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A Computational Study on Addition of Grignard Reagents to Carbonyl Compounds

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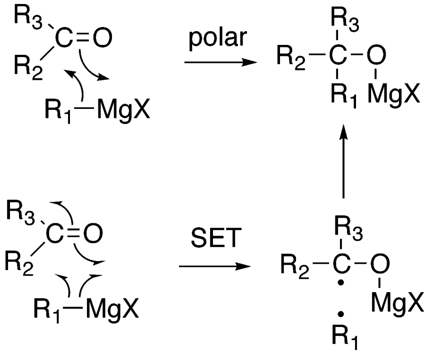
The mechanism of stereoselective addition of Grignard reagents to carbonyl compounds has been investigated using B3LYP density functional theory calculations. The study of the reaction of methylmagnesium chloride and formaldehyde in dimethyl ether revealed a new reaction path involving carbonyl compound coordination to magnesium atoms in a dimeric Grignard reagent. The structure of the transition state for the addition step shows that an interaction between a vicinal-magnesium bonding alkyl group and C═O causes the C−C bond formation. The simplified mechanism shown by this model is in accord with the aggregation nature of Grignard reagents and their high reactivities toward carbonyl compounds. Concerted and four-centered formation of strong O−Mg and C−C bonds was suggested as a polar mechanism. When the alkyl group is bulky, C−C bond formation is blocked and the Mg−O bond formation takes precedence. A diradical is formed with the odd spins localized on the alkyl group and carbonyl moiety. Diradical formation and its recombination were suggested to be a single electron transfer (SET) process. The criteria for the concerted polar and stepwise SET processes were discussed in terms of precursor geometries and relative energies.

Introduction

The Grignard reaction has a 100 year history, is one of the most important organic reactions for C−C bond formation,[1] and is still indispensable in current organic syntheses. The structures of Grignard reagents have been gradually revealed by X-ray analyses and other spectroscopic methods;[1b,c] however, the detailed mechanism (in particular, C−C bond formation) of carbonyl addition of Grignard reagents is still unclear. The mechanism is considered to be complex, and it varies depending on alkyl groups, halogens, solvent, concentration, and temperature. The two mechanistic possibilities, polar vs SET (single-electron transfer), shown in Scheme 1 have been discussed for many years.[1b,c,f−l]

SCHEME 1. Two Traditional Mechanisms for $C-R_1$ Bond Formation



Numerous stereoselective carbonyl additions of Grignard reagents, including enantioselective examples, have been developed recently. Such stereoselective additions have been considered through the polar mechanism, and Cram's selectivity involving chelation control is used in order to explain the high diastereoselectivity.[2,3] Since the detailed C−C bond formation steps including transition states are not clear, further development of efficiency (improving yields), chemoselectivity (minimizing side reactions), and stereoselectivity in addition steps is difficult. The purpose of the work described in this paper is (1) to elucidate the addition process using simplified and realistic systems and (2) to investigate the polar vs SET mechanisms by a theoretical study. Using B3LYP calculations of various model systems herein, we would like to show that four-membered rings containing two Mg atoms in a Schlenk equilibrium control Grignard reactions.

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[1] (a) Grignard, V. *C. R. Hebd. Seances Acad. Sci.* **1900**, *130*, 1322. (b) *Handbook of Grignard Reagents*; Silvermann, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996. (c) *Grignard Reagents New Developments*, Richey, H. G., Jr., Ed.; Wiley: New York, 2000. (d) Wakefield, B. J. In *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995. (e) Kharasch, M. S.; Reinmuth, O. In *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: Englewood Cliffs, NJ, 1954. (f) Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545. (g) Ashby, E. C.; Becker, W. E. *J. Am. Chem. Soc.* **1963**, *85*, 118. (h) Maruyama, K.; Katagiri, T. *J. Am. Chem. Soc.* **1986**, *108*, 6263. (i) Holm, T. *Acta Chem. Scand.* **1966**, *20*, 2821. (j) Smith, S. G.; Su, G. *J. Am. Chem. Soc.* **1964**, *86*, 2750. (k) Ashby, E. C.; Laemmle, J.; Newmann, H. M. *Acc. Chem. Res.* **1974**, *7*, 272. (l) Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* **1989**, *111*, 4912.

[2] (a) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031. (b) Ko, K.-Y.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 5353. (c) Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484.

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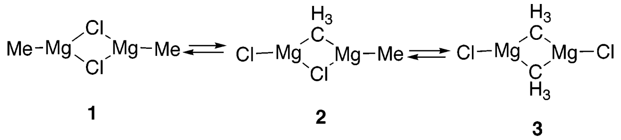
10.1021/jo026017c CCC: $22.00

SCHEME 2. Schlenk Equilibrium for Methylmagnesium Chloride



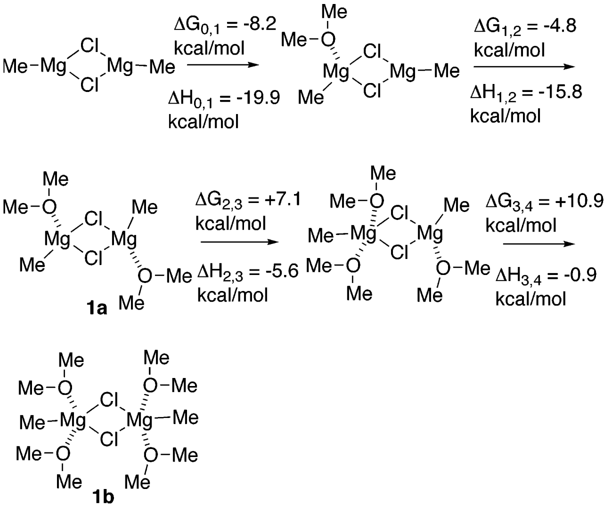
Computational Methods

Geometries were fully optimized by the B3LYP density functional theory (DFT) method[4] together with the SCRF[5] solvent effect (dimethyl ether Me_2O, dielectric constant = 5.02). The basis set used is 6-31G*. Vibrational frequency calculations gave a sole imaginary frequency for all transition structures, which verifies that the obtained geometries are correctly of the saddle point. From the reactant precursor, partial geometry optimizations were repeatedly carried out with the fixed Mg- - -O and C- - -C distances. Through the partial optimizations, an approximate transition state (TS) structure could be obtained. Next, by the use of the approximate structure and the force constants, TS geometries were determined. In this case, the negative values (ca. −0.05 hartree/au**2) of the Hessian diagonal force constants of the bond-forming Mg- - -O and C- - -C distances should be included in the input line. All calculations were performed using GAUSSIAN 98[6] installed on a Compaq ES40 computer (Information Processing Center, Nara University of Education).

