Mechanism of Grignard Reagent Formation. The Surface Nature of the Reaction

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The reaction of organic halides (Br, Cl, I) with magnesium metal to yield what is referred to today as a Grignard reagent has been known since the turn of the century.[1] The name derives from its discoverer, Nobel laureate Victor Grignard. How this reagent is formed, that is, how a magnesium atom is inserted into a carbon-halogen bond, is the subject of this Account.

$$RX + Mg \rightarrow RMgX$$

Kharasch and Reinmuth,[2] persuaded by the work of Gomberg and Bachman[3] as well as by product analyses of many Grignard formation reactions that existed in the literature prior to 1954, speculated that the reaction involved radicals and that the radical reactions might involve "surface adherent radicals, at least in part". The mechanism they suggested postulated a surface of magnesium containing some monovalent magnesious species. The monovalent magnesium could be formed when one added iodine as an "activator" or from some Wurtz reaction which produced MgX_2. Disproportionation of MgX_2 on the metal surface would produce a magnesious species (Mg) whose interaction with the magnesium metal surface would lead to what Kharasch and Reinmuth refer to as "points of unsaturation" on the surface. (See Scheme I.)

Kharasch and Reinmuth also proposed that the side products observed during the formation of Grignard reagents such as those due to dimerization, disproportionation, and reaction with solvent resulted from "surface-adherent" radicals. They viewed these side reactions as taking place at the solid-liquid interface.

It was shortly after the publication of the Kharasch-Reinmuth book[2] that we commenced our study into the mechanism of the Grignard formation reaction. It was decided that besides product analyses the *stereochemistry* of the reaction would be used as a probe. In other words, does the insertion of a magnesium atom into the carbon-halogen bond lead to inversion of configuration, retention of configuration, or complete loss of configuration (racemization)? In order for this type of an investigation to be conducted, a chiral halide that would not ionize in solution in the presence of metal ions was needed. The first system that came to mind was the cyclopropyl system since it was known that even cyclopropyl tosylates do not solvolyze at an appreciable rate,[4] i.e., cyclopropyl tosylate in acetic acid at 25 °C had $k_1 = 5.7 \times 10^{-13}$ s^{-1} and 1-methylcyclopropyl tosylate under the same conditions gave $k_1 = 6.2 \times 10^{-10}$ s^{-1}. Another system that meets the above criterion is the vinyl system. The lack of reactivity of vinyl halides toward S_N1 reactions is well-known and is exemplified by the low solvolysis rate of 2-propenyl triflate[5] in 80% ethanol at 25 °C, k_1 being 9.8×10^{-8} s^{-1}.

Scheme I
Kharasch-Reinmuth Mechanism for Grignard Reagent Formation

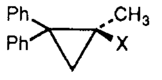
$$(1)\ (Mg^0)_x(Mg^\bullet)_{2y} + RX \longrightarrow [(Mg^0{}_x)(Mg^\bullet)_{2y-1}(^\bullet MgX) + R^\bullet] \longrightarrow (Mg^0)_{x-2}(Mg^\bullet)_{2y}(MgX)(MgR)$$

$$(2)\ (Mg^0)_{x-2}(Mg^\bullet)_{2y}(MgX)(MgR) + RX \longrightarrow (Mg^0)_{x-4}(Mg^\bullet)_{2y+2} + 2RMgX$$

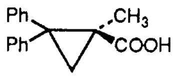
Another criterion that must be met is that, once formed, the carbon-magnesium bond should be configurationally stable under the conditions of the reaction. At the time we were designing our system, this information was not available. However, as will be demonstrated, both the cyclopropyl-magnesium bond and the vinyl-magnesium bond do in fact retain their configurations.

Chiral Systems

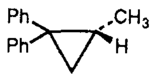
(a) Cyclopropyl. The cyclopropyl system selected for investigation was 1-halo-1-methyl-2,2-diphenylcyclopropane (**1**, X = Cl, Br, I). The absolute configurations of **1** (X = Cl, Br, I) as well as their derivatives **2** and **3** have been established.[6,7] With this knowledge as well as the specific rotations in hand, one is now able to determine the stereochemistry and optical purities of the products resulting from the conversion of **1** to, for example, **2** or **3**. All stereochemical structural formulas in this Account are written in their absolute configurations.



(*S*)-(+)-**1**: X = Cl, Br, I



(*S*)-(−)-**2**



(*R*)-(−)-**3**

(b) Vinyl. The chiral vinyl systems used in this study were (4-methylcyclohexylidene)bromomethane (**4**) and chiral (4-methylcyclohexylidene)bromoethane (**5**). The absolute configurations and optical purities have

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[1] Grignard, V. *C. R. Hebd. Seances Acad. Sci.* **1900**, *130*, 1322. For a 1971 symposium celebrating 100 years since Grignard's birth, see: *Bull. Soc. Chim. Fr.* **1972**, 2131.

[2] Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*; Prentice-Hall: New York, 1954.

[3] Gomberg, M.; Bachman, W. E. *J. Am. Chem. Soc.* **1927**, *49*, 236.

[4] Schleyer, P. v. R.; Sliwinski, S. W.; van Dine, G. W.; Schöllkopf, U.; Paust, J.; Echenberger, K. *J. Am. Chem. Soc.* **1972**, *94*, 125.

[5] Stang, P. S.; Summerville, R. *J. Am. Chem. Soc.* **1969**, *91*, 4600.

[6] Walborsky, H. M.; Pitt, C. G. *J. Am. Chem. Soc.* **1962**, *84*, 4831.

[7] Walborsky, H. M.; Barash, L.; Young, A. E.; Impastato, F. J. *J. Am. Chem. Soc.* **1961**, *83*, 2517.

