Surface Nature of Grignard Reagent Formation.[1] Chiral 1-Methylspiro[2.5]octylmagnesium Bromide

C. Hamdouchi, M. Topolski, V. Goedken, and H. M. Walborsky*

Dittmer Laboratories of Chemistry, Florida State University, Tallahassee, Florida 32306

Received December 15, 1992

The synthesis of chiral 1-bromo-1-methylspiro[2.5]octane (**13**) is described. The absolute configuration of **13** has been established as (*S*)-(+). From stereochemistry, product analysis, and radical trapping experiments it is concluded that the reaction of chiral **13** with magnesium to form the corresponding Grignard reagent occurs mainly on the surface of the magnesium.

Introduction

The surface nature of Grignard reagent formation had been proposed by us 28 years ago[2] and elaborated upon in 1973.[3] Additional evidence in support of our mechanism has been provided recently.[4] This mechanism is based on stereochemical analyses, radical trapping experiments, and product distributions observed during Grignard reagent formation using a variety of probes. The mechanism, based on our experimental findings, is shown in Scheme I.[5]

The first step, which is rate determining, involves an electron transfer from the magnesium surface into the σ^* antibonding orbital of the carbon–halogen bond to produce a tight radical anion–radical cation pair as a transition state or intermediate. The radicals involved in this process are obtained either directly via a concerted electron transfer–bond breaking from the magnesium surface (pathway 2) and/or by dissociation, if it is an intermediate, of the tight radical anion–radical cation (pathway 3) to form a loosely associated alkyl radical–magnesious halide. Stereochemical analysis and radical trapping experiments in several systems depicted in Figure 1 provided us with evidence that most, but not all, of the radicals produced during the Grignard reagent formation remain at the surface. At the same time, examination of product distribution allowed us to conclude that only a small fraction of radicals leave the surface to get lost into the bulk solvent, whereas the remaining radicals undergo surface disproportionation and dimerization.

Recently, another view for Grignard reagent formation has been proposed which involves a mathematical model based on kinetic analysis of product distribution.[6] In order to be able to utilize the existing kinetic data, obtained under homogeneous conditions, all the radicals formed must "*leave the surface and diffuse freely in solution at all times*", and then most of them can return to the magnesium surface to form Grignard reagent. That is the basic assumption of the diffusion model, D-model, for Grignard reagent formation. In a later paper it is stated that "the radicals are not *in solution* in the same sense as radicals formed homogeneously instead, D-model radicals belong to *surface*-radical pairs...."[6d] In essence, the authors suggest that radicals, though they leave the surface, do not really go into the bulk of the solvent. Instead a thin diffusion layer is formed close to the surface, and the radicals are said to be able to return to the surface before

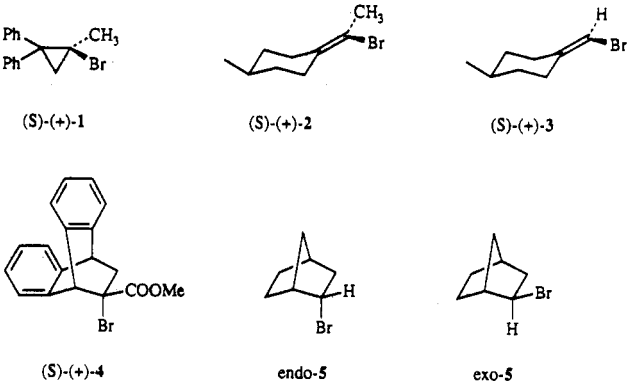
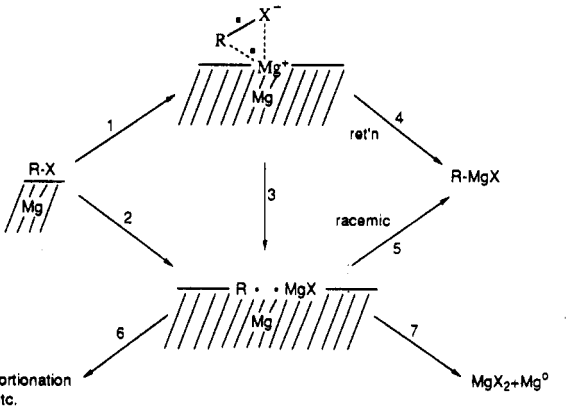


Figure 1. Systems used for stereochemical investigations.