Results and Discussion

A. Structures of Grignard Reagents. Grignard reagents (RMgX) in ether solution form aggregates.[7,1b,c] The degree of aggregation depends on halogens (X), concentration, alkyl group R, and solvents. For simple alkyl or aryl magnesium chlorides in diethyl ether, the predominant species is considered to be a solvated halogen-bridged dimer.[1f,g] Axten et al. revealed that the dimer of MeMgCl is much more stable than the monomer by ab initio calculations.[8]

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 dimers of the Schlenk equilibrium (Scheme 2) have been investigated by B3LYP/6-31G* calculations. The coordination of solvent, dimethyl ether, was included along with the SCRF solvent effect. In Figure S1 (Supporting Information), three constitutional isomers of $(Me{-}Mg{-}Cl)_2(Me_2O)_n$ (n = 2 and 4) are compared. For both n = 2 and 4, **1** is most stable and has two bridged Cl atoms. This result is in accord with Axten's results,[8] although our present model with ether molecules is more realistic. The structure shows good resemblance to the crystal structures of halogen-bridged dimers $(MgX)_2$ moiety.[9]

How many ether molecules are favored by the Schlenk dimer, $Me{-}Mg{-}Cl_2{-}Mg{-}Me$ in Scheme 3? The geometry of **1b** (four ethers) is compared to that of **1a** (two ethers). In **1a**, two Mg−O distances (2.103 and 2.109 Å) are close to that (2.104 Å) of the MgO ionic crysral. In **1b**, they are 2.265, 2.261, 2.272, and 2.272 Å and are larger than those in **1a**. Despite the large Mg−O affinity, two Mg atoms do not favor the coordination of four ether molecules. Thus, **1a** is a saturated complex, although there seems to be room on the two Mg atoms for further nucleophilic coordination. Mg atoms seem to persist in tetracoordination. Ether solvation to the Schlenk equilibrium does not block reaction channels completely.

To confirm the saturation in **1a**, free-energy changes for the following stepwise clustering reactions were calculated

$$(Me{-}Mg{-}Cl)_2(Me_2O)_{n-1} + Me_2O \rightarrow (Me{-}Mg{-}Cl)_2(Me_2O)_n$$

When the addition of the nth ether molecule gives a negative $\Delta G_{n-1,n}$ value, the addition is favored. In contrast, a positive $\Delta G_{n-1,n}$ value means that the nth molecule is not bound to the $(n-1)$ cluster (repulsive). The calculated values are $\Delta G_{0,1} = -8.2$, $\Delta G_{1,2} = -4.8$, $\Delta G_{2,3} = +7.1$, and $\Delta G_{3,4} = +10.9$ kcal/mol as shown in Scheme 3. $\Delta H_{n-1,\,n}$ values are also shown in Scheme 3. Additions of the third and fourth ether molecules are less exothermic ($\Delta H_{2,3} = -5.6$ and $\Delta H_{3,4} = -0.9$ kcal/mol), which are overcome by entropy changes leading to the positive $\Delta G_{2,3}$ and $\Delta G_{3,4}$ values.

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(4) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1998**, *37*, 785.

(5) Onsager, L. *J. Am. Chem. Soc.* **1938**, *58*, 1486.

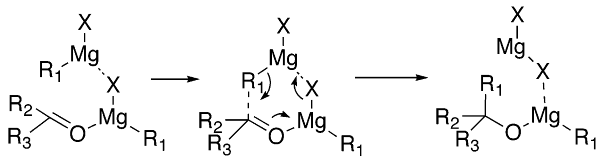
(6) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A.7*; Gaussian, Inc., Pittsburgh, PA, 1998.

(7) Schlenk, W.; Schlenk, W., Jr. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 920.

(8) Axten, J.; Troy, J.; Jiang, P.; Trachtman, M.; Bock, C. W. *Struct. Chem.* **1994**, *99*, 5.

(9) (a) Spek, A. L.; Voorbergen, P.; Schat, G.; Blomberg, C.; Bickelhaupt, F.; *J. Organomet. Chem.* **1974**, *77*, 147. (b) Toney, J.; Stucky, G. D. *J. Chem. Soc., Chem. Commun*, **1967**, 1168.

SCHEME 4. Termolecular Polar Mechanism Proposed by Swain[10a] and Ashby[10b]

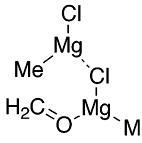


Clearly, the third and fourth molecules cannot be bound to the $(Me{-}Mg{-}Cl)_2(Me_2O)_2$ cluster, **1a**. Therefore, **1a** is a saturated shell. Since the double trigonal-bipyramidal geometry of **1b** ($n = 4$) in Figure S1 does not involve significant steric congestion, expulsion of $n = 3$ and 4 ether molecules arises from the poor ability of Mg atoms for the fifth coordination. Among Schlenk equilibrium dimers in Figure S1 and Scheme 3, **1a** is a most likely reactant for Grignard reactions.

B. Additions of Grignard Reagents to Carbonyl Compounds without Solvent Molecules. The SET mechanism is known to be operative for reactions of Grignard reagents and aromatic ketones such as benzophenone.[1f,h,k,l] In reactions of Grignard reagents and aliphatic ketones and aldehydes, the polar mechanism seems to be major.[1b,c] The reactions of aliphatic ketones and aldehydes are more widely utilized in organic syntheses. Thus, at first, the polar addition mechanism was examined.

