ORGANIC
LETTERS

2011
Vol. 13, No. 8
2046–2049

How To Prepare a Chiral Grignard Reagent: A Theoretical Proposal

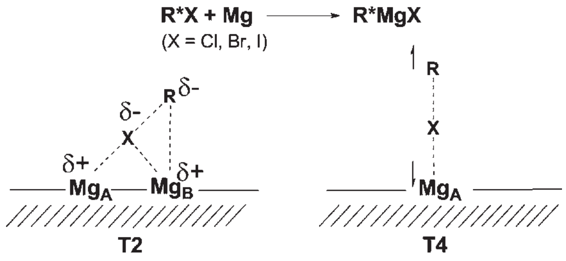
Zhe-Ning Chen, Gang Fu, and Xin Xu*

State Key Laboratory of Physical Chemistry of Solid Surfaces; College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China

xinxu@xmu.edu.cn

Received February 18, 2011

ABSTRACT



It is shown that two competitive pathways (T2 vs T4) exist for Grignard reagent formation. While the nonradical pathway T2 leads to retention of the configuration, the radical pathway T4 gives racemization. Our calculations suggest the way that T2 can be enhanced, which should be of significance to prompt new synthesis approaches for the preparation of chiral Grignard reagents.

Recently, the chiral Grignard reagent (R*MgX, X = Cl, Br, I), where the magnesium atom is bonded directly to the asymmetric carbon center, has attracted growing attention, as it is a potential building block in stereoselective synthesis and can be used as a probe molecule in the mechanistic investigation.[1,2] However, very few optically enriched Grignard reagents are known up to now, because Grignard reagent formation (denoted as GRF hereinafter) usually involves radical intermediates such that R*X would have lost its stereochemical configuration during the reaction.[3] Fundamental questions thus emerge: Is it possible to directly synthesize a chiral Grignard reagent? If so, how to prepare it?

The desire to better control GRF demands an atomic level understanding of its mechanism. On the basis of the results of product analyses, Walborsky et al.[3a,b] postulated a mechanism that involves an inner sphere electron transfer and/or an outer sphere electron transfer. The former leads to a tight radical pair, where a radical anion ($^{\bullet}R{-}X^{-}$) is in close association with a univalent magnesium cation ($^{\bullet}Mg^{+}$). Collapse of this tight radical pair gives a Grignard reagent with complete retention of its configuration. The latter leads to a loose radical pair of the carbon radical $R^{\bullet}$ and $^{\bullet}MgX$, where $R^{\bullet}$ can rotate by 180° relative to the surface, yielding a racemic Grignard reagent. A key integrant in the Walborsky mechanism is that $R^{\bullet}$ remains adsorbed at the Mg surface until it undergoes radical reduction to form RMgX.[3a−d] However, Garst et al.[3c,d] provided compelling experimental evidence showing that $R^{\bullet}$ can actually diffuse in solutions, leading to large extents of racemization. Garst et al.[3c,d] also suggested that there must be an alternative, pathway **X**, that competes with the radical pathway to account for the observed partial retention of configuration.[3c,d] Even though its nature remains to be explored, Garst et al. postulated that, along pathway **X**, there is no intermediate $R^{\bullet}$ or, if there is, it has an extremely short lifetime.[3c,d] On the basis of their photomicrography results, Bowyer and co-workers[4] claimed that the rate-limiting step in GRF is not a step-wised electron transfer/bond cleavage process, instead it is a process involving a magnesium atom direct insertion into the R−X bond. Although modern computational tools should, in principle,

---

(1) Hoffmann, R. W.; Hölzer, B.; Knopff, O.; Harms, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3072.

(2) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225.

(3) Some reviews: (a) Hamdouchi, C.; Walborsky, H. M. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996; Chapter 10. (b) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286. (c) Garst, J. F.; Ungváry, F. In *Grignard Reagents: New Developments*; Richey; H. G., Jr., Ed.; Wiley: Chichester, UK, 2000; Chapter 7. (d) Garst, J. F.; Soriaga, M. P. *Coord. Chem. Rev.* **2004**, *248*, 623.

(4) Beals, B. J.; Bello, Z. I.; Cuddihy, K. P.; Healy, E. M.; Koon-Church, S. E.; Owens, J. M.; Teerlinck, C. E.; Bowyer, W. J. *J. Phys. Chem. A* **2002**, *106*, 498.

(5) Davis, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 4145.

(6) Liu, L.; Davis, S. R. *J. Phys. Chem.* **1991**, *95*, 8619.

(7) Jasien, P. G.; Abbondondola, J. A. *THEOCHEM* **2004**, *671*, 111.

