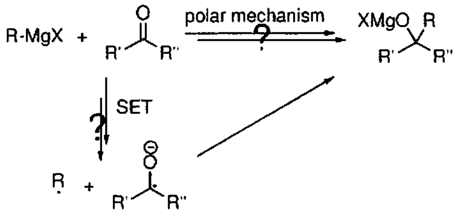


- SET mechanism was proposed by Blicke and Powers (1929). EPR(ESR) results reinforced this hypothesis.
  EPR Maruyama K. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 897. Researches were done mainly for Ph_2CO.

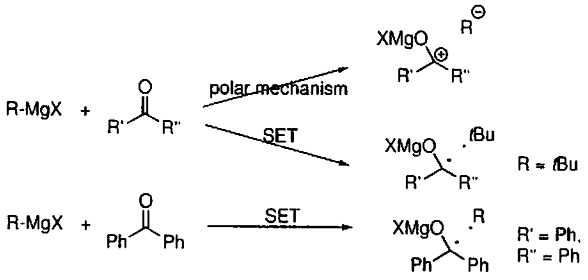


Maruyama (1964)

Why this difference occurs? And, which is "right" mechanism?

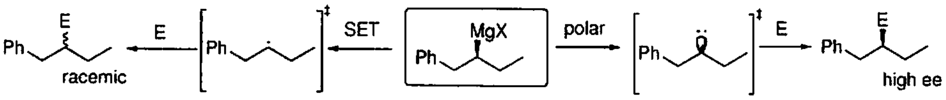


Recent research reveals that both mechanisms exist for the addition of Grignard reagent to carbonyl compounds. For most of compounds, reaction proceeds with polar mechanism. But the reaction of benzophenone and its derivatives proceed with SET mechanism. Reaction also proceed with SET, when we use bulky Grignard reagent such as *t*-BuMgBr.



Today, I would like to demonstrate how these results were obtained. In order to investigate this problem, **chiral Grignard reagent** was researched and played very important role.

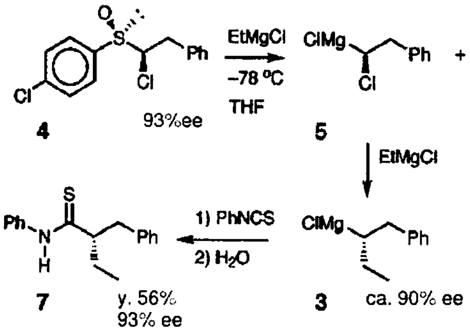
- If reaction mechanism is SET, radical spieces are generated. Since radical spieces racemize rapidly, final product should be racemic.
- If reaction mechanism is polar, (hopefully) reaction proceeds with retention or inversion at stereo center, resulted in maintaining high *ee* value.



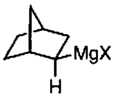
Angew. Chem. Int. Ed. **2000**, *39*, 3073.

Asymmetric Synthesis of a Chiral Secondary Grignard Reagent**

Reinhard W. Hoffmann,* Bettina Hölzer, Oliver Knopff, and Klaus Harms

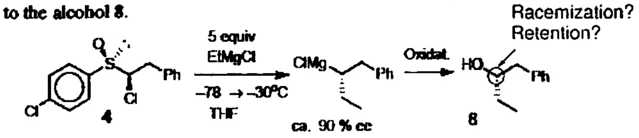


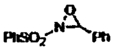
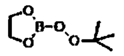
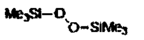
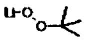
- First example of the **asymmetric** synthesis of a Grignard reagent, in which the magnesium-bearing carbon is **a sole stereogenic center**. (*c.f.* previously reported chiral Grignard is compound like **2**)
- The synthesized Grignard reagent(**3**) has at least 90% ee, and configurationally stable at −30°C.
- This reagent can be used for mechanistic study — we can know whether Grignard reaction proceeds **stereo-retentive or not**.



2

Table 1. Stereochemical course of the oxidation of the Grignard reagent 3 to the alcohol 8.