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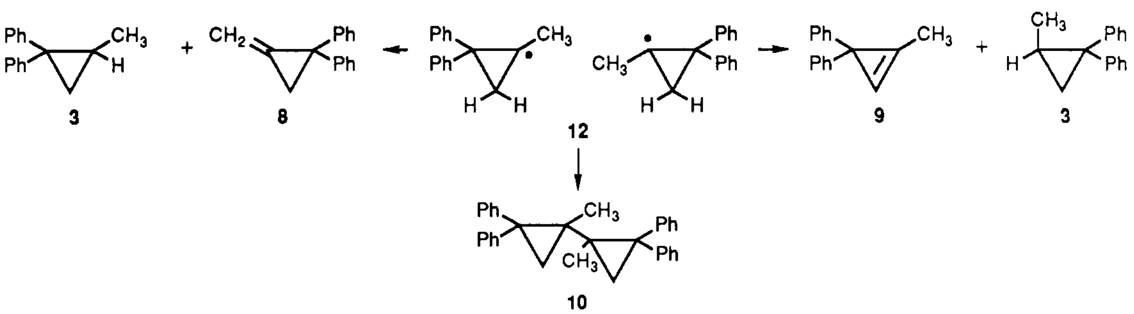
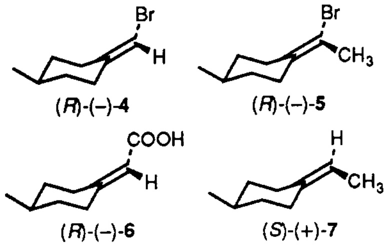
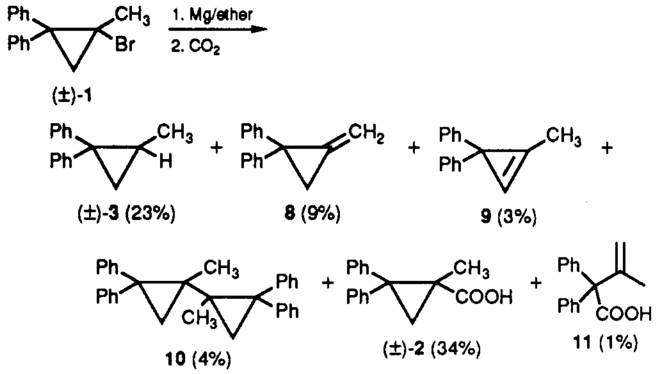


been determined[8-10] for 4 and its related carboxylic acid 6 as well as for 5 and its related hydrocarbon 7.

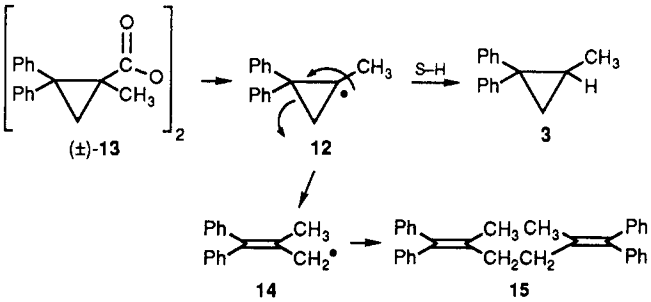


The Radical-Surface Nature of the Reaction

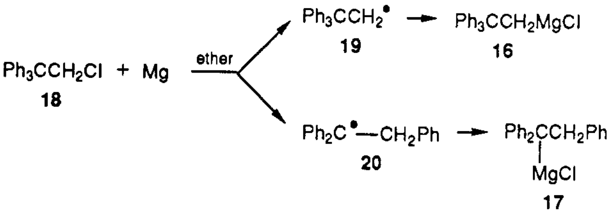
It has been recognized and generally agreed upon that the formation of Grignard reagents involves the intermediacy of free radicals.[2,3,11-13] Product analyses provided the major evidence: the formation of biphenyl in the reaction of magnesium with bromobenzene,[14] the lack of stereospecificity in the reaction of geometrically isomeric vinyl halides,[15] and as we have shown, the loss of optical activity in the reaction of chiral cyclopropyl halides.[16] Moreover, the hydrocarbon fraction from the reaction of the cyclopropyl halide[16] consisted of products that were entirely different from those obtained from the corresponding radicals generated in solution under homogeneous conditions. The hydrocarbons 3 and 8–10 result from the disproportionation and dimerization of the cyclopropyl radical[17] 12 on or at the surface of magnesium. Some of hydrocarbon 3 may also be formed as the result of hydrogen abstraction from solvent by radical 12 leaving the surface. This was demonstrated by performing the reaction in diethyl ether-d_{10}. A 20% yield of 3 was isolated which was shown to contain 7% deuterium in the 1-position.



When radical 12 is generated in ether solution by decomposition of the diacyl peroxide 13, the hydrocarbons formed[18] are 3 and 15 in a ratio of 1.3:1. Radical 12 abstracts a hydrogen atom from diethyl ether (S–H) to form 3 and also ring opens to the more stable allyl radical 14, which dimerizes to yield 15. This dimer is not observed in Grignard formation although radical 14 is a precursor to 11.



Grovenstein,[19] after showing that the Grignard reagents 16 and 17 from the reaction of 2,2,2-triphenylethyl chloride 18 with magnesium in diethyl ether were stable, concluded that the rearrangement products observed (17–41%) were due to radical 19 being formed during the Grignard formation step. Radical 19 rearranged by phenyl migration to radical 20. The results of Grovenstein,[19] which involved a magnesium surface, should be contrasted with those of Curtin,[20] who generated radical 19 under homogeneous conditions following the radical decarbonylation procedure of Winstein and Seubold.[21] Under these homogeneous conditions radical 19 rearranges *completely* to radical 20



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(8) Perkin, W. H.; Pope, W. L. *J. Chem. Soc.* **1911**, *99*, 1510.

(9) Gerlach, H. *Helv. Chim. Acta* **1966**, *49*, 1291.

(10) Walborsky, H. M.; Banks, R. B. *Bull. Soc. Chim. Belg.* **1980**, *89*, 849 and references cited therein.

(11) Ashby, E. C. *Q. Rev., Chem. Soc.* **1967**, *21*, 259.

(12) Walborsky, H. M.; Young, A. E. *J. Am. Chem. Soc.* **1961**, *83*, 2595. Walborsky, H. M. *Rec. Chem. Prog.* **1962**, *23*, 75.

(13) Grootveld, H. H.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron Lett.* **1970**, 1999.

(14) Antunis, M.; van Schoote, J. *Bull. Soc. Chim. Belg.* **1963**, *72*, 787.

