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MECHANISM OF GRIGNARD REAGENT FORMATION. FURTHER EVIDENCE FOR THE SURFACE NATURE OF THE REACTION.[1]

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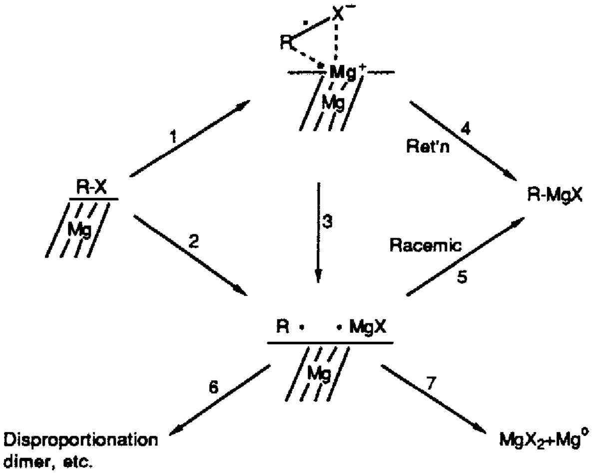
Summary: The use of Rieke magnesium permits one to obtain reaction with (S)-(+)-1-bromo-1-methyl-2,2-diphenylcyclopropane (**1**) at -65°C to yield a chiral Grignard reagent that is 33-43% optically pure.

Kinetic[3] and product[4] analyses (including stereochemistry[4c,e,f]) as well as the study of magnesium surfaces[5] have resulted in a reasonable picture of the mechanism of Grignard formation.[4a,f] There is general agreement that the reaction involves the intermediacy of free radicals[4,6] but there is a disagreement as to whether these radicals remain for the most part on the surface of the magnesium[7] or "diffuse freely in solution at all times".[8]

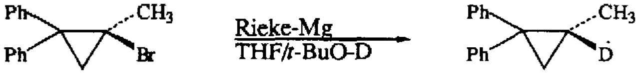
Twenty eight years ago[9] it was shown that the reaction of chiral (S)-(+)-1-bromo-1-methyl-2,2-diphenylcyclopropane (**1**) with magnesium powder resulted in the formation of a chiral Grignard reagent as evidenced by the fact that upon carbonation of the reaction mixture an optically active acid was obtained with an optical purity of *ca.* 12-18%. It was reasoned that the partial racemization observed occurred at the Grignard formation step. Thus was based on two observations. One, that the 1-methyl-2,2-diphenylcyclopropyl σ radical was incapable of maintaining its configuration when it was generated in solution from a variety of chiral precursors.[4e] It was also subsequently established by the esr experiments of K.U. Ingold that the 1-methylcyclopropyl radical inverts its configuration with a rate of 2×10^{11} s^{-1} at 71°C. Two, that once formed the Grignard reagent in solution was optically stable.[4a,9] It was inferred that the cyclopropyl radical intermediate interacted with the surface of the magnesium and thus enabled it to partially maintain its configuration. A mechanism, essentially that shown in Scheme **1**, was postulated.[4a,9]

Scheme 1.



Recently[7] we published the results of the reduction of a number of chiral R-Br derivatives in which the bromine was attached to sp^3 and sp^2 hybridized carbon as well as to a cyclopropyl carbon atom. The chiral bromides were treated with magnesium in CH_3O-D. It was shown that the reduction involved the deuterolysis of the Grignard reagent by CH_3O-D to yield R-D. Only the surface nature of the Grignard formation reaction (Scheme **1**) provided a reasonable explanation for the chirality and deuterium incorporation observed in the product.

Rieke-magnesium,[11] prepared by the reduction of magnesium bromide with potassium, is a highly reactive form of magnesium which enables one to form Grignard reagents at -78°C or lower. The high reactivity is believed to be due to the greater surface area[11] (15 mμ particles *vs* ~ 200 mμ for powdered magnesium). We now wish to report our results on the reaction of (S)-(+)-**1** with Rieke-Mg. Our results are summarized in Table **1**.



(S)-(+)-**1** (R)-(-)-**2**

Table **1** - Reaction of (S)-(+)-**1** with Rieke-Mg in THF/*t*-BuO-D.

Run	T, °C	*t*-BuO-D equiv.	Yield, %	D, %[a]	O.P., %[b]
1	-65	2	98	86	41
2	-65	4	94	92	43
3	-65	100	86	92	33
4	+20	4	92	89	18

a) Determined by NMR, ± 3% b) optical purity ± 0.5%

The reaction of (S)-(+)-1 with Rieke-Mg was conducted in THF in the presence of *t*-BuO-D. In a separate experiment it was shown that *t*-BuO-D did not react with Rieke-Mg under the conditions of our experiments. If the *radical* leaves the surface of the magnesium and enters the solvent phase then complete racemization would be expected and also some of the reactive σ radical would be expected to abstract a hydrogen atom from the solvent.[4a,e] On the other hand if the *Grignard reagent* leaves the surface it will be quenched by *t*-BuO-D to yield (R)-(-)-2 with an optical purity which will depend on whether pathway **1**, **4** or pathway **2**, **5** is responsible for Grignard formation (Scheme **1**).

As one can see from Table **1** the isolated yields of **2** are almost quantitative with a very high deuterium content. Moreover at -65°C the optical purity ranges from 33-43%. It should be appreciated that when the 1-methyl-2,2-diphenylcyclopropyl radical is generated in a THF solution rather than on a surface one not only observes complete loss of optical activity but the reaction products are different as well.[4e,12] Furthermore it is important to note that under the above conditions but *using powdered magnesium (~ 200 mμ) instead of Rieke-Mg* *no reaction occurred.* Also of significance is the decrease in optical purity to 18% when the reaction is carried out at +20°C.

The above results are compatible with the mechanism shown in Scheme 1. The observation that reaction occurs at -65°C with Rieke-Mg (0.1 mμ)[13] and not with powdered magnesium (~200 mμ) speaks for the surface nature of the initial electron transfer reaction from the magnesium surface to the σ^* orbital of the C-Br bond (step 1) and is consistent with the fact that this step is rate determining.[3] The anion-radical cation-radical intermediate on the surface of the magnesium can collapse to yield Grignard reagent with retention of configuration (step 4) or dissociate at the surface to give a radical pair (step 3) which upon recombination (step 5) would yield mainly but not exclusively racemic Grignard reagent.[7] The same radical pair could be formed directly by electron transfer (step 2).[4,7,9] The rate of step 4 would be expected to be faster than step 3 because of enthalpy as well as entropy considerations and this rate difference would be magnified at lower temperatures leading to the higher optical purity observed at -65°C *vs* + 20°C. The Rieke-Mg therefore plays an important role in the initial electron transfer step since the optical purity of **2** at + 20°C is the same for both Rieke-Mg and ordinary powdered magnesium.[4,7,9] The high deuterium incorporation is a reflection of the degree of Grignard reagent formation and is a qualitative affirmation that very little reaction of the radical with other hydrogen atom sources occurs[4a] under these conditions.

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