Oxidant		Yield (8) [%]	ee (8) [%]
$MoO_5 \cdot Py \cdot DMPU$[a]	9	84	92
	10	80	91
	11	80	88
	12	20	82
$Ti(OiPr)_4/tBuOOH$	13	82	71 Racemization
		75	32
O=O		89	15

[a] Py = Pyridine, DMPU = *N,N'*-dimethylpropylene urea.

- The author checked whether it can be used for mechanistic study.
- Oxidation was chosen as model reaction.
- Oxidation with molybdenum peroxide resulted in high ee, while oxidation with dioxygen gas resulted in very low ee.
- All configurations at hydroxy group are *S*, denoting reaction proceeds stereo-retentively.

■Summary Chiral Grignard reagent was synthesized as shown in scheme. The author demonstrated that these chiral Grignard reagents could be used as a probe, to gather the knowledge of mechanism.

Chem. Comm. **2001**, 491.

Concerted and stepwise Grignard additions, probed with a chiral Grignard reagent

Reinhard W. Hoffmann* and Bettina Hölzer

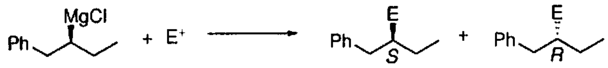
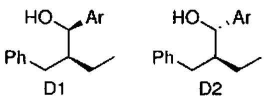


Table 1 Trapping of the Grignard reagent **6** (*ca.* 90% ee) with various electrophiles

Electrophile	Product(s)	Configuration[a]	Yield (%)	ee (%)
CO_2	HOOC-CH(Et)Bn **8**	*S*	80	92
PhNCO	PhNHCO-CH(Et)Bn **9**	*S*	60	89
PhNCS	PhNHCS-CH(Et)Bn **10**	*S*	56	91
ArCHO[b]	ArCHOH-CH(Et)Bn	n.d.	41	D1: 89 D2: 84
PhCHO	PhCHOH-CH(Et)Bn	*S*	42	D1: 88 D2: 84
C_6F_5CHO **11**	C_6F_5CHOH-CH(Et)Bn	n.d.	45 racemization	D1: 43 D2: 47
Ph_2CO **12**	Ph_2COH-CH(Et)Bn	—	85	12

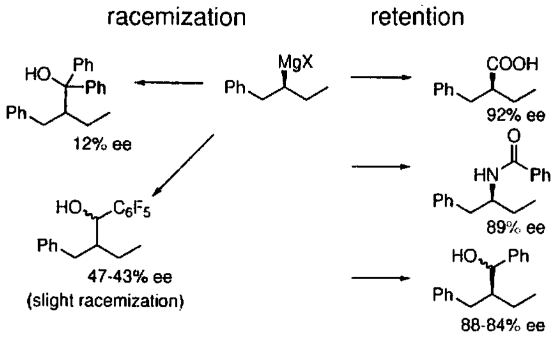
[a] At the former Grignard C-atom. [b] Ar = *p*-MeO-C_6H_4—. n.d.: not determined.



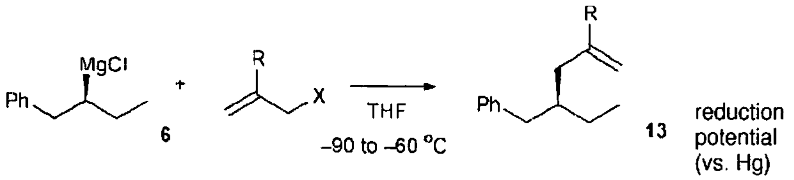
(or vice versa)

- Reaction between chiral Grignard reagent and electrophiles.
- All determined absolute configuration is *S* → **retentive** configuration.
- D1 and D2 mean diastereomers; ee values were determined for each diastereomer.
- Reaction with CO_2 resulted in obtaining product with high ee value, while only 12% ee is obtained when Ph_2CO is used as electrophile.
- The author suggest that the ee value of each reaction depicts the "nucleophilicity" for each reaction.

■Summary Reaction with chiral Grignard reagent shows there exist both two mechanism for this reaction. One is polar (nucleophilic) reaction, and the other is SET-induced reaction.