(15) Yoshina, T.; Manabe, Y.; Kikuchi, Y. *J. Am. Chem. Soc.* **1964**, *86*, 4670. Martin, G. J.; Martin, M. L. *Bull. Soc. Chim. Fr.* **1966**, 1635. Martin, G. J.; Naulet, N. *Ibid.* **1970**, 4001.

(16) (a) Walborsky, H. M.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3288. (b) *Baskerville Chem. J.* **1965**, *14*, 1. (c) Walborsky, H. M.; Aronoff, M. S. *J. Organomet. Chem.* **1973**, *51*, 33.

(17) For a review of the cyclopropyl radical, see: Walborsky, H. M. *Tetrahedron* **1981**, *37*, 1625. Boche, G.; Walborsky, H. M. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley and Sons Ltd.: London, 1987; Chapter 12.

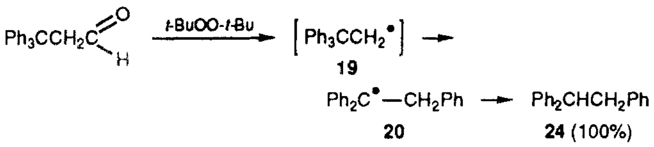
(18) (a) Walborsky, H. M.; Chen, C.-J.; Webb, J. L. *Tetrahedron Lett.* **1964**, 3551. (b) Walborsky, H. M.; Chen, C.-J. *J. Am. Chem. Soc.* **1971**, *93*, 671.

(19) Grovenstein, E., Jr.; Cottingham, A. B.; Gelbaum, L. T. *J. Org. Chem.* **1978**, *43*, 3332.

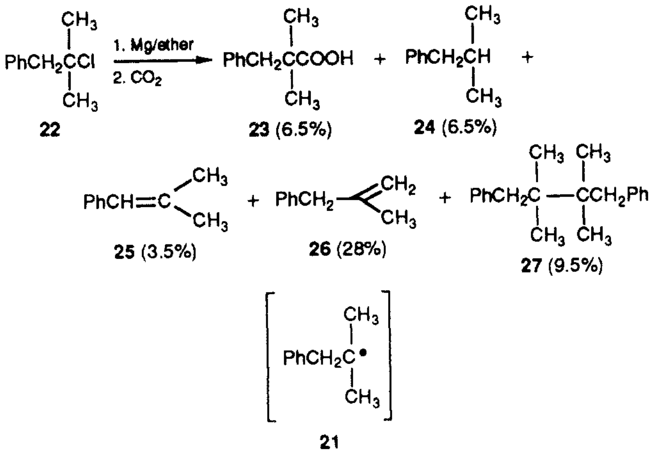
(20) Curtin, D. Y.; Hurwitz, M. J. *J. Am. Chem. Soc.* **1952**, *74*, 5381.

(21) Winstein, S.; Seubold, F. H., Jr. *J. Am. Chem. Soc.* **1947**, 2916.

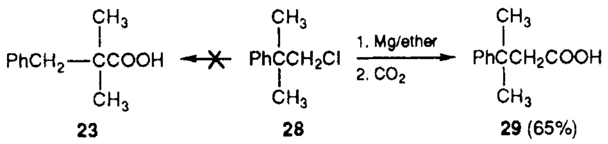
to yield the hydrocarbon **24** as the sole product.



The radical–surface nature of Grignard formation also finds support in the work of Rüchardt and Trautwein[22] outlined below. These workers observed a product distribution similar to that obtained in the reaction of (±)-**1** with magnesium. The tertiary radical **21** accounts for all the products formed by disproportionation, dimerization, and possible abstraction of hydrogen from solvent.



Further evidence to support the radical–surface nature of the reaction is provided by the reaction of neophyl chloride (**28**) with magnesium.[22] Carboxylation yields only one carboxylic acid, **29**, in 65% yield and no **23**.



Under heterogeneous conditions the primary neophyl radical **36** does not rearrange to the tertiary radical **31**. However, under homogeneous conditions the radical decarbonylation reaction of Winstein and Seubold[21] on **32** gives rise to a mixture of hydrocarbons (**24** and **33**) in a 1:1 ratio, which shows that the neophyl radical **30** has partially rearranged to the tertiary radical **31**. Also, thermal decomposition of the *tert*-butyl perester of **29** in ether solvents[23] yields a mixture of hydrocarbons resulting from the involvement of unrearranged radical **30** and rearranged radical **31**. The relative yields of the hydrocarbon products show that 78% of product resulted from the rearranged radical **31**. Product analysis clearly demonstrates that striking differences exist when *identical* radicals are produced under homogeneous conditions and under conditions where a solid reactive surface is available.

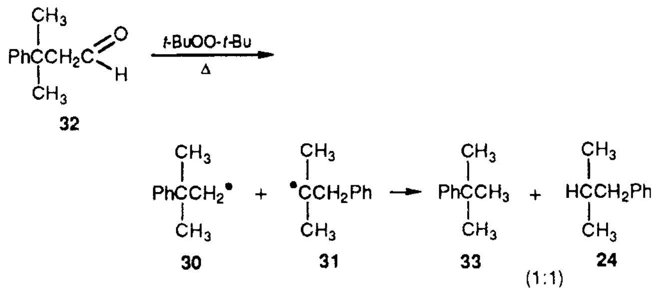
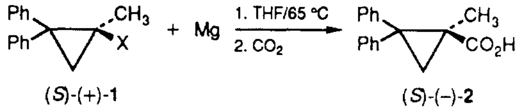
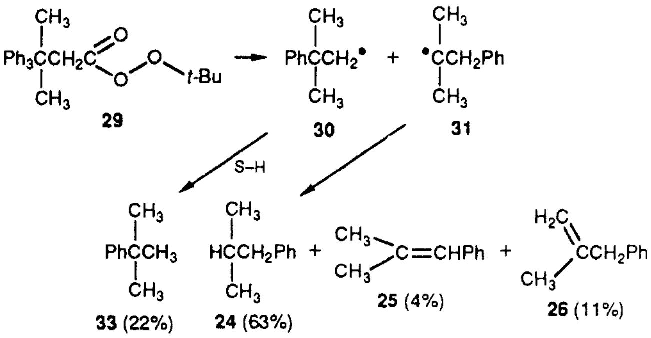


Table I
Stereochemistry of Grignard Reagent Formation[16]



X	T, h	yield, %	opt. purity, %
Cl	0.5	81	27
Cl	3.0	89	26
Br	0.5	70	19
Br	3.0	79	11
I	0.5	40	2
I	3.0	36	2



Stereochemistry of the Grignard Formation Reaction

The results of the reaction of (*S*)-(+)-**1** (X = Cl, Br, I) with powdered magnesium[24] (200 μm) are shown in Table I. At the outset we note that the acid obtained is optically active. This represents the *first example of an optically active Grignard reagent* where the magnesium atom is bonded directly to the asymmetric center.[12] Moreover, the reaction has proceeded with overall retention of configuration.