Scheme I. Mechanism for Grignard Reagent Formation



(1) This paper is dedicated to Professor Virgil Goedken, whose untimely death occurred Dec 22, 1992.

(2) (a) Walborsky, H. M.; Young, A. E. *J. Am. Chem. Soc.* **1961**, *83*, 2595. (b) Walborsky, H. M. *Rec. Chem. Prog.* **1962**, *23*, 75. (c) Walborsky, H. M.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3288. (d) Walborsky, H. M.; Young, A. E. *Baskerville Chem. J.* **1965**, *14*, 1.

(3) Walborsky, H. M.; Aronoff, M. S. *J. Organomet. Chem.* **1973**, *51*, 33.

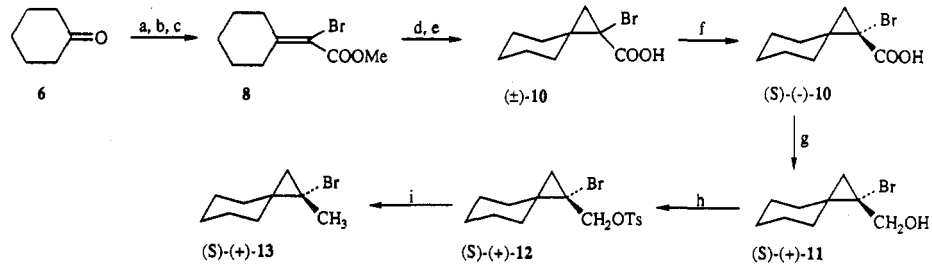
(4) (a) Walborsky, H. M.; Rachon, J. *J. Am. Chem. Soc.* **1989**, *111*, 1896. (b) Rachon, J.; Walborsky, H. M. *Tetrahedron Lett.* **1989**, *30*, 7345. (c) Walborsky, H. M.; Topolski, M. *J. Am. Chem. Soc.* **1992**, *114*, 3455. (d) Walborsky, H. M.; Zimmermann, C. *J. Am. Chem. Soc.* **1992**, *114*, 4996.

(5) (a) Walborsky, H. M.; Banks, R. B. *Bull. Soc. Chim. Belg.* **1980**, *89*, 849. (b) Walborsky, H. M. *Tetrahedron* **1981**, *37*, 1625. (c) Boche, G.; Walborsky, H. M. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons Ltd: London, 1987; Chapter 12. (d) Boche, G.; Walborsky, H. M. *Cyclopropane Derived Reactive Intermediates*; John Wiley & Sons, London, 1990. (e) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286. (f) Walborsky, H. M. *Chem. Unserer Zeit.* **1991**, *25*, 108.

(6) (a) Garst, J. F.; Deutch, J. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1986**, *108*, 2490. (b) Garst, J. F.; Swift, B. L. *J. Am. Chem. Soc.* **1989**, *111*, 241. (c) Garst, J. F.; Swift, B. L.; Smith, D. W. *J. Am. Chem. Soc.* **1989**, *111*, 234. (d) Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95. (e) Walling, C. *Acc. Chem. Res.* **1991**, *24*, 255. (f) Garst, J. F.; Ungvary, F.; Batlaw, R.; Lawrence, E. L. *J. Am. Chem. Soc.* **1991**, *113*, 5392. (g) Root, K. S.; Hill, C. L.; Lawrence, L. M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 5405.

0022-3263/93/1958-3148$04.00/0

Scheme II. Synthesis of (*S*)-(+)-1-Bromo-1-methylspiro[2.5]octane[a]



[a] (a) $(EtO)_2P(O)CH_2COOMe$; *t*-BuO^-; (b) Br_2; (c) MeO^-; (d) $(CH_3)_2{}^+S(O)CH_2{}^-$; (e) ^-OH; H_3O^+; (f) resolution–dehydroabietylamine; (g) $LiAlH_4$; (h) TsCl; (i) L-Selectride (Aldrich).

anything happens to them. It is not clear, however, what the thickness of this diffusion layer is. For example, several thousand angstroms have been suggested in one case.[6f] Drawing a line through a log/log plot,[6a] log (RMgX/RMgX) vs log *k*, from data extracted from the literature for *three* primary alkyl halides gave a predicted slope of $^1/_2$ provided that the basic parameter δ is a constant. This plot is the basis of the diffusion model. In order to accommodate the results obtained in the reaction of cyclopropyl bromide with magnesium it has been suggested that δ has different values for each particular system, solvent, temperature, etc. However, the experimental data upon which the modified D-model is based have been questioned.[4d]