- These results explain that both SET initiated process and concerted polar addition are occuring in the reaction mixture.
- These results also imply that even in the reaction of Ph_2CO and Grignard reagent, some of it is proceeding with concerted addition mechanism.

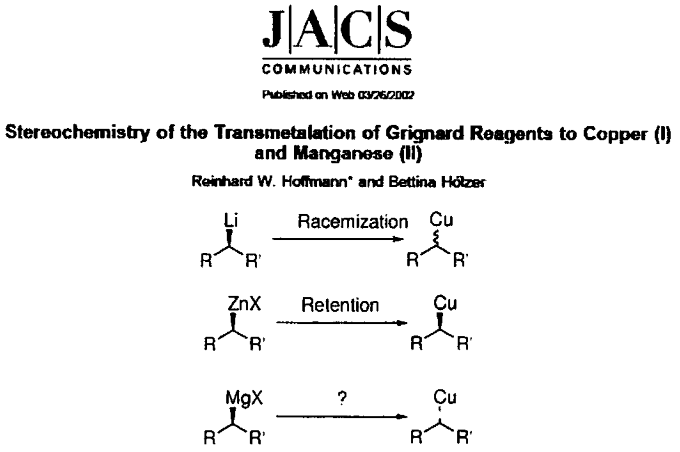


				reduction potential (vs. Hg)
R = H	X = Cl	ca. 90 %	ee 70 %	-1.91V
R = H	X = Br	ca. 90 %	ee 57 %	-1.29V
R = H	X = I	ca. 90 %	ee 0 %	-0.23V
R = CO_2Et	X = Br	79 %	ee 0 %	

- The author also examined the reaction between allylic halides and Grignard reagent.
- Result can be summarized as follows: "The larger reduction potential, the more SET-prone reaction." Reduction potential for allyl chloride, bromide and iodide are -1.91, -1.29, -0.23V *vs.* Hg, respectively.

At this point, it was assumed that the reduction potential of electrophile strongly correlates with SET-induced mechanism. The author also examined transmetal reaction, and the result reinforced this hypothesis.

JACS 2002, *124*, 4204.


J|A|C|S
COMMUNICATIONS
Published on Web 03/26/2002

Stereochemistry of the Transmetalation of Grignard Reagents to Copper (I) and Manganese (II)

Reinhard W. Hoffmann* and Bettina Hölzer

- Transmetalaion of organo**lithium** → copper (I): **racemization** is major.
- Transmetalaion of organo**zincate** → copper (I): complete **retention**.
- Secondary organocuprate is known to be configurationally stable.
- The author examined transmetalation of organomagnesium reagent.

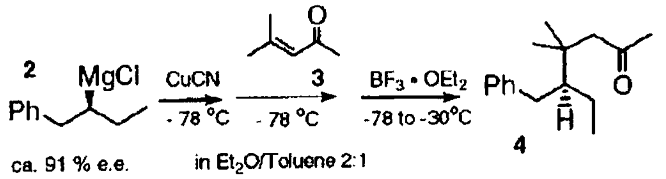
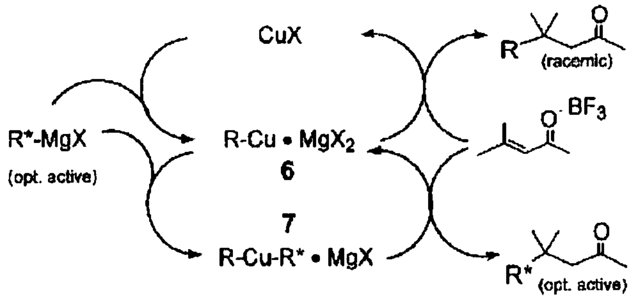


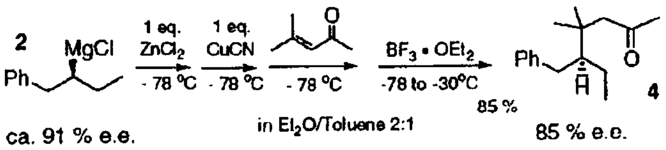
Table 1: Copper-Mediated Couplings of **2** in Et_2O/Toluene