First, a mechanism without solvent was examined for simplification and initial formation of a carbonyl−Mg atom complex was expected. The previously proposed polar addition mechanism is shown in Scheme 4,[10] which has been quoted widely.[11]

We have checked the potential intermediacy of precursor **4**. However, the initial geometry of the model **4** converged by geometry optimization to that of $MeMgCl_2$-$MgMe{-}{-}{-}O{=}CH_2$ **5**.



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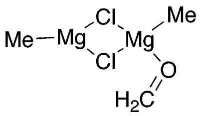

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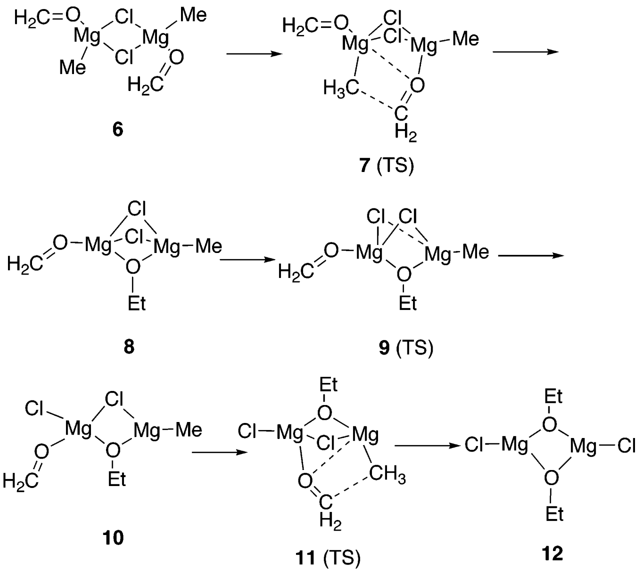
The convergence arises from the stability of the two-chloride-bridged structure in the Schlenk equilibrium (i.e., **1** in Scheme 2). Thus, the proposed concerted mechanism containing a cyclic transition state in Scheme 4 is unlikely for Grignard reactions. This result is in contrast to the carbonyl additions with organolithium reagents.[12] The formation of a 1:1 complex was reported for the reactions of Grignard reagents and ketones.[1i,j] Also, stoichiometric amounts of Grignard reagent to carbonyl compounds are generally enough. Therefore, an intermediate model **6** consisting of $MeMgCl_2MgMe$ and two formaldehyde molecules was calculated (Scheme 5 and Figure 1). Solvent ether molecules will be taken into account in Figure 2. In the reactant-like complex **6**, $H_2C{=}O$ molecules are bound to Mg atoms. One $H_2C{=}O$ is shifted leftward to be linked with the left methyl group. At the same time, the carbonyl oxygen of $H_2C{=}O$ is directed to the left Mg atom. Thus, a concerted C- - -C and O- - -Mg bond formation is shown at TS **7** (see reaction-coordinate vectors in Figure S5 of Supporting Information). A C−C covalent bond (1.525 Å in **8**) is established, and the original dichloride bridge **6** in the square is replaced to the dichloride and oxygen bridge. The presence of two strong Mg−O bonds (1.943 and 2.008 Å) in the bridge of **8** is reflected by a large exothermic energy (−49.3 kcal/mol). The triply bridged structure of **8** is presumably caused by preference of tetracoordination of magnesium atoms. The reaction pathway **6** → **7**(TS) → **8** would be very important among the polar Grignard reaction; the minimum essential is a four-center reaction (Scheme 6).

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



[a] The **6** → **7** → **8** process is shown in Figure 1, and the **8** → **9** → **10** → **11** → **12** is in Figure S2.

For the addition transition state structure **7**, a remarkable feature has been found: the bond-forming carbonyl carbon and the Me group do not reside on the same magnesium but on the vicinal magnesium of the bridged dimer. The dichloride- and O-bridged product **8** has newly formed Mg−O and C−C bonds. The energy barrier for this process (**6** → **7**(TS)) is very small (+2.4 kcal/mol).

The first addition product **8** can proceed to the second addition stage (Scheme 5 and Figure S2). The intermediate **8** transforms to **10** through bridged-Cl opening TS **9**. Structure **10** undergoes the second addition step (**10** → **11**(TS) → **12**), similar to the first addition step (**6** → **7**(TS) → **8**). The final product **12** is highly stable caused by four Mg−O bonds. Although the energy barrier for the second addition step (+12.9 kcal/mol) is larger than the first addition step (+2.4 kcal/mol), transformation of **10** to **12** is a highly exothermic process (−97.5 − (−52.6) = −44.9 kcal/mol).

The calculation of the bromide analogue for the first critical addition step **6−Br** → **7−Br** (TS) → **8−Br** was

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(10) (a) Swain, C. G.; Boyles, H. B. *J. Am. Chem. Soc.* **1951**, *73*, 870. (b) Ashby, E. C.; Duke, R. B.; Newmann, H. M. *J. Am. Chem. Soc.* **1964**, *89*, 1967.

(11) For example, see: Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry Part B: Reactions and Synthesis*; Plenum Press: New York, 1990; p 376.

(12) Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016.