10.1021/ol200450b

provide an atomic level understanding of GRF,[5–8] no such study concerning the chirality of RMgX has been realized up to now. In this contribution, we present a systematic DFT study of GRF. Our purpose is to understand (1) how the R–X is activated, (2) what factors determine the reactivity, and (3) under what condition the product will maintain its chirality. We expect that answers to these questions will stimulate a new synthesis approach to directly prepare the chiral Grignard reagent.

At first, the reactions of Mg_4 with methyl halides (CH_3X, X = Cl, Br, I) are used as model systems to explore all possible R–X activation mechanisms by Mg surfaces. Here, we have located four possible pathways in which **T1**–**T3** belong to the concerted nonradical processes, while **T4** leads to the formation of radical species (see Figure 1). The calculated energetics and the stereochemistry of the products are listed in Table 1.

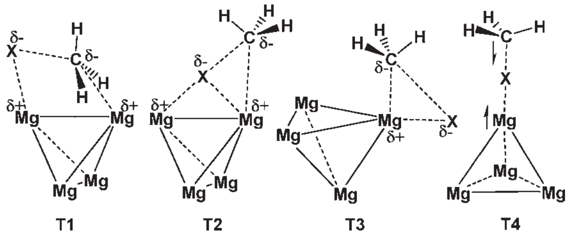


Figure 1. Possible pathways for H_3C-X bond activation by Mg_4 cluster. No pathway is found for X approaching a face of Mg_4.

Table 1. Calculated Reaction Barriers and Stereochemistry of the Reaction Products of ($CH_3X + Mg_4$)

			$\Delta H^{\ddagger}$ (kcal/mol)			
pathway	reaction mode	active site	Cl	Br	I	stereo configuration of product
T1	four-centered	Mg–Mg pair	22.1	18.2	14.4	inversion
T2	four-centered	Mg–Mg pair	16.4	15.0	16.7	retention
T3	three-centered	single Mg	20.6	20.8	24.3	retention
T4	radical	single Mg	7.5	5.0	4.6	racemization

Although **T1** and **T2** both involve four-center transition states, the geometric difference between them is dramatic. In **T1**, the C–X bond is nearly in parallel with a Mg–Mg bond. Unlike that in **T1**, CH_3X adsorbs obliquely in **T2**, with the X atom approaching a Mg–Mg bridge site. Our calculations show that **T1** depends strongly on the strength of the C–X bond. The general trend of the reactivity of CH_3X via **T1** is Cl (22.1 kcal/mol) < Br (18.2) < I (14.4). On the other hand, the calculated barriers for **T2** are nearly constant (15.0–16.7 kcal/mol). This can be rationalized by the competition between two opposing factors—the bond strength and the bond polarity of the forth-breaking C–X bond.[9] In a previous work, Porsev and Tulub[8a] have compared the **T1** and **T2** pathways for CH_3Cl activation and suggested that **T2** is more favorable. Our calculations show that **T2** is feasible for X = Cl or Br, while **T1** favors over **T2** when X = I. **T3** belongs to the oxidation addition mechanism, which occurs through a cyclic three-center transition state, with simultaneous formation of the new $Mg-CH_3$ and Mg–X bonds. Previously, Jaisen[7] claimed that such a process cannot be obtained over Mg clusters. Here we actually locate **T3** for each CH_3X. The calculated barriers of **T3** follow the trend Cl (20.6 kcal/mol) < Br (20.8) < I (24.3), in antiparallel with the polarity of the C–X bond. Hence, the three-center pathway is generally less favorable than the four-center counterpart. By using the open-shell wave functions, we are able to find diradical transition states (**T4**), as shown in Figure 1. Geometrically, the $Mg\cdots X\cdots CH_3$ in **T4** is nearly linear. Spin analysis shows that one spin density is delocalized over the Mg_4 cluster, while the other opposite spin density is located mainly on the carbon atom. Thus, the direct product of **T4** is a radical pair involving $^{\bullet}Mg_4X$ plus $CH_3^{\bullet}$. The calculated barriers for **T4** decrease from Cl (7.5 kcal/mol), to Br (5.0), to I (4.5), consistent with the decreasing tendency of the C–X bond strength. Significantly, in the viewpoint of the activation barrier heights, **T4** is superior to those of the concerted transition states (**T1**–**T3**).