In recent publications[6d,f] the question of typicality of the systems we used to establish and support our mechanism was raised. It was suggested that the retention of configuration observed in 1-methyl-2,2-diphenylcyclopropyl bromide resulted from the unusual stability of the intermediate anion-radical which, in turn, was due to the pseudoconjugation of the cyclopropyl ring with the phenyl groups. The chiral vinyl systems were also referred to as atypical. In order to clear up this problem we have selected a purely aliphatic cyclopropyl system for the investigation of the Grignard reaction mechanism involving stereochemical analysis, radical trapping experiments, and product distribution.

Results

We have designed and synthesized for this investigation a tertiary, chiral cyclopropyl bromide, 1-bromo-1-methylspiro[2.5]octane (**13**). This molecule does not contain any aromatic or vinyl moiety which could be responsible for the alleged unusual stability[6f] of the intermediate anion-radical produced during Grignard reagent formation. At the same time, the presence of the cyclopropyl ring assured us that the Grignard reagent formed from this bromide would be configurationally stable as it is in the case of thoroughly investigated 1-methyl-2,2-diphenylcyclopropyl bromide (**1**, X = Br).[2-5] The synthesis of **13** is depicted in Scheme II.

The preparation starts with cyclohexanone (**6**) which is converted by the Horner procedure to methyl cyclohexylideneacetate (**7**) in 90% yield. The ester **7** is converted to methyl α-bromocyclohexylideneacetate (**8**) in two steps involving addition of bromine followed by treatment of the dibromo intermediate with sodium methoxide. Compound **8** is obtained in 79% overall yield. We have found that the elimination reaction with sodium methoxide is superior to that using triethylamine or the thermal elimination originally suggested by Karrer and Smith.[7]

Cyclopropanation of **8** to **9** was achieved (71% yield) by the use of dimethylsulfoxonium methylide.[8] Saponification of **9** yielded racemic acid **10** in 78% yield.

Resolution[9] of (±)-**10** into its enantiomers was achieved by using purified dehydroabietylamine as a resolving agent. Bromo acid (−)-**10** was obtained in optically pure form after several recrystallizations of the salt. Additionally, we were able to obtain the other enantiomer, (+)-**10**, by liberating the partially enriched (+)-**10** found in the mother liquors. When the hexane solution of this partially enriched (+)-**10** was seeded with a crystal of the racemic acid only (±)-**10** precipitated leaving behind, in solution, further enriched (+)-**10**. Repeating this procedure allowed us to isolate (+)-**10** of very high optical purity. Optical purities of (+)- and (−)-**10** were determined by the NMR technique employing a chiral derivatizing agent.[10] Diastereomeric amides **14** formed with (*S*)-(−)-α-methylbenzylamine were prepared by standard procedure. Initially, (±)-**10** was converted to the mixture of diastereomeric amides **14** and an NMR spectrum was taken. The signals belonging to methyl groups and cyclopropyl ring protons were distinct, and a 50:50 integration indicated that amide formation was not diastereoselective, as required by the method. When the optically active samples were converted to amide **14** the NMR analysis indicated that (−)-**10** was optically pure whereas the optical purity of (+)-**10** was 94%. Both enantiomers of cyclopropyl bromide **13** could now be obtained by following three simple steps involving reduction to optically pure carbinol **11** with lithium aluminum hydride (70%), tosylation (**12**, 77%), and reduction to **13** in 95% yield by L-Selectride.

Finally, in order to obtain the absolute configuration of **10**, the amide **14** obtained from (−)-**10** and (*S*)-(−)-α-methylbenzylamine was subjected to X-ray analysis which established the absolute configuration of (−)-**10** as (*S*) (see Experimental Section).

Grignard reactions described in this work were conducted with Rieke magnesium[11] unless stated otherwise. To determine product distribution racemic bromide **13** was treated with Rieke magnesium in ether[4c] in the presence of *tert*-butyl alcohol-*O*-*d* (Scheme III). The reaction afforded a 70% yield of 1-methylspiro[2.5]octane (**15**), which was 33% deuterated according to NMR analysis, as the main products. This indicates that the yield in the Grignard reagent formation step is 23%. Other products found were 2,3-diethoxybutane (diethyl ether

(7) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1948**, *31*, 1067.