An interesting effect of halogen was revealed. One observes that the retention of optical activity and/or configuration varies in the direction Cl > Br ≫ I with the cyclopropylmagnesium iodide being essentially racemic. Also of interest is the fact that the yield of acid varies in the same direction, Cl > Br ≫ I. Finally, Table I discloses that whether the reaction is carried out over $^1/_2$ or 3 h, neither the yield nor the optical activity is seriously affected. The implication is that once the Grignard reagent is formed, it is configurationally stable.

The configurational stability of the Grignard reagent was confirmed by the following series of experiments. First, it was demonstrated that halogen–lithium exchange between (*S*)-(+)-**1** bromide and *n*-butyllithium proceeded with 100% retention of optical activity and configuration as evidenced by the fact that the acid (*S*)-(−)-**2** produced by subsequent carbonation was optically pure. Although the lithium reagent[18a,25] was

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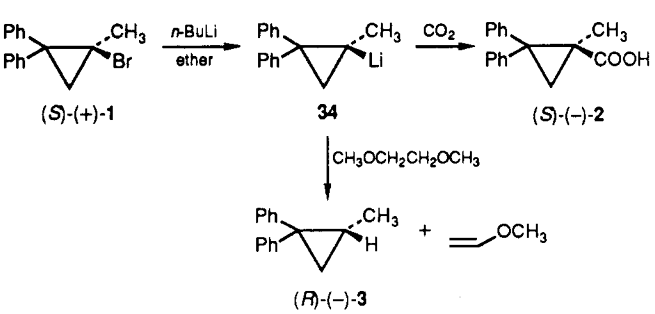
(22) Rüchardt, C.; Trautwein, H. *Chem. Ber.* **1962**, *95*, 1197.
(23) Rüchardt, C.; Hecht, R. *Chem. Ber.* **1965**, *98*, 2471.

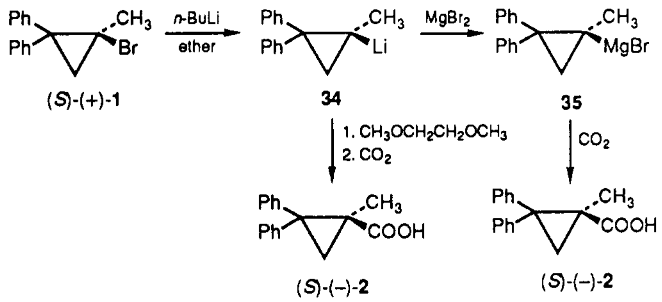
(24) Spectroscopic analysis[16a] of the magnesium revealed the following percentages of trace elements: Al, 0.006; Ca, 0.01; Cu, 0.001; Fe, 0.0043; Mn, 0.005; Ni, 0.0005; Pb, 0.006; Si, 0.005; Sn, 0.01; Zn, 0.002.



(*S*)-(+)-**1** **34** (*S*)-(−)-**2** (*R*)-(−)-**3**

stable at room temperature over a reasonable length of time, it decomposed rapidly in the presence of 1,2-dimethoxyethane to yield 85% optically pure hydrocarbon (*R*)-(−)-**3** and methyl vinyl ether.

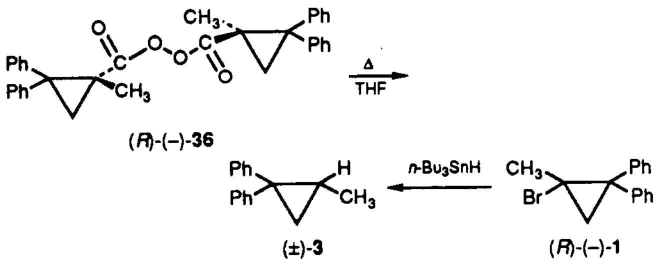
One was now in a position to prepare an optically pure Grignard reagent by treating the lithium reagent **34** with anhydrous magnesium bromide to yield **35**.



(*S*)-(+)-**1** **34** **35** (*S*)-(−)-**2** (*S*)-(−)-**2**

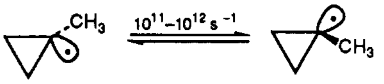
Carbonation of **35** gave rise to optically pure (*S*)-(−)-**3**. In order to be certain that we were carbonating the Grignard reagent **35** and not the lithium reagent **34**, we repeated the reaction. This time, after treatment of **34** with magnesium bromide, an excess of 1,2-dimethoxyethane was added to destroy any lithium reagent **34** that might be present, and again carbonation yielded 100% optically pure acid, (*S*)-(−)-**2**. In this manner the configurational stability of the Grignard reagent **35** was established. Hence, the racemization that is observed in the formation of Grignard reagent by reaction of (*S*)-(+)-**1** (X = Cl, Br, I) must have occurred during the formation of the Grignard reagent and not afterward.