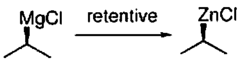
entry	copper salt	equiv	**4**: yield (%)	**4**: ee (%)
1	CuCN	1.00	80	0
2	CuCN	0.50	75	12
3	CuCN	0.10	70	30
4	CuCN	0.05	50	34
5	$EtCuCN{\cdot}MgCl$	1.00	61	23
6	$EtCuCN{\cdot}MgCl$	0.10	48	60
7	$[(MeCN)_4Cu]PF_6$	1.00	66	31
8	$[(MeCN)_4Cu]PF_6$	0.10	53	65
9	$[(MeCN)_4Cu]PF_6$	0.05	50	66



- Entry 1 shows that transmetalation to Cu (I) completely racemize the stereocenter.
- But when they decreased the amount of Cu (entry 2-4), ee gradually rose to 34%.
- The author considered that, there are at least two pathway (RMgX → **6** → Product / RMgX → **7** → Product.)
- In transmetalation to Cu, CuCN causes SET, and the product is racemic.
- But if **6** exists in the system, **7** generates without SET mechanism, then product is (partially or fully) optically active.
- This hypothesis is reinforced when they used $EtCuCN{\cdot}MgCl$ as copper (I) source (entry 5-6).
- The author compared the reduction potential of CuCN and of $RCuCN{\cdot}MgCl$, where CuCN is stronger oxidant (high reduction potential), then stated that this result is reasonable.
- In the case of $[(MeCN)_4Cu]PF_6$ (entry 7-9), reaction proceeds stereoretentively; it seems that the rate of two transmetalation reaction (CuX → **6**, **6** → **7**) are similar.

Then, the author examined transmetalation to other metals.





- In sequential transmetalation to Zn then Cu, stereocenter is well preserved.

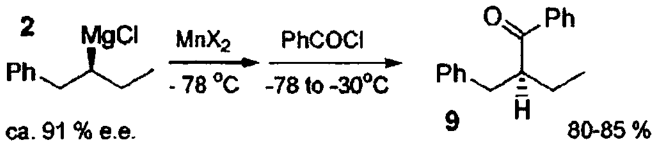
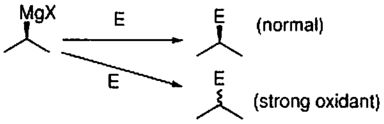


Table 2: Manganese-Mediated Couplings of **2**

entry	manganese salt	**10**: yield (%)	**10**: ee (%)
1	$MnCl_2$	78	53
2	MnI_2	80	58
3	$MnCl_2{\cdot}2LiCl$	85	55
4	$EtMnCl{\cdot}MgCl_2$	59	69

- In transmetalation to Mn, stereocenter is partially preserved.
- Reaction with $EtMnCl{\cdot}MgCl_2$ lead to higher ee.
- The author suggest that, there also exist two transmetalation cycles.
- (In my opinion, if the author suggest that there exist two transmetalation cycles, they should show experimental data such as the effect of the amount of manganese.)

From these results, we can observe both SET and concerted polar mechanism for diverse reactions with Grignard reagents. And, the tendency for SET can be summarized and generalized by the value of reduction potential. Stronger oxidant (higher reduction potential) lead to SET reaction.



From theoretical aspect, addition to carbonyl compound was also studied, and result was almost same with these results. Theoretical study shows both polar and SET mechanism exist, and reduction potential is very important. But, polar mechanism in it is different from what we have long believed; four-centered reaction mechanism was depicted as "plausible." Also, bulkiness of the reagent is described to be very important.