(8) (a) Corey, E. J.; Tschaykovsky, M. J. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (b) Hamdouchi, C. *Tetrahedron Lett.* **1992**, *33*, 1701.

(9) Wilen, S. H.; Collet, A.; Jacques, J. *Tetrahedron* **1977**, *33*, 2725.

(10) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

(11) (a) Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 7178. (b) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775. (c) Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301.

Scheme III. Product Distribution from the Reaction of (±)-13 with Rieke Magnesium

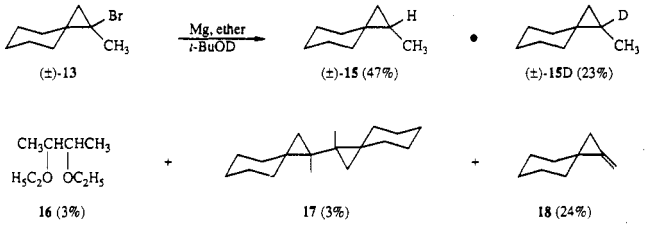
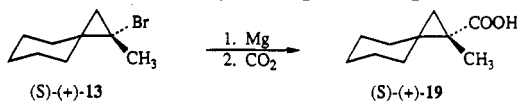


Table I. Stereochemistry of Grignard Reagent Formation



run	solvent	time, h	yield, %	optical purity, %
1	ether	2	25	10
2	THF	2	58	13

dimer, **16**; 3%), the cyclopropyl radical dimer **17** (3%), and a nonvolatile polymeric residue which by NMR was shown to contain aliphatic protons and some ether moieties. The volatile products were isolated by preparative gas chromatography, and their structures were proven by spectroscopic analyses and comparison with authentic samples. The authentic sample of spiro hydrocarbon **15** was obtained in 70% yield from bromide **13** by lithium–halogen exchange with *tert*-butyllithium followed by protonation with methanol. The authentic sample of the ether dimer **16** was prepared according to a literature procedure.[12]

As in the case of the previously investigated Grignard reaction of cyclopropyl bromide,[4d] we were unable to find and isolate the exocyclic cyclopropyl olefin **18** from the reaction mixture. Since we had suspected that olefin **18** would not be stable under the Grignard reaction conditions, we synthesized an authentic sample in 60% yield by zinc-induced elimination of the tosylate **12** in DMF. The Grignard reaction of **13** was repeated in the presence of this olefin and under the same conditions (1 h at room temperature). The olefin **18** was shown to undergo complete polymerization.

In order to determine the amount of radicals leaving the surface during Grignard reagent formation from racemic **13** two radical trapping experiments were performed. In the first experiment the reaction was run in the presence of radical trap deuterated[4c] dicyclohexylphosphine. 6% Deuterium incorporation into product **15** was found by mass spectrometry. In the second trapping experiment Grignard reaction of **13** was conducted in perdeuterated ether with mechanically activated magnesium.[13] A total amount of 13% of radicals were found to leave the surface and be trapped by the solvent as evident from the deuterium incorporation into product **15**.

To establish the stereochemistry of the reaction optically pure (*S*)-(+)-**13** was treated with Rieke magnesium at room temperature in both ether and THF and the reaction mixture carbonated. The results are shown in Table I.

The reaction in ether resulted in a 25% yield of optically active acid **19** along with 42% of racemic hydrocarbon **15**. Since the specific rotation of **19** was very small, we determined the optical purity of the acid by the more accurate NMR procedure. Hence, (*S*)-(−)-α-methylbenzylamide (**20**) was prepared; the diastereoisomeric excess determined by NMR from the signals corresponding to the cyclopropyl protons was found to be 10%. Reaction in THF afforded a much higher yield of the Grignard reagent (58%) and only 20% of racemic hydrocarbon **15**. The optical purity of the acid **19** was found to be 13%.

In order to establish the absolute configuration of the acid formed after Grignard reaction, optically pure (*S*)-(+)-**13** was treated with *tert*-butyllithium in ether solution followed by carbonation to yield optically pure (+)-**19** as determined by NMR analysis of its (*S*)-(−)-α-methylbenzylamide derivative. Since lithium–halogen exchange followed by carbonation is known to proceed with complete retention of configuration[14] the (*S*) configuration is assigned to (±)-**19**; this establishes that the Grignard reagent formation reaction proceeds with retention of configuration. By contrast, when optically pure bromide **13** was reduced under homogenous conditions with lithium naphthalenide (1 equiv),[15] in THF at room temperature, the resulting acid **19** isolated in 21% yield after carbonation was found to be completely racemic (Scheme IV). These results are consistent with and supportive of the surface nature of the Grignard reagent formation.