The stereochemistry of product is often used as a probe of the reaction mechanism.[3] Although the methyl halide does not have optical activity, it can serve as a prototype to demonstrate how configuration changes along different transition states. We performed detailed intrinsic reaction coordinate (IRC) calculations for X = Cl and concentrated on the configurational change of the CH_3 group (see the SI for details). It is found that the configuration is inversed in the product via **T1**, while the original configuration is retained in the product via **T2** or **T3**. Here **T4** leads to a sp^2 carbon center of free radical. Hence, a racemic product is anticipated.

Experimentally, Walborsky and co-workers provided the first example for stereochemistry of the chiral Grignard reagent formation.[3b] On the basis of the results of a cyclopropyl system, they showed that up to 27% retention of optical activity was achieved. To account for these stereochemistry experiments, we propose here that not only the radical but also the nonradical mechanism should be involved in GRF, and the most plausible combination is **T2** plus **T4**. We notice that, over the Mg_4 cluster models, the predicted barrier for **T2** is too high to be competitive with **T4**. Previously, Jaisen and Abbondondola[7] have shown that the calculated barrier for C–Cl bond cleavage generally decreases with the size of the Mg clusters being increased. However, the transition states they located bear more resemblance to **T1**, rather than **T2**, in structure. To elucidate the cluster size effect, we further extend our investigation to bigger Mg clusters. Unlike those used in Jaisen's study,[7] where the larger magnesium clusters were built up from the

---

(8) (a) Porsev, V. V.; Tulub, A. V. *Dokl. Phys. Chem.* 2006, *409*, 634. (b) Porsev, V. V.; Tulub, A. V. *Dokl. Phys. Chem.* **2008**, *419*, 71.

(9) Fu, G; Xu, X; Wan, H. L. *Catal. Today* **2006**, *117*, 133.

transition state structures of smaller clusters by adding Mg atoms to give the clusters a pseudospherical shape, we choose a set of the most stable Mg_n clusters ($n = 5, 7, 9, 10, 11, 15, 17, 20$) with high symmetry, as found in the recent theoretical study of Jellinek and Acioli.[10,11] We will then concentrate on the most viable pathways **T2** and **T4**.

When $n > 4$, the Mg_n cluster exhibits a diversity of reactive sites and is expected to have rich chemistry. Here, we employ Mg_9 as an instructive case to demonstrate how frontier orbitals affect the reactivities and how to characterize the reactivity of a specific site. Theoretically, the most stable structure of Mg_9 is of D_{3h} symmetry, having two kinds of inequivalent Mg atoms (Mg_A and Mg_B) as shown in Figure 2. The frontier molecular orbitals of Mg_9 and CH_3Cl are also illustrated in Figure 2. We can see that the highest occupied molecular orbital (HOMO) of Mg_9 mainly derives from 3s orbitals of Mg_A atoms, while the lowest unoccupied molecular orbital (LUMO) is mostly made of 3p orbitals of Mg_B atoms. On the other hand, the HOMOs of CH_3Cl are degenerate, having heavy lone-pair character of Cl, while the major contribution of the LUMO of CH_3Cl corresponds to the σ^* orbital of the C−Cl bond.

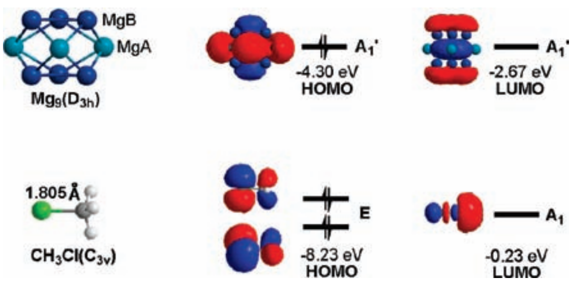


Figure 2. Frontier orbitals of Mg_9 and CH_3Cl. Inequivalent Mg atoms are identified as Mg_A and Mg_B, respectively.