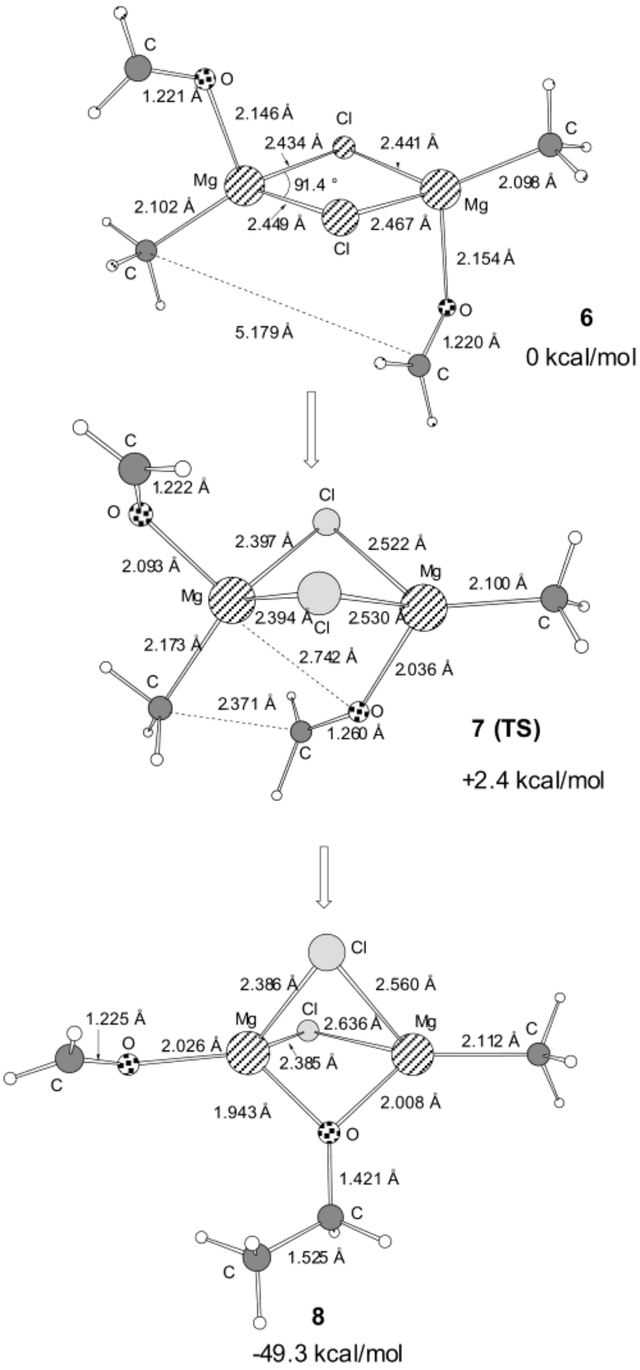


FIGURE 1. Carbonyl addition 1:1 complex (no solvent molecule) (the first stage) corresponding to that of Scheme 5. In Figure S3 of Supporting Information, geometries of the bromide analogue are shown. The geometry of **6** was determined in the reaction coordinate to **7**(TS). A symmetric reactant geometry (C_{2h}) is 1.8 kcal/mol less stable than **6**.

also carried out. The structure of the intermediates and transition state and energy barriers are similar to those of the chloride models (Figure S3 in Supporting Information). This similarity suggests that the addition with bromo−Grignard reagent requires dimeric species. Although Grignard reagents are known to be in a different aggregate state depending on halogen atoms,[1f,g] this result shows that the reactivity toward carbonyl compounds does not depend on Br or Cl.

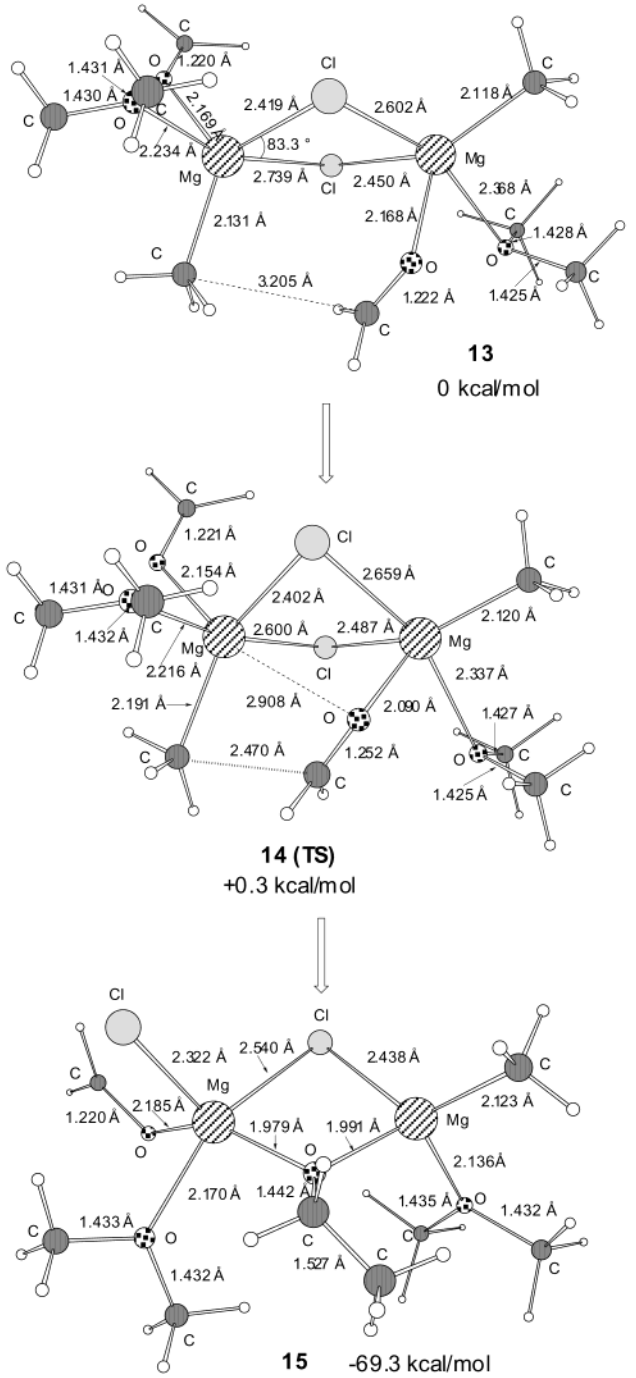
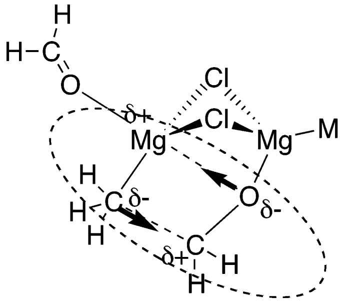


FIGURE 2. Carbonyl addition process (with two solvent molecules) corresponding to that of Scheme 7.