As noted earlier, the product distribution of the hydrocarbons produced in the Grignard formation reaction implicated radical intermediates produced on the surface of the magnesium and this distribution differed greatly from the products obtained when the same radical was produced under homogeneous conditions. What are the stereochemical consequences of generating radical **12** from a chiral precursor? When **12** is generated by decomposition of the diacyl peroxide (*R*)-(−)-**36** in THF or by the reaction of tri-*n*-butyltin hydride with (*R*)-(−)-**1** (X = Br), the resulting hydrocarbon **3** is essentially racemized.[17,18b]



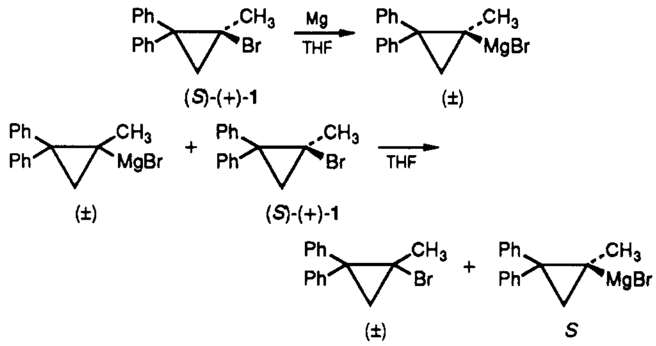
(*R*)-(−)-**36** (±)-**3** (*R*)-(−)-**1**

It is now clear that this result was to be expected since recent ESR measurements by Johnston and Ingold[26] have shown that the 1-methylcyclopropyl radical at 71 °C has an inversion frequency in solution of 2×10^{11} s^{-1}. Ab initio calculations[27] on this same radical gave 9×10^{12} s^{-1} as the inversion frequency at −173 °C in the gas phase. Such inversion frequencies would



exceed the rate of diffusion of such radicals, which unless constrained in a cage[18b] or on a surface[16] would be expected to lose configuration. This provides further evidence for the surface nature of the reaction since we observe that (*S*)-(+)-**1** (X = Cl, Br) yields chiral (*S*)-(−)-**2** with partial retention of optical activity (optical purity ~15–27%) and configuration (~63–64%).

However, one must consider the possibility that the observed optical activity was not due to the surface but was the result of metal–halogen exchange[28] between racemic Grignard reagent and chiral halide, a reaction that is known to occur with retention of configuration. Let us assume that we start with chiral (*S*)-(+)-**1** (X = Br), which undergoes reaction with magnesium to form racemic Grignard reagent in solution due to the radical nature of the reaction. As the reaction proceeds, we will have a fraction of racemic Grignard reagent (x) and ($1 - x$) of chiral bromide. Now if halogen–metal exchange occurs between racemic Grignard reagent and chiral bromide, this could lead to formation of partially optically active Grignard reagent as is actually observed.



(*S*)-(+)-**1** (±) (±) (*S*)-(+)-**1** (±) *S*

In order to test this possibility, a solution of racemic Grignard reagent was prepared from (±)-**1** (X = Br) and magnesium in THF in a separate experiment. The solution was separated from unreacted magnesium, and to the solution containing the racemic Grignard reagent was added a solution of chiral (*S*)-(+)-**1** (X = Br). After the mixture was refluxed for 3 h and then treated with carbon dioxide, the acid **2** obtained was *completely racemic*. This result excludes halogen–metal exchange as a source of the optical activity observed.

The results obtained with the vinyl system parallel those found with the cyclopropyl system.[12] As can be seen, the reaction of (*R*)-(−)-**4** with magnesium powder followed by carbonation yielded acid (*R*)-(−)-**6** in 40–45% optical purity and with overall retention of configuration. The recovered starting bromide from

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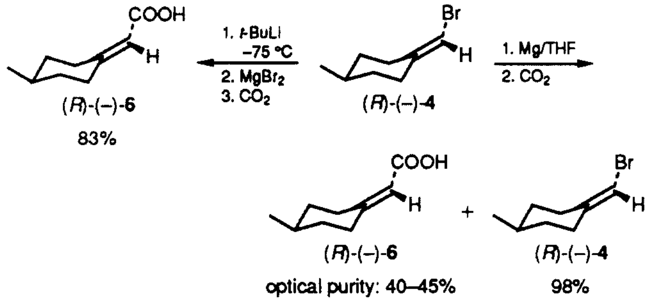
(25) Walborsky, H. M.; Impastato, F. J.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3283.

(26) Johnston, L. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1986**, *108*, 2343.

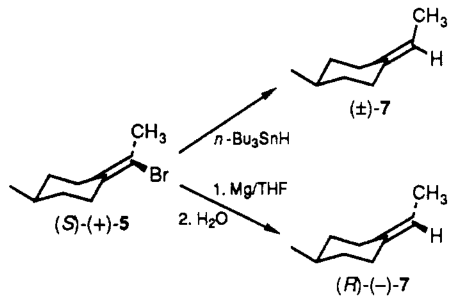
(27) Zerbetto, F.; Zgiarski, M.; Siebrand, W. *J. Am. Chem. Soc.* **1989**, *111*, 2799.

(28) Zakharkin, L. I.; Okhlobystin, Y. O.; Bilevitch, K. A. *Tetrahedron* **1965**, *21*, 881; *J. Organomet. Chem.* **1964**, *2*, 309.

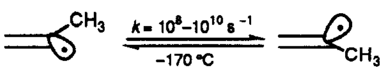


the reaction was 98% optically pure, showing that the loss of optical activity was not due to racemization of starting bromide. Moreover, allowing the reaction to proceed for 1 h or 4 h did not affect the optical purity nor the yield of product,[10] which speaks for the stability of the vinyl Grignard reagent once it is formed. Nevertheless, the Grignard reagent was prepared indirectly by treatment of (*R*)-(−)-**4** with *tert*-butyllithium at −75 °C to produce the corresponding vinyllithium. Anhydrous magnesium bromide was added, and since there seemed to be no apparent reaction at −75 °C, the reaction mixture was allowed to warm to ambient temperature. Carbonation of the reaction mixture gave (*R*)-(−)-**6** which was 83% optically pure (91% overall retention of configuration). The small loss of configuration is believed due to partial racemization of the precursor lithium reagent prior to reaction with magnesium bromide.[10]

Reaction of (*S*)-(+)-**5** with powdered magnesium also resulted in partial retention of optical activity as evidenced by hydrolysis of the Grignard reagent to yield (*R*)-(−)-**1** with an optical purity of 18% and overall retention of configuration.

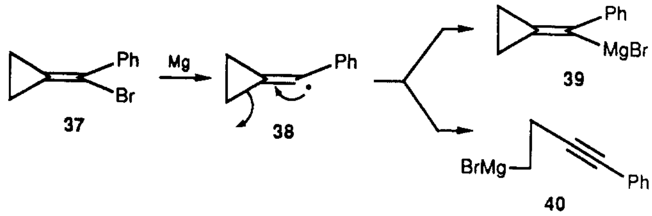


Treatment of (*S*)-(+)-**5** to generate **7** via a free-radical precursor under homogeneous conditions resulted[29] in completely racemized (±)-**7**. This result was expected since Fessenden and Schuler[30] reported that the vinyl radical inverts its configuration at a rate between 10^8 and 10^{10} s^{-1} at −170 °C.