Discussion

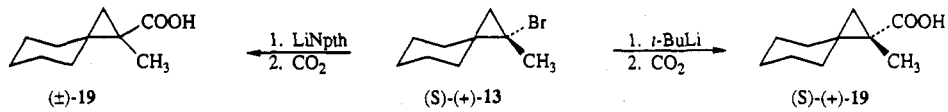
As one can see from the product distribution, based on Grignard quenching by *tert*-butyl alcohol-*O*-*d* in ether, the products are 23% of Grignard reagent indicated by the amount of **15**-*d*, and 47% of **15**. The latter arises both from the disproportionation of the cyclopropyl radical on the surface of magnesium and reaction with the solvent. Additionally, 3% of dimer **17** was isolated which accounts for 6% of the cyclopropyl groups. The total material balance is 76%, which leaves up to 24% unaccounted for. This we ascribe to olefin **18**, which, once formed, was consumed to give rise to a mixture of polymers. In our earlier investigation on the Grignard reaction with 1-bromo-1-methyl-2,2-diphenylcyclopropane (**1**, X = Br) in ether[3] (Scheme V) a similar product distribution was observed, i.e., 23% of 1-methyl-2,2-diphenylcyclopropane, 34% of Grignard reagent, and 16% of mixture of olefins and dimer resulting from disproportionation and dimerization. This is also consistent with our recent finding on the reaction of cyclopropyl bromide with magnesium in ether[4d] where only 25% of cyclopropylmagnesium bromide was detected along with 25–30% of cyclopropane.

Radical trapping experiments such as the use of deuterated dicyclohexylphosphine and Grignard reaction in perdeuterated ether as solvent provided strong evidence that only a small fraction of the radicals leave the surface and that most of the cyclopropane formed is a result of disproportionation on the surface. The D-model predicts that the major source of cyclopropane is the reaction of the cyclopropyl radical with solvent. However, all the systems we have previously examined using radical trap-

(12) Helmkamp, G. K.; Lucas, H. J. *J. Am. Chem. Soc.* **1952**, *74*, 951.
(13) Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698.

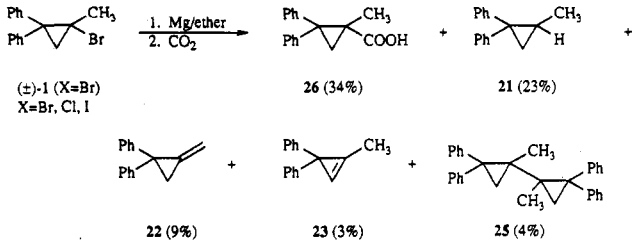
(14) (a) Applequist, D. E.; Peterson, A. H. *J. Am. Chem. Soc.* **1961**, *83*, 862. (b) Walborsky, H. M.; Impastato, F. J.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3283. (c) Walborsky, H. M.; Barash, L.; Impastato, F. J. *J. Am. Chem. Soc.* **1961**, *83*, 2517. (d) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785. (e) Letsinger, R. J. *J. Am. Chem. Soc.* **1950**, *72*, 4842.
(15) (a) Bank, S.; Jucket, D. A. *J. Am. Chem. Soc.* **1975**, *97*, 7742. (b) Garst, J. F.; Barbas, J. T.; Barton, F. E. *J. Am. Chem. Soc.* **1968**, *90*, 7159. (c) Garst, J. F. *Acc. Chem. Res.* **1971**, *4*, 400.