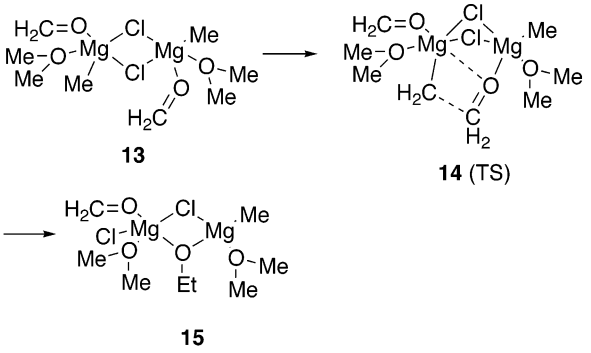
The high reactivity of Grignard reagents toward carbonyl compounds can be understood by the model of Scheme 6 starting from the coordination of the magnesium to carbonyl oxygen and transforming C−Mg to strong C−C and O−Mg bonds.

C. Additions with Solvent Molecules. The polar addition process was investigated with solvent molecules (dimethyl ether) as a more realistic system. Two $H_2C{=}O$ molecules were added to the sole reactant **1a** in Scheme 3 and Figure S1, **13**. The dimer **13**, a transition state **14**, and a product **15** were calculated (Scheme 7). Their geometries are shown in Figure 2. The obtained

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



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

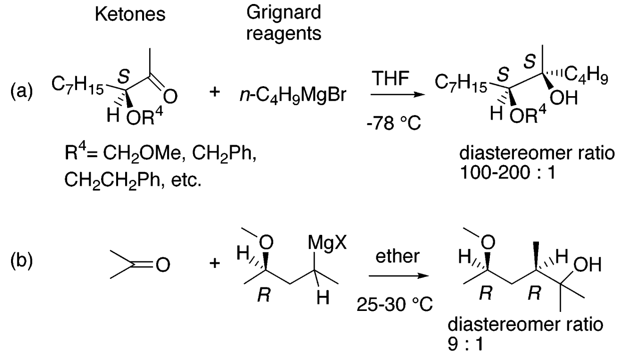


structure for the precursor **13** has dimeric five-coordinated magnesiums.[13] The structure is similar to the reported X-ray structure having dimeric five-coordinated magnesium atoms.[14] As in the nonsolvated model system (**7**(TS) in Figure 1), the bond-forming carbonyl carbon and Me group reside on vicinal magnesiums of the bridged dimer in the addition transition state structure **14**(TS) (see reaction-coordinate vectors in Figure S5 of Supporting Information). The energy barrier for this process is very small (+0.3 kcal/mol) and shows that the process is very facile. Conversion from **13** to the product **15** takes place exothermically (−69.3 kcal/mol). Thus, the dichloride-bridged four-membered structure is retained in the transition state.

In Figure 2, the Me_2O molecules do not affect the polar reaction path significantly in comparison with the path in Figure 1. However, some bond distances are appreciably different between the two precursors **6** (Figure 1) and **13** (Figure 2). A Mg−Cl distance is 2.449 Å in **6**, while it is 2.739 Å in **13**. Next, $Mg{-}OMe_2$ distances of **1a** (Figure S1) and **13** are compared. The distance 2.368 Å in **13** is larger than that in **1a** (2.109 Å). These results indicate that the tetravalent Mg atoms form tight covalent and coordination bonds and the pentavalent Mg atoms form somewhat loose chemical bonds.

D. Chelation Controlled Addition Models. High diastereoselectivity for the addition of Grignard reagents to carbonyl compounds is explicable by the proposed four-centered process (Scheme 6). Reactions of chiral carbonyl compounds (Scheme 8a) and chiral Grignard reagents (Scheme 8b) are examined. The examples of (Scheme 8a) are stereoselective addition reactions of Grignard reagents to chiral α-alkoxy ketones.[2a] The reaction examples of (Scheme 8b) are additions of chiral γ-alkoxy magnesium halides to ketones.[15] Some other examples of chiral Grignard reagents such as tetrahydroisoquinoline Grignards discovered by Seebach[16] and α-alkoxy Grignard reagents[17] were also reported. Because a stable coordination of ether (solvent) to magnesium is shown in the model system of Figure 2, the coordination of ether oxygen in substrates to magnesium may work effectively to form chelation. The proposed mechanism of chelation controlled addition could be determined by theoretical study.

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*

As an example of Scheme 8a, a reaction between MeMgCl and 2-methoxyacetaldehyde as a model for chelated carbonyl compounds was employed. According to the dimeric forms in Scheme 3 and Figure S1, the dimeric addition process of ($MeMgCl/OHCCH_2OMe$) was examined. In Figure S4a (Supporting Information) and Scheme 9a-1, a reaction pathway with effective chelation at Mg was obtained. The polar addition precursor as a dimer **16**, transition state **17**, and product **18** have similar feature to that of the solvent-attached MeMgCl/$O{=}CH_2$ system in Figure 2. In the first addition transition state structure **17**, the bond-forming carbonyl carbon and Me group reside on vicinal magnesiums of the bridged dimer. The dichloride-bridged four-membered structure is retained in the transition state as well. Because of chelation of OMe group, the aldehyde was configurationally fixed. Thus, the present model calculation has revealed that the chelation control results in the highly stereoselective addition processes observed. The reaction occurs via a dimeric form which has not been considered so far. This model uses achiral substrates and does not create asymmetric carbons. However, through replacement of H by an *n*-heptyl group (C_7H_{15}) on α-carbon of the aldehyde in addition to some other substitutions (Scheme 9a-2), the stereoselective pathway

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[13] The Schlenk-type isomers of the nonsolvated precursor **6** and the solvated precursor **13** were calculated. Those MgMe/ClMg or $MgMe_2Mg$ bridged isomers were confirmed to be less stable than **6** or **13**, respectively.