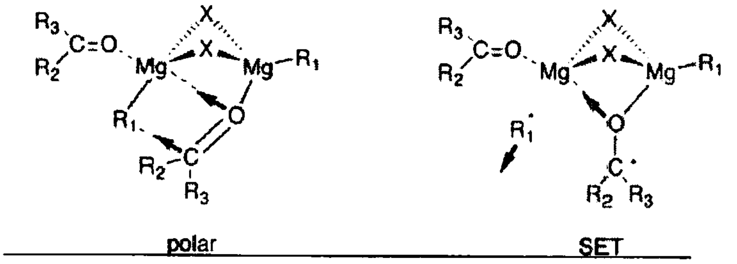
---

2 Theoretical Study

J. Org. Chem. **2002**, *67*, 9346.

A Computational Study on Addition of Grignard Reagents to Carbonyl Compounds

Shoko Yamazaki and Shinichi Yamabe*

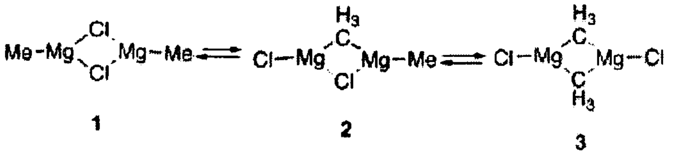


Key points:

- **Halogen-bridged dimer** is a predominant spieces.
- **Four-centered mechanism** is more plausible than Swain and Ashby's.
- The **bulkiness** of Grignard reagents and ketone turns reaction mechanism into radicalic one.
- Stereoselective reactions can be explained in this model.

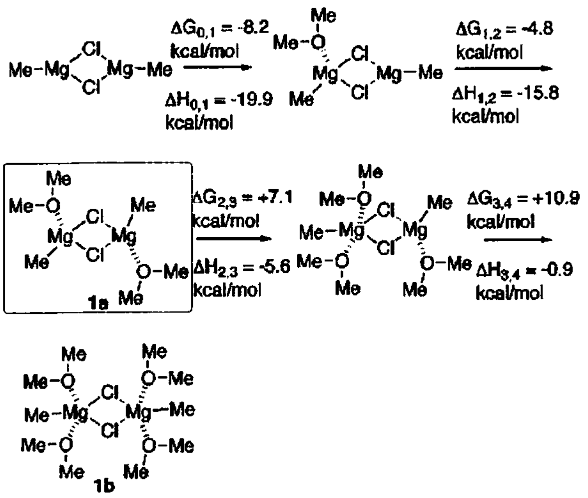
2.1 Predominant spieces and structure of intermediates

SCHEME 2. Schlenk Equilibrium for Methylmagnesium Chloride



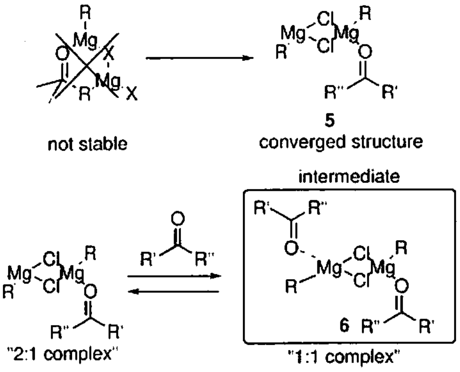
- In the solution of Grignard reagent, organomagnesium spieces are in the equilibrium called "Schlenk equilibrium."
- First, the author calculated which state of equilibrium is the most stable one. Result explains that, **Halogen-briged dimer** or **1**, is the most stable spieces.

SCHEME 3. Free Energy Differences $\Delta G_{n-1,n}$ and Enthalpy Differences $\Delta H_{n-1,n}$ by Addition of Me_2O Molecules Successively to $(Me-Mg-Cl)_2$, $(Me-Mg-Cl)_2(Me_2O)_{n-1} + Me_2O \rightarrow (Me-Mg-Cl)_2(Me_2O)_n$



- The author also investigated how many solvent molecules coordinate to Schlenk dimer(**1**). Result shows that Schlenk dimer with two solvent molecules(**1a**) is the most stable spieces.