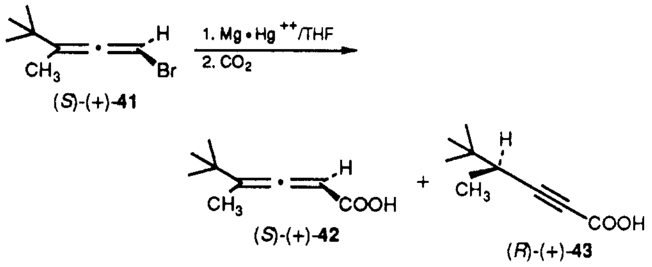
Consistent with the above findings are the observations of Yoshino, Manube, and Kikushi.[31] These workers found that treating *cis*- and *trans*-β-bromostyrene with magnesium in ether resulted in 68% retention of configuration starting with the cis bromide and 59% retention for the trans bromide. They also concluded that the loss of configuration occurred during the formation of the Grignard reagent. Martin, Mechin, and Martin[32] reported on the stereoselectivity of vinyl Grignard reagent formation with a series of geometric isomers of vinyl bromides. For example, *cis*-1-bromo-1-hexene gave a Grignard reagent containing 85% of the cis isomer, and *trans*-1-bromo-1-hexene yielded a Grignard reagent that was 60% trans. The data from six vinyl halides provided definitive evidence that the reaction of isomerically pure vinyl bromides with magnesium was nonstereospecific. However, overall retention of configuration was observed in all cases and is in conformity with the surface nature of the reaction.

Derocque and Sundermann's[33] study of the reaction of cyclopropylidenephenylmethyl bromide (**37**) with magnesium in ether is also informative. These workers



observed that under these conditions the radical **38** formed unrearranged Grignard reagent **38** and rearranged Grignard reagent **40** in approximately a 1:1 ratio. When the radical **38** was generated in solution with tri-*n*-butyltin hydride rather than on a magnesium surface, the ratio of **39** to **46** was 1:9.

Finally, of interest is the report of Landor et al. on the reaction of chiral (*S*)-(+)-1-bromo-3,4,4-trimethylpenta-1,2-diene (**41**) in THF with magnesium activated by mercuric chloride. After carbonation of the Grignard reagent, the reaction yielded a mixture of chiral allenic acid **42** and chiral acetylenic acid **43**. Unfortunately, insufficient details were given to ascertain the stereoselectivity of the reaction, but that some optical activity with overall retained configuration in **42** is observed is significant and again speaks for the surface nature of the reaction.



Mechanism of Grignard Reagent Formation

On the basis of the stereochemical results observed in the reaction of (*S*)-(+)-**1**, (*R*)-(−)-**4**, and (*S*)-(+)-**5** with magnesium powder and the products obtained from **1**, a free-radical reaction on the surface of magnesium was postulated as the mechanism of Grignard reagent formation.[10,12,15,16] The original mechanism was proposed[16a] in 1964 and was elaborated[16c] upon in 1973.

As we have previously proposed and discussed,[16] the mechanism of Grignard reagent formation, as pictured in Scheme II, occurs at the magnesium surface–solution interface. The cyclopropyl or vinyl halide accepts an

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[29] Walborsky, H. M.; Rachon, J. *J. Am. Chem. Soc.* **1989**, *111*, 1896.
[30] Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *39*, 2147.
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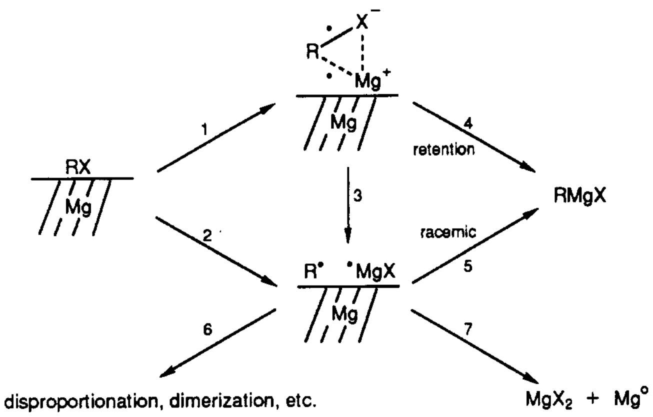
[33] Deroque, J.; Sundermann, F. *J. Org. Chem.* **1974**, *39*, 1411.

Scheme II
Proposed Mechanism for Grignard Formation

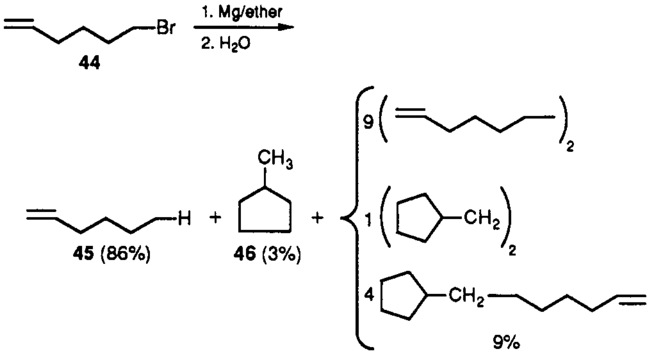


electron into its carbon–halogen antibonding orbital from the magnesium surface pathway (pathway 1), inner sphere, to produce a radical anion in close association with a univalent magnesium cation. Collapse of the tight anion radical–cation radical pair leads to formation of a Grignard reagent that has completely maintained its configuration (pathway 4). Alternatively, the tight anion radical–cation radical pair may proceed by pathway 3 to a loose radical pair. This same radical pair may be formed directly by pathway 2, outer sphere, and it is here that racemization can occur by having the carbon radical rotate by 180° relative to the surface. Combination of the carbon radical with the magnesious halide radical produces largely racemic Grignard reagent, pathway 5. The kinetic analyses of Grignard formation by Whitesides and co-workers,[34] Vogler and co-workers,[35] Molle, Bauer, and Dubois,[36] and Yurachenko and co-workers[37] are also consistent with pathway 1 and/or 2 being involved in the rate-determining step.