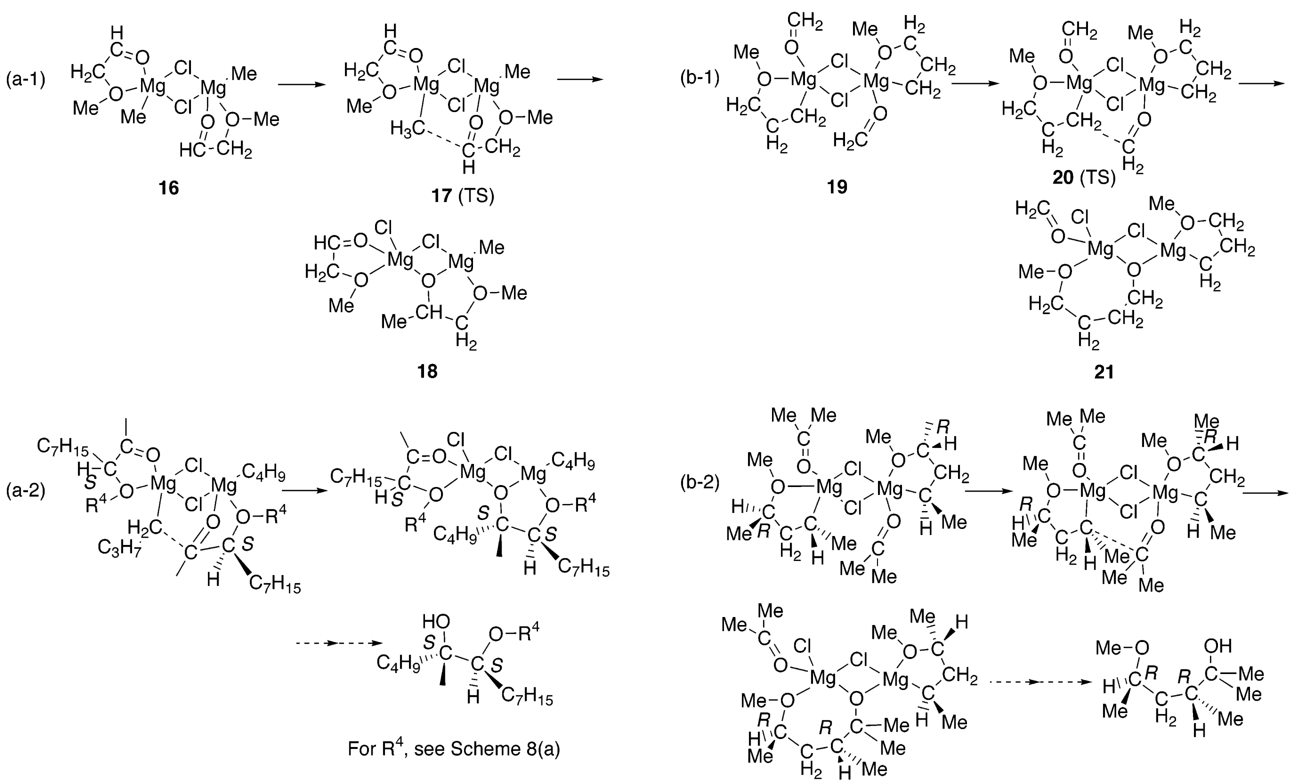
[14] Marsch, M.; Harms, K.; Massa, W.; Boche, G.; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 696.

[15] Miles, W. H.; Rivera, S. L.; del Rosario, J. D. *Tetrahedron Lett.* **1992**, *33*, 305.

[16] (a) Seebach, D.; Syfrig, M. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 248. (b) Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1. (c) Zhang, P.; Gawley, R. E. *Tetrahedron Lett.* **1992**, *33*, 2945.

[17] McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5422.

SCHEME 9. (a) Reaction of Methylmagnesium Chloride and 2-Methoxyacetaldehyde (a-1) and Its Extension to the Chiral Reaction (a-2) and (b) an Example of Scheme 8b.[a]



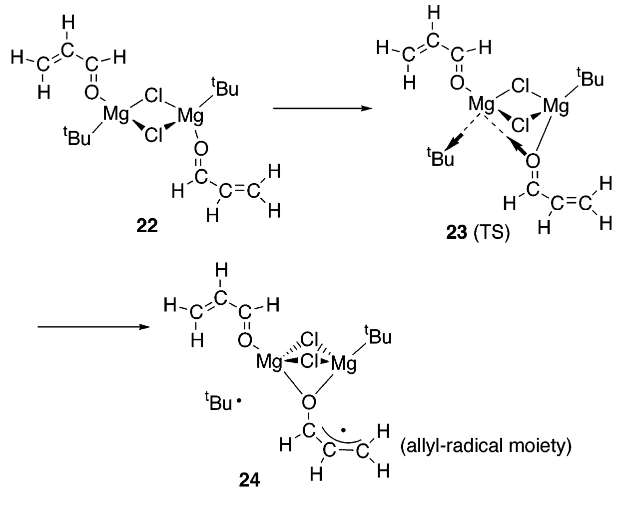
[a] Geometries of **16**, **17** (TS), and **18** of (a-1) are shown in Figure S4a of Supporting Information. Geometries of **19**, **20** (TS), and **21** of (b-1) are shown in Figure 4Sb of Supporting Information.

can be explained as follows. The alkyl group (C_7H_{15}) would locate on the outside of the dimer. The configuration is fixed by chelation. The nucleophile (*n*-C_4H_9 group) would attack from the less hindered side (H side). The stereochemical result is the same as Cram's original concept.[3] The result from the extension of the model study is in accord with the major product stereochemistry in Scheme 8a.

As an example of Scheme 8b, reaction between 3-methoxypropylmagnesium chloride, which is a model for chelated Grignard reagents, and formaldehyde was adopted. The first addition process of ($MeOCH_2CH_2CH_2$-$MgCl/O{=}CH_2)_2$ was examined (Scheme 9b-1). In Figure S4b of Supporting Information, a pathway with the effective chelation was also obtained in this model reaction. Thus, the example of Scheme 8b also shows that the effective chelation control works in a dimeric form as well as that of Scheme 9a. When the magnesium-substituted carbon configuration is fixed by chelation, stereoselection by steric effects could occur. In the example of Scheme 9b-2, the stereoselectivity is determined by the step of the formation of the conformationally stable Grignard reagent. Various remote steric effects based on the chelation control to create diastereomeric carbons have been suggested so far.[13,14] The present dimeric intermediate model rather than the monomeric one may describe the stereochemistry of Grignard reactions reasonably in the framework of the polar mechanism.

E. A Model for SET. To make the four-center reaction in Scheme 6 ready, steric congestion between the alkyl group R_1 and the carbonyl carbon needs to be avoided. In Scheme 10, a reaction was examined by the use of a bulky system, **22**.