Similar to those of Mg_4, we have located the transition state structures for the activation of CH_3Cl over the Mg_9 cluster (see the SI for details). For **T2**, our calculations show that inequivalent Mg−Mg pair leads to different reactivity in which the transition state via Mg_A-Mg_B is 1.4 kcal/mol lower in energy than that via Mg_B-Mg_B. This can be attributed to the more favorable orbital interaction involved in the former case: the C−Cl σ^* orbital points to Mg_A with appreciable electron density of the Mg_9 HOMO, while the lone-pair of Cl approaches the adjacent Mg_B where the Mg_9 LUMO protrudes outward (cf. Figures 1 and 2). Castleman et al.[12] have investigated the dissociative adsorption of H_2O over Al cluster anions. Interestingly, they suggested that such kind of Al−Al pair offers the active site and claimed that the interaction is initiated by the "nucleophilic" attack of water toward the Al surface. However, in our case, the reaction of CH_3Cl with Mg_9 is more "electrophilic" than "nucleophilic" as HOMO of CH_3Cl is too low-lying, while HOMO of Mg_9 is relative high-lying, liable to donate electrons to LUMO of CH_3Cl. Unlike that in **T2**, only a single Mg atom is required as the active site in **T4**. Interactions in **T4** are also sustained by the electron donation from Mg clusters to σ^* of the C−Cl bond. Our calculations show that **T4** over Mg_A is 0.5 kcal/mol more favorable than **T4** over Mg_B. We further perform test calculations by using other Mg clusters. The conclusion can be drawn that the best active site, either for **T2** or for **T4**, is where there exists high electron density in HOMO of each Mg cluster (i.e., the Mg_A sites). Our calculations also suggest that such sites are generally associated with the Mg atoms with low coordination. These findings lend some support to the experimental observations that GRF accelerates at the defect site of Mg surfaces, i.e. at corners, or at edges.[13]

We would like to make some connections between our **T2** and **T4** and those models proposed in the literature. **T4** carries a clear radical nature, which offers a quantitative model for Garst's radical pathway,[3c,d] leading to large extents of racemization. It may also be related to Walborsky's "loose radical pair".[3a,b] An interesting feature of **T4** is its geometry. $R^\bullet$ is sufficiently separated from the Mg surface to permit rotation. It shall first diffuse in solution and then rebound to the surface, leading support to Garst's "D model".[3c,d] **T2** provides a way to characterize Garst's pathway **X**[3c,d] or Bowyer's concerted insertion mechanism[4] and shows some similarities to Walborsky's tight radical pair.[3a,b] Since the R−X molecule possesses an electric dipole moment, it polarizes Mg as it approaches the Mg surface with halogen X pointing toward Mg_A at which the large lobe of electron density of HOMO locates. In such a way, the interaction between Mg HOMO and R−X σ^* is initiated, resulting in a net electron transfer to yield a negatively charged RX moiety. There may be no radical character explicitly shown in **T2**, which, instead, carries some charge separation. Thus a more polar solvent may favor **T2** over **T4**.

Since ionization potentials (IPs) of Mg clusters generally correlate with their energy levels of HOMOs, we expect that IPs would also correlate with the barrier heights via **T2** and **T4** (see Figure 3). Here, the active Mg_A sites are chosen in a manner as discussed above, and the IPs are estimated by the vertical detachment energies (VDEs). Indeed, the calculated barriers of **T2** and **T4** both correlate well with the IPs, albeit with different slopes. With decrease of IPs as Mg clusters grow large, the gaps between two series of barriers become narrow, from 8.9 kcal/mol for Mg_4, to 5.8 kcal/mol for Mg_{10}, to 1.7 kcal/mol for Mg_{17}. This indicates that along with the increased size of Mg clusters, the nonradical route (**T2**) becomes competitive with the radical route (**T4**). Hence there is indeed a chance for partial retention of the configuration in GRF.

The involvement of the nonradical pathway shall also depend on the nature of halides. For Mg_4, we find that the energy difference between **T2** and **T4** increases from 8.9 kcal/mol for Cl, to 10.0 kcal/mol for Br, to 12.1 kcal/mol for

---

(10) Jellinek, J.; Acioli, P. H. *J. Phys. Chem. A* **2002**, *106*, 10919.

(11) Acioli, P. H.; Jellinek, J. *Phys. Rev. Lett.* **2002**, *89*, 213402.

(12) Roach, P. J.; Woodward, W. H.; Castleman, A. W., Jr.; Reber, A. C.; Khanna, S. N. *Science* **2009**, *323*, 492.

(13) (a) Teerlinck, C. E.; Bowyer, W. J. *J. Org. Chem.* **1996**, *61*, 1059. (b) Koon, S. E.; Oyler, C. E.; Hill, J. H. M.; Bowyer, W. J. *J. Org. Chem.* **1993**, *58*, 3225.

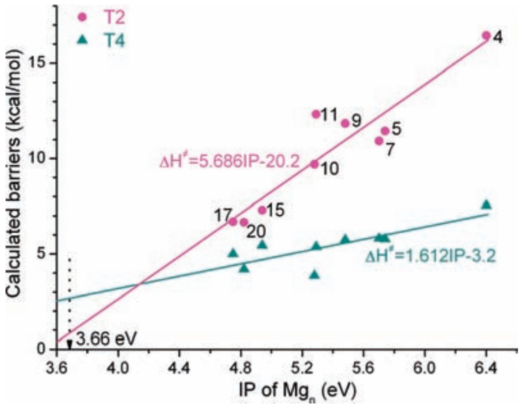


Figure 3. Plots of calculated barriers of **T2** or **T4** versus the IPs of Mg_n clusters. Arabic numbers represent the value of *n* for Mg_n clusters. The position for the work function of polycrystalline Mg (3.66 eV[14]) is indicated.