Also in agreement is the observed effect of halogen (RX) on the stereochemistry as well as yields of Grignard reagent formed (Table I). The bond energy as well as the reduction potential of the carbon–halogen bond decreases in the order Cl > Br > I. The optical purities of the acid formed on carbonation of the precursor Grignard reagent are in the same order, 27%, 19%, and 2% for the chloride, bromide, and iodide, respectively. The isolated yields of acid fall in the same order, 81%, 70%, and 40%. These data are consistent with the amount of loose radical pair formed, pathways 2 and 3, as reflected in the strength of the carbon–halogen bond (reduction potential), i.e., the weaker the bond (lower reduction potential), the greater the amount of loose radical pairs.

The carbon radicals in the loose radical pair may escape capture by the magnesious halide and undergo characteristic radical reactions of disproportionation and dimerization which are responsible for the observed CIDNP effect,[38a] most occurring at the surface of the magnesium but some escaping into solution as evidenced by deuterium incorporation in **3** when the solvent was diethyl ether-d_{10}. This would account for the hydrocarbon products observed in the reaction of **1** (X = Br) with magnesium as discussed earlier. Recent XPS analysis[36b] of the Grignard formation reaction also speaks for the surface nature of the reaction, as does low-temperature EPR analysis.[39]

Since our early work,[16] others have adopted the radical–surface mechanism for Grignard formation[33–40] which is depicted in Scheme II. More recently, however, a group of workers[41] questioned this mechanism and proposed that all the radicals produced in Grignard formation leave the surface and "diffuse freely in solution at all times". They propose a diffusion model (D model) in which rate data obtained under homogeneous conditions are used for their calculations. Applying their model to the reaction of 5-hexenyl bromide, they were able to account for the product distribution that had been observed for this reaction.[38d,42]



It should be noted that in hydrolysis of the Grignard reagents from 5-hexenyl bromide the main product is 1-hexene (**45**), formed by 5-hexenyl Grignard reagent, and that there is only a 3% yield of methylcyclopentane (**46**), which results from the cyclopentylcarbinyl Grignard reagent. Under homogeneous solution conditions, however, the reverse is found.[43] For example, reduction of **44** with tri-*n*-butyltin hydride, which also involves the formation of a 5-hexenyl radical, leads to formation of **46** in 78% yield and only a 7% yield of **45**. This contrasts with what is observed in the formation of Grignard reagents from **44** with magnesium, in spite of

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(34) (a) Roger, H. R.; Hill, C. L.; Fugiwara, Y.; Rogers, R. J.; Mitchell, H. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 217. (b) Rogers, H. R.; Rogers, R. J.; Mitchell, H. L. *J. Am. Chem. Soc.* **1980**, *102*, 231. (c) Barber, J. J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 239. (d) Root, K. S.; Deutch, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1981**, *103*, 5475.

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(42) Comparable yields of open **47** and cyclized product **43** have been found by other workers: Lamb, R. C.; Ayers, P. W.; Toney, M. K.; Garst, J. F. *J. Am. Chem. Soc.* **1966**, *88*, 4261. Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1970**, *92*, 6609. Kossa, W. C.; Rees, T. C.; Richey, H. G. *Tetrahedron Lett.* **1971**, 3455. Ohno, M.; Shimizu, K.; Ishizaki, K.; Sazaki, T.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 729.

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Table II
Reaction of RBr with Magnesium in Methanol-*O-d*

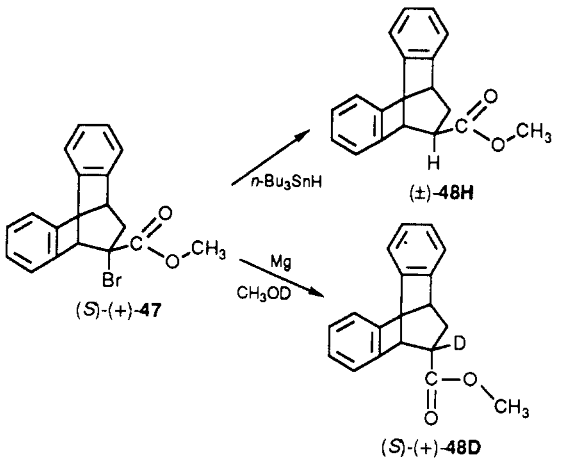
RBr	yield, % RH + RD	yield, % RD	opt. purity, %	retentn of confign, %
1	87	100[a]	23	72
5	70	93[a,b]	60	80
47	94	95[c]	11	44[d]

[a] Determined by Professor Roy King, University of Florida, using mass spectrometry. [b] Minimum value. [c] Determined by NMR, minimum value. [d] Overall inversion as expected; see ref 49.

the fact that the 5-hexenyl radical is also involved.

Although the evidence that we have presented so far seems to militate against a "radical diffusing freely in solution at all times" in the Grignard reagent formation reaction, it was thought desirable to further test this hypothesis. The cyclopropyl and vinyl radicals, being σ radicals, are comparable in their reactivities to the σ phenyl radical.[17] The phenyl radical abstracts a hydrogen from the methyl group of methanol with a pseudo-first-order rate[44] (k_1) of 3.5×10^6 s^{-1}. We had also demonstrated that the cyclopropyl radical **12**, when generated in methanol by decomposition of its precursor diacyl peroxide, not only abstracted a hydrogen from methanol to give **3** but yielded approximately an equal amount of the ring-opened dimer **15** as well.[45] With this knowledge in mind it was decided to allow (*S*)-(+)-**5** and (*S*)-(+)-**1** (X = Br) to react with powdered magnesium in methanol-*O-d*.[46,47] If the radical leaves the surface to "flow freely in solution", then the hydrocarbons formed from (*S*)-(+)-**5** and (*S*)-(+)-**1** (X = Br) should contain appreciable amounts of hydrogen due to abstraction by the radical of a hydrogen from the methyl group of methanol-*O-d*. Moreover, considerable amounts of the ring-opened dimer **15** would be expected to be formed in the case of the cyclopropyl radical **12**. If on the other hand the radical does not leave the surface but takes on another electron to form Grignard reagent (Scheme II), then this reagent would react with the deuteron of methanol-*O-d* to give RD. Since chiral substrates will be used, the optical purities of the resulting hydrocarbons will also be of interest since the inversion frequencies of the cyclopropyl (10^{11}–10^{12} s^{-1})[26,27] and vinyl radicals (10^8–10^{10} s^{-1})[30] are known.