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

Although benzophenone $Ph_2C{=}O$ is a better (bulky) and realistic ketone, calculations are too time-consuming. Here, a model conjugate ketone, *cis*-acrolein, was adopted. From **22**, the four-center reaction path was traced but could not be obtained. The nucleophilic center is blocked inside the ^tBu group. Other paths were sought starting

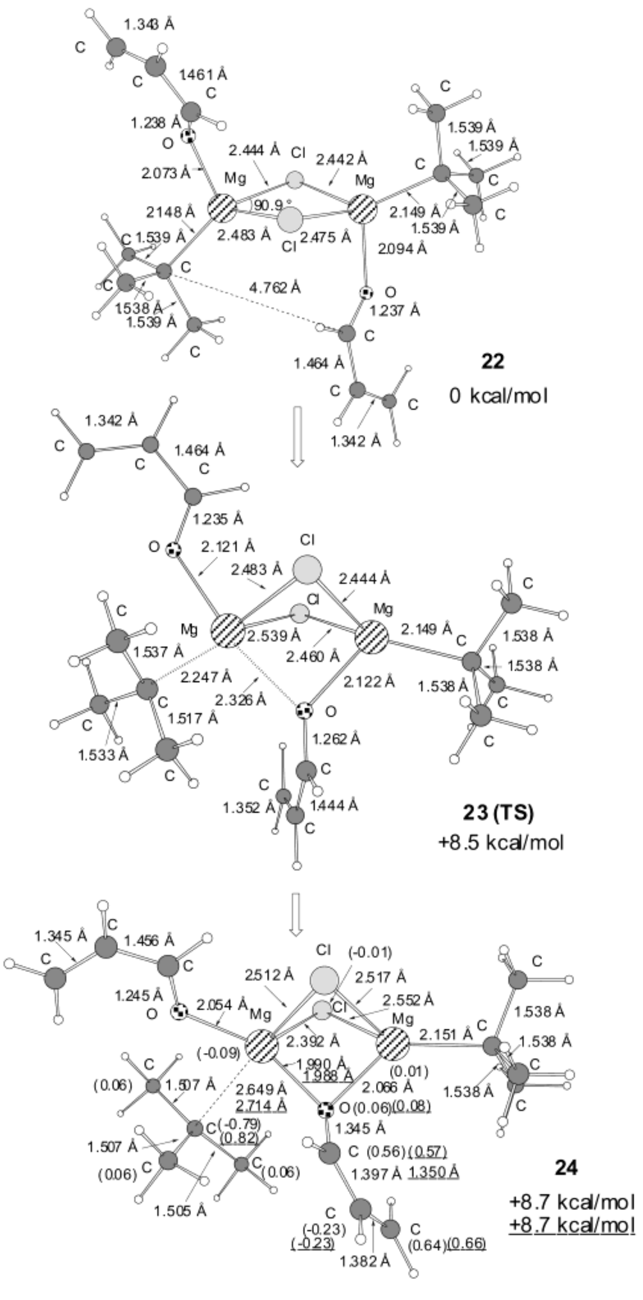


FIGURE 3. Geometries of $(^{t}\mathrm{Bu{-}Mg{-}Cl})^{2}\cdot(\mathrm{acrolein})_2$ optimized by (U)B3LYP/6-31G*SCRF. Those models are explained in Scheme 10. For **23** and **24**, the singlet biradical state was calculated with the symmetry-broken (iop(4/13 = 1)) initial orbitals. In **24**, the triplet-spin geometry optimized data are shown by the underlined numbers. In **24**, spin densities are exhibited in paretheses.

from the dimeric reactant (precursor), **22**. As a result, a singlet biradical forming path was found uniquely and is shown in Scheme 10 and Figure 3. The carbonyl oxygen approaches the left-side Mg, which is similar to the four-center reaction in Scheme 6. However, instead of the simultaneous C- - -C bond formation, the ^{t}Bu group is pushed away from Mg. The motion is described in TS **23** (see reaction-coordinate vectors in Figure S5 of Supporting Information).[18] A singlet biradical **24** is yielded, where the spin densities are localized on the tertiary carbon of ^{t}Bu and on three carbon atoms of the reaction-center acrolein. Noteworthy is a very small spin density on the left-side Mg atom despite the Mg−C homolytic dissociated product. The left-side Mg persists the tetravalency, and the ^{t}Bu group has been pushed away. In **24**, two singlet radical centers ($^{t}\mathrm{Bu}^{\bullet}$ and $\mathrm{O{-}CH{=}CH{-}CH_2}^{\bullet}$) are distant, and the corresponding triplet state has a similar geometry and similar spin density (except signs) distributions.[19] In **24**, an allyl radical moiety is formed. Radical−radical recombinations leading to the normal Grignard addition and the conjugate addition are possible. In fact, the reactions of α,β-unsaturated carbonyl compounds (e.g., 3-hexen-2-one, 4-methyl-3-penten-2-one, 2-cyclohexenone, *tert*-butyl crotonate, and crotonaldehyde) give 1,2-adducts and 1,4-adducts.[20] Both polar and homolytic mechanisms for conjugate addition are suggested, depending on the substrate and the substrate conformation by kinetic study.[20a]

The singlet biradical intermediate **24** is less stable ($\Delta E_{\mathrm{el}} = +8.7$ kcal/mol, the difference of total electronic energies) than precursor **22**. When the *tert*-butyl group

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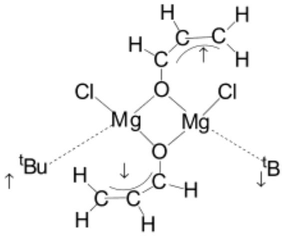
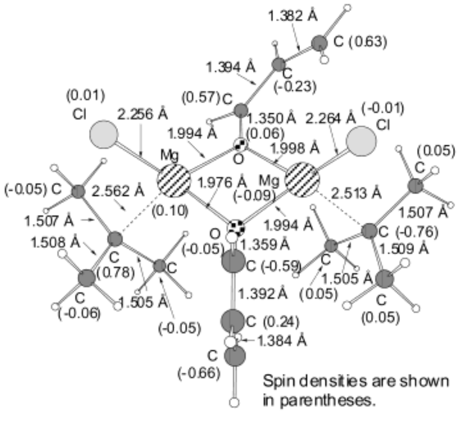
[18] When the Mg- - -O distance is decreased, the Mg- - -C distance is enlarged gradually. The partial optimizations with a fixed Mg- - -O distance were repeated, and a complex potential surface with various extremely shallow energy minima was found. A local minimum with smaller relative energy than that (=8.5 kcal/mol) of **23** (TS) was sought. However, the attempted geometry converged to that of **24** probably due to the complex potential curve and spin contamination, and **24** was calculated to be slightly less stable than **23** (TS).