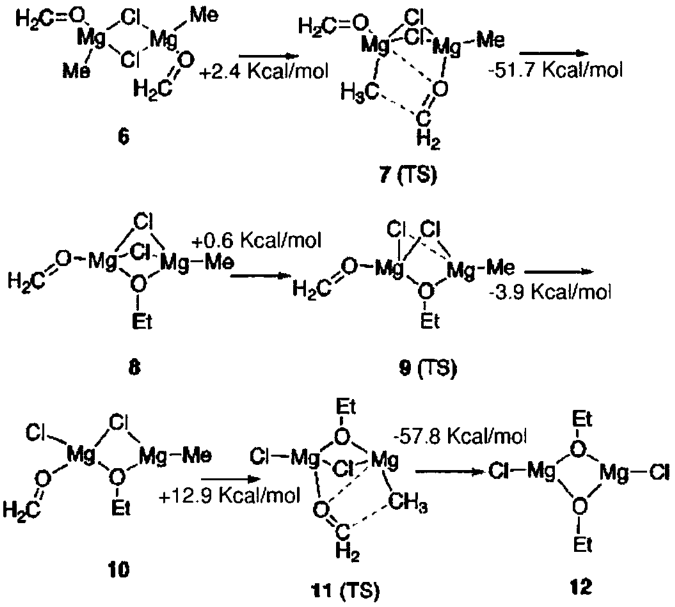
2.2 Polar addition mechanism



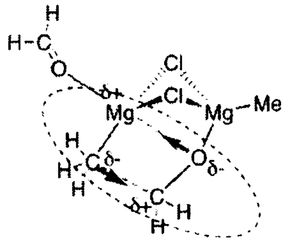
- Intermediate based on Ashby's mechanism (**4**) is not stable according to calculation. Optimized structutre coverged to **5**.
- In Grignard reaction, formation of 1:1 complex (Grignard : ketone) is observed (*J. Org. Chem.* **1961**, *26*, 4214.) Therefore, the author assumed that the dimer **6** is the intermediate.

The author started calculation from this complex, and yielded the following mechanism.

SCHEME 5. Reactions between the Schlenk Dimer and Two Formaldehyde Molecules[a]

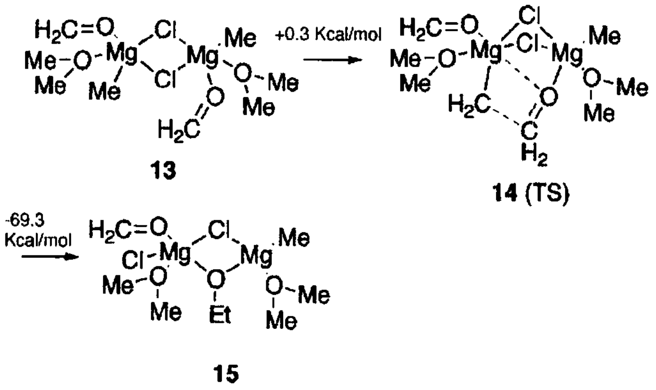


SCHEME 6. A Four-Center Reaction in 7(TS)



- Four-center transition state is essential.
- Carbonyl carbon and Me group do not connected to the same Mg atom; they are connected to the *vicinal* Mg atom.

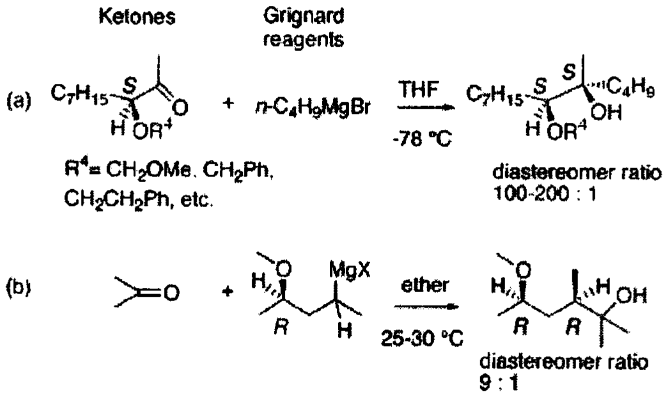
SCHEME 7. The First C—C Bond-Forming Reaction in Figure 2



- With solvent molecule, **13** is suggested as a intermediate, and **14** is a transition state.
- This intermediate with solvent corelate well with various X-ray structure of Grignard reagents.
- 5-coordinated intermediate is observed.

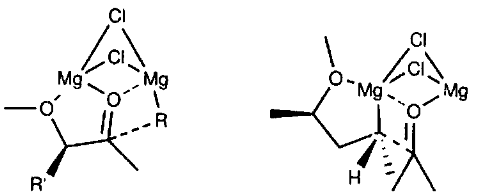
With this coordination model, we can explain the stereoselectivity of α-alkoky Grignard reagent and α-alkoky ketone well.