Recognizing that cyclopropyl and vinyl radicals are σ-type radicals[17] whereas the 5-hexenyl radical is a π type, we therefore also included in our study (*S*)-(+)-**47**,[48] which would give rise to a *planar delocalized radical*. The three chiral bromides **1**, **5**, and **47** were treated with magnesium powder in methanol-*O-d*, and the results are shown in Table II. It is clear that very little, if any, hydrogen abstraction from the methyl group of methanol-*O-d* occurred. Moreover, no ring-opened dimer **15** was observed in the product. Essentially all of the product resulted from deuterolysis of the Grignard reagent formed from **1**, **5**, and **47** to the corresponding products in 23%, 60%, and 11% optical purities. Only a surface-controlled radical intermediate would account for such results. Of special significance is the observation that even (*S*)-(+)-**47**, which would give rise to a planar delocalized π radical intermediate, results in product (*S*)-(+)-**48D** that is 11% optically pure. Significantly when (*S*)-(+)-**47** is treated with tri-*n*-butyltin hydride, the product **48H** is completely racemic, showing that under homogeneous conditions the radical intermediate is indeed achiral. Recent work by Ashby and Oswald,[50] using dicyclohexylphosphine as a radical trap,[51] showed that in the reaction of 5-hexenyl bromide with magnesium only ca. 20–25% of the π radicals leave the surface. This should be viewed as a maximum value since the use of dicyclohexylphosphine as a radical trap has been criticized in that the trap itself may induce radical reactions.[52] The same criticism[53] can be made of the use of 2,2,6,6-tetramethylpiperidine-*N*-oxyl to detect radicals during Grignard reagent formation.[54] This reagent suffers from another difficulty in that the *N*-oxyl radicals may themselves be adsorbed on the metallic surface[55] and hence may only be trapping other surface-adsorbed radicals.



In connection with the surface nature of the reaction, one would predict that the greater the surface area, the greater the reactivity. The use of Rieke magnesium[56] provides a 0.1-μm particle size, which enables one to carry out the reaction at −65 °C. Thus, (*S*)-(+)-**1** (X = Br) in THF with 4 equiv of 1,1-dimethylethanol-*O-d* at −65 °C gives[57] a 94% yield of (*R*)-(−)-**3** with 94% deuterium incorporated and an optical purity of 43%. Ordinary, powdered magnesium (200 μm) does not react at −65 °C. However, at +20 °C, using Rieke magnesium, the optical purity of the product is decreased to 18%. The observation that reaction occurs at −65 °C with Rieke magnesium (0.1 μm) and not with powdered magnesium (~200 μm) speaks for the surface nature

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(47) For a discussion of the methanol–magnesium system in Grignard formation, see ref 46.

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(49) Overall inversion as expected; see: Annino, R.; Erickson, R. E.; Michalovic, J.; McKay, B. *J. Am. Chem. Soc.* **1966**, *88*, 4424. Brewster, J. *Ibid.* **1956**, *78*, 4061.

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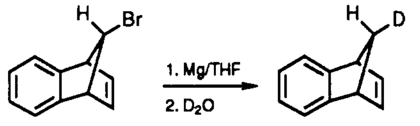
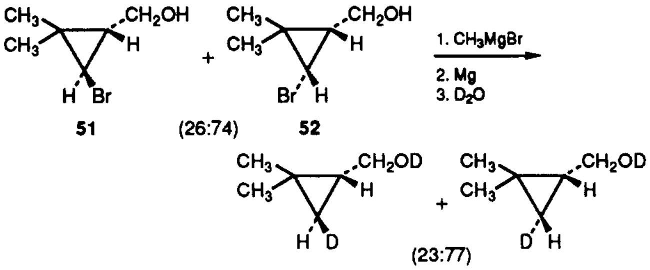
of the initial electron transfer reactions, either inner sphere (pathway 1) from the magnesium surface to the σ^* orbital of the carbon–halogen bond or outer sphere (pathway 2) as depicted in Scheme II. This is consistent with steps 1 and/or 2 being rate determining.[34d,35-37] Enthalpy considerations would suggest that step 4 would be faster than step 3 and that this rate difference would be magnified at lower temperatures, leading to the higher optical purity observed at −65 °C vs +20 °C.

Further evidence for the surface nature of Grignard reagent formation can be found in the work of Buske and Ford,[40] who showed that both *syn-* and *anti-*7-bromobenzonorbornadiene gave an identical mixture of deuterated product (57% syn and 43% anti) when reduced, under homogeneous conditions, with tri-*n*-butyltin deuteride. However, treatment of the anti isomer (**49**) with magnesium metal followed by deuterolysis yielded the *anti-*7-deuteriobenzonorbornadiene (**50**) with 86% retention of configuration.

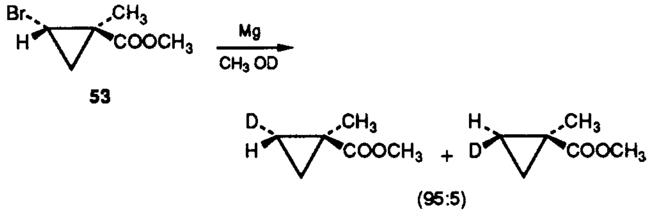


49 **50**

Richey and Moses[58] showed that almost complete retention of configuration was obtained when a 26:74 mixture of **51** and **52** was treated as shown. A similar result was obtained by Kirmse[59] in the reduction of **53** with magnesium in methanol-*O*-*d*.



51 (26:74) **52**



53

Conclusion. From the evidence presented we conclude that in Grignard reagent formation the magnesium surface plays a major role and that the mechanism of the reaction is not compatible with radicals that "are not adsorbed at the surface but diffuse freely in solution".[41]

I am grateful to all of my students, referenced in this Account, for their contributions to the work described herein, to the National Science Foundation for its generous support, and to my colleague Professor Werner Herz for comments on the manuscript.

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