[19] The second Mg- - -O approach is possible via a route corresponding to **8** → **10** → **12** in Figure S2. A symmetric singlet-spin radical geometry **25** was obtained.



25
+14.1 kcal/mol



Since four radical centers are distant with each other, triplet and quartet spin states have almost the same energies as that of the open singlet (**25**). The triplet or quartet radicals have also the same symmetric structures as that of **25**. The triplet or quartet radicals would be related to intermediates detected by ESR spectroscopy (ref 1h and (a) Maruyama, K.; Hayashi, J.; Takagiri, T. *Chem. Lett.* **1987**, 731. (b) Maruyama, K. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 897).

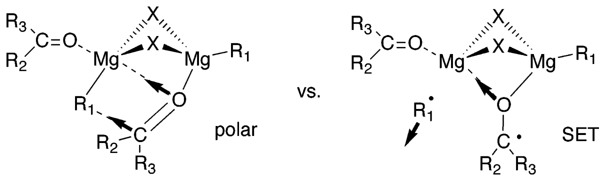
[20] (a) Holm, T. *Acta Chem. Scand.* **1991**, *45*, 925. (b) Coburn, E. R. *Organic Synthesis*; Wiley & Sons: New York, 1955; Collect. Vol. No. III, p 696. (c) Munch-Petersen, J. *Organic Synthesis*; Wiley & Sons: New York, 1973; Collect. Vol. No. V, p 762. (d) Prout, F. S.; Hartman, R. J.; Huang, P.-Y.; Korpics, C. J.; Tichelaar, G. R. *Organic Synthesis*; Wiley & Sons: New York, 1963; Collect. Vol. No. IV, p 93.

is separated infinitely, the instability, $\Delta E_{\text{el}} = +13.7$ kcal/mol, was calculated. However, the instability is canceled out in Gibbs free energies. This Gibbs free energy (T = 300 K) of $^{t}\text{Bu}^{\bullet}$ and the residual radical ($=(\mathbf{24}-{}^{t}\text{Bu})^{\bullet}$) is 1.0 kcal/mol smaller (more stable) than that of **22**. As the temperature is raised (T > 300 K), the biradical separated state is further more stable than precursor **22**. This stability ($\Delta G = -1.0$ kcal/mol, $T = 300$ K) of the homolytically dissociated products (two doublet radicals, $^{t}\text{Bu}^{\bullet}$ and $(\mathbf{24}-{}^{t}\text{Bu})^{\bullet}$ compared to **22** is in sharp contrast to the significant instability ($\Delta G = +24.9$ kcal/mol) of homolytically dissociated products from **6** (Figure 1), $\text{Me}^{\bullet}$, and the residual radical, $(\mathbf{6}-\text{Me})^{\bullet}$. The precursor **6** cannot cause such a reaction as in Figure 3. SET is entropy-driven in the reaction between ^{t}Bu−Mg−Cl and acrolein.

In view of the present calculated results, the SET mechanism would be described as follows. Basically, the polar four-center reaction in Scheme 6 gives C−C bond formation. However, when the alkyl group is bulky, only the two-center (Mg−O) reaction takes place. The alkyl−Mg bond is cleaved homolytically owing to the persistent Mg tetravalence and stability of the resultant radical species. Biradical intermediates are, thus, formed not by a single electron transfer but by the C−Mg homolytic scission.

Concluding Remarks

SCHEME 11. Slightly Different Geometric Changes Lead to Two Mechanisms



This work has revealed a new mechanism of additions of Grignard reagents to carbonyl compounds. The mechanism has been thought to be very complex by aggregation and a competing SET mechanism. No attempts to elucidate the correlation between the Schlenk equilibrium and the addition path have been made so far. However, our results seem to provide simple and realistic pathways. The Grignard addition occurs in a dimeric dichloride bridged form. A vicinal-magnesium bonding alkyl and C=O interaction causes C−C bond formation via a four-center interaction in Scheme 11 (polar mechanism). When the interaction is improbable owing to the steric effect, the Mg- - -O=C bond formation precedes the C−C bond formation and the Mg−C bond is ruptured (SET). The rupture is caused by the preference of the tetravalency of the Mg atom, where the preference is ambiguous (e.g., elongation and weakening of the bridged Mg−Cl bonds) in the polar mechanism.

Solvent ether molecules may be bound effectively and flexibly to Mg atoms for their tetravalency. When only the reactants $(\text{R}_1-\text{Mg}-\text{X})_2$ and $(\text{R}_2\text{R}_3\text{C}=\text{O})_2$ are taken into account (e.g., in Scheme 5), trivalent Mg states such as **10** and **12** are inevitably formed. The solvent molecules compensate for lack of chemical bonds on Mg atoms through participation by appropriate Mg−O coordination bonds. Even in this case they do not interfere with intrinsic reaction channels.

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Supporting Information Available: Supporting Information Available. Optimized structures of **1a**−**3a**, **1b**−**3b**, **9**(TS), **10**, **11**(TS), **12**, **6**−**Br**, **7**−**Br**(TS), **8**−**Br**, **16**, **17**(TS), **18**, **19**, **20**(TS), **21** (Figures S1−S3, S4a, S4b). Reaction−coordinate vectors for **7**(TS), **14**(TS), **23**(TS) (Figure S5), Cartesian coordinates, total energies and imaginary frequencies for TS in all the optimized geometries. This information is available free of charge via the Internet at http://pubs.acs.org.

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