SCHEME 8. Stereochemistry of the Reported Reactions by the Use of Chiral Ketones (a)[2a] and Grignard Reagents (b)[15, a]

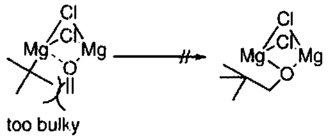


[a] Asymmetric carbon atoms are denoted by *R* or *S*

- Chelation occurs from the direction described in scheme.
- Both stereoselectivity (α-alkoxy Grignard reagent and ketone) were well explained.

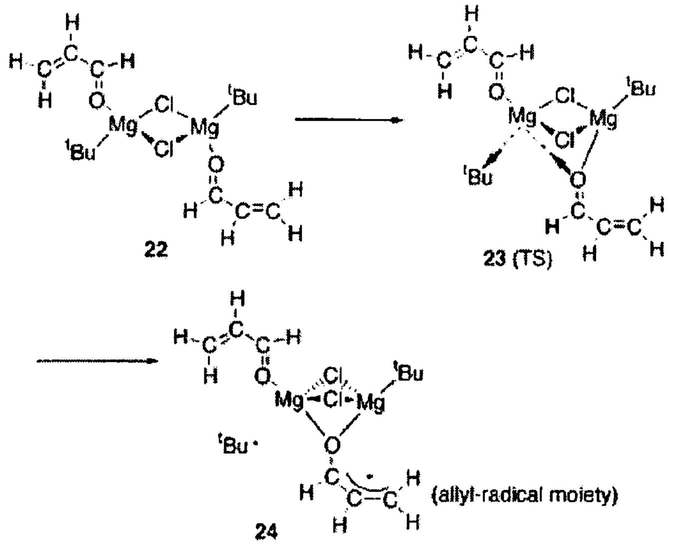


Polar mechanism was well described. Then, how it will be if Grignard reagent is bulky? Since steric conjestion hinders the formation of four-centered transition state.

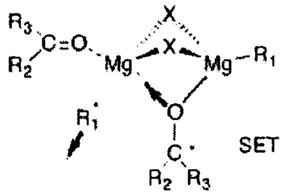


2.3 SET mechanism

SCHEME 10. A Singlet-Biradical Forming Process[a]



[a] The Mg---O bond formation proceeds and the left side ᵗBu group is pushed away via homolytic C−Mg cleavage

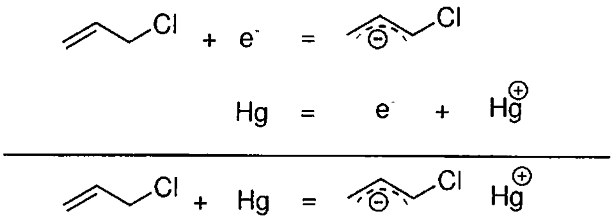


- If Grignard reagent is bulky, C-C bond forming is hindered.
- This tendency is promoted further, when ketone is bulky.
- Vibration mode demonstrates the leaving of *t*-Bu group.
- Observation on spin density reveals singlet biradical forming in the reaction.
- Spin (radical) is localized on *t*-Bu group and allyl bond.
- Note that radical was **not** observed on magnesium, nor oxygen.

3 Appendix

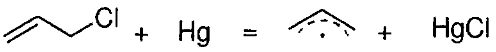
■Reduction potential Reduction potential is an indicator that tells how readily (or hardly) the material is reduced. In general, if reduction potential is high, it means that the material is easily reduced.

Strict (scientific) notation is given as following: X's reduction potential *vs.* Y means, the difference of electric potential between X and Y. For example, if allylchloride's reduction potential *vs.* Hg is -1.91...



$\Delta E = -1.91$V.

... should be 'original' description. But, concerning the meaning of the sentence in paragraph, and the reactionality of the allylhalide, it should be...



$\Delta E = -1.91$V.

... instead.

It should be noted that reduction potential is relative value (not an absolute value).