I, while for Mg_{17}, these differences are calculated to be 1.7, 2.5, and 8.6 for X = Cl, Br, I, respectively. Experimentally, Walborsky et al.[3b] showed that, for a cyclopropyl system, up to 27% retention of optical activity was achieved for X = Cl, while those for X = Br and I were 19% and 2%, respectively. All these suggest that chloride is the best candidate for the preparation of a chiral Grignard reagent.

In the common method of preparing a Grignard reagent, metallic Mg is used as turnings, chips, or powders. Undoubtedly, the Mg used behaves as bulky magnesium, whose electronic nature can be significantly different from that of a Mg cluster at nano scale. For instance, a 1.1 eV gap exists between HOMO and LUMO for Mg_{17} and the calculated IP (4.75 eV) is significantly higher than the work function of polycrystalline Mg (3.66 eV[14]). By using linear fitting, the predicted barriers can be extrapolated to the IP of 3.66 eV. As shown in Figure 3, the **T2** and **T4** lines intersect when IP is around 4.1 eV. This gives a strong indication that the nonradical mechanism (**T2**) can have a chance to be competitive with or even dominant over **T4** if Mg_A sites are preserved on bulky Mg. This can be rationalized by considering that **T2** belongs to a two-electron reduction process, which benefits more from low IP than the single electron process (**T4**).

Mechanisms of GRF can be divided into two parts, organic and inorganic.[3c,d] The organic part traces R from RX to the products, while the inorganic part traces Mg from bulk Mg to RMgX. The inorganic mechanism has received far less attention than the organic part. Our calculations reveal that GRF can be facilitated by two factors concerning the inorganic part of Mg, i.e., low coordinated Mg_A sites in conjunction with low IP. However, these two factors are hard to reconcile in standard experimental condition. On one hand, a Mg cluster has abundant low-coordinated sites, but its high IP restricts the reactivity and propensity for **T2**. On the other hand, the bulk Mg has low IP, but lacks reactive sites. We suggest that Rieke Mg[15] should have high reactivity and stereoselectivity at the same time, as it is well-divided Mg with rich Mg_A sites, while it is of micro scale with bulk-like IP.

Clearly the organic part of the GRF mechanism, i.e., the nature of the R group, is another key factor that influences the reactivity as well as the stereoselectivity. Here, we explore the R effect by using cyclopropyl chloride and vinyl chloride with Mg_{17} being used as the model surface. Our calculations have shown that the predicted bond energies for cyclopropyl chloride and vinyl chloride are 83.5 and 87.7 kcal/mol, respectively, which are significantly larger than that for methyl chloride (76.2 kcal/mol). The calculated barrier of **T4** increases from methyl chloride (5.0 kcal/mol), to cyclopropyl chloride (8.0 kcal/mol), and to vinyl chloride (11.9 kcal/mol), indicating that **T4** is enthalpy controlled. Significantly, for vinyl chloride, GRF actually proceeds via **T2** instead of **T4**, such that **T2** is 2.0 kcal/mol more favorable than **T4** on Mg_{17}. This finding echoes Garst's postulation that there shall be a dominant nonradical mechanism for vinyl and aryl halides,[3c,d] and also provides theoretical support to Walbosky's experiments on the difference of the vinyl and cyclopropyl systems in stereochemistry.[3a,b]

In summary, our calculations suggest that in certain conditions, the nonradical pathway (maintenance of chirality) can indeed be dominant over the radical one (racemazation) such that the chirality in the reactant can be retained in the product. We show that chloride is better than other halides in maintaining its optical configuration. We suggest that Rieke Mg should be good for reactivity as well as for stereoselectivity. Our calculations reveal that the vinyl system is more optically stable than cyclopropyl and alkyl systems during GRF. We anticipate that these findings can prompt new synthesis approaches for the preparation of chiral Grignard reagents.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (Grant Nos. 91027044 and 20923004), and the Ministry of Science and Technology (Grant Nos. 2007CB815206 and 2011CB8504).

Supporting Information Available. Computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(14) Lide, D. R., Eds. *CRC Handbook of Chemistry and Physics*, 74th ed.; CRC Press: Boca Raton, FL, 1993; pp 12−105.

(15) Rieke, R. D. *Science* **1989**, *246*, 1260.