Scheme IV. Establishing the Absolute Configuration of (+)-19



(±)-19 (S)-(+)-13 (S)-(+)-19

Scheme V. Product Distribution in the Reaction of 1-Bromo-1-methyl-2,2-diphenylcyclopropane with Magnesium



(±)-1 (X=Br) X=Br, Cl, I 26 (34%) 21 (23%)

22 (9%) 23 (3%) 25 (4%)

Table II. Balance of the Products Formed during the Grignard Reagent Formation in Diethyl Ether

	Grignard formed (%)	solvent attack (%)	b (%)	ref
this work	23	13[a]	64	
(S)-(+)-1	34	1.4[a]	65	3
cyclopropyl bromide	25[c]	3[a,c]	72[c]	4d
cyclopropyl bromide	51	20–30	8	6f

[a] Amount detected from the reaction with deuterated ether. [b] Accounts for the remaining amount of cyclopropyl radical which dimerized and disproportionated. [c] Experimental findings.

ping experiments, including the cyclopropyl system, showed very little solvent attack[4d] (Table II).

Moreover, the use of deuterated dicyclohexylphosphine, which has been shown to be an effective radical trap[16] and has been used by Ashby[17] and us[4c,d] for Grignard reaction investigation, showed in all cases that only a very small fraction of radicals leaves the surface. During Grignard formation from cyclopropyl bromide only 4% of radicals were trapped, and from **13** we were only able to trap 6%.

Because of the net retention of configuration in Grignard reagent formation with **1–4**, Garst dismissed these systems as being "atypical".[6d,f] Moreover, he cited Boche's work in which partial retention was observed in the homogeneous solution reductions of **1** (X = Cl, Br, I) by alkali naphthalenides[18] as evidence that the 1-methyl-2,2-diphenylcyclopropyl radical is capable of partially maintaining its configuration *in solution* in spite of the large amount of evidence to the contrary.[5b] He claimed that this could account for the Grignard result and was therefore supportive of the D-model. The problem with this citation is another observation made by Boche, namely that the alkali naphthalenide reduction is halogen dependent and that the retention of configuration observed is in the order of I > Br > Cl whereas in Grignard reagent formation the order is just the reverse, Cl > Br > I. The retention observed is believed to be caused by the two geminal aromatic rings having a lower reduction potential than the carbon halogen bond so that the first electron will go

Table III. Stereochemistry of Grignard Reagent Formation

	solvent	time, h	yield, %	opt purity, %
(S)-(+)-13	THF	2.0	58[a]	13[a]
	Et_2O	2.0	25[a]	10[a]
(S)-(+)-1	THF	0.5	70[a]	19[a]
	THF	3.0	79[a]	11[a]
	Et_2O	0.5	26[a]	20[a]
(S)-(+)-3	THF	1–4	25[a]	42[a]
(S)-(+)-2	MeOD		93[b]	60[b]
(S)-(+)-4	MeOD		95[b]	11[b]
exo-5	Et_2O			100:0[c]
endo-5	Et_2O			50:50[c]

[a] Reaction was carbonated; yield and optical purity of the acid. [b] Grignard reagent was quenched by MeOD present in the reaction mixture; yield and optical purity of the hydrocarbon. [c] Balance of deuterated exo:endo after quenching with *tert*-butyl alcohol-*O*-*d* at −70 °C.

into the aromatic moiety and the second into the σ^* antibonding orbital. The retention is a result of an intramolecular electron transfer to yield the configurationally stable anion. Clearly, Boche's results have no bearing on Grignard reagent formation; moreover, it should be noted that magnesium metal does not react with the geminal phenyl groups in 1-methyl-2,2-diphenylcyclopropane (**21**).

Nevertheless, we set out to experimentally test the speculation made by Garst and to this end prepared chiral **13** which is devoid of geminal phenyl rings. This would eliminate the possibility of "pseudoconjugative stability" of the radical anion in solution which is allegedly responsible for the net retention observed in **1**. As predicted by the surface nature of Grignard reagent formation, the reaction of (*S*)-(+)-**13** with Rieke magnesium at room temperature in ether and in THF gave in both cases an optically active Grignard reagent, which after carbonation, gave an acid showing net retention of configuration. It is clear that this result is not compatible with the basic assumption of the D-model that "all radicals leave the surface and diffuse freely in solution at all times".[20] More evidence that the surface is necessary for the retention of configuration observed was provided when optically pure cyclopropyl bromide (*S*)-(+)-**13** was reduced under homogeneous condition. The total racemization observed is a result of the fact that in solution the free tertiary cyclopropyl radical **13** reaches its inversion equilibrium before it is trapped by a second bimolecular electron transfer from an alkali metal naphthalenide to yield after carboxylation the racemic acid **19**. Finally, it should be also pointed out that all of the systems in which we have investigated the stereochemistry of Grignard reagent formation (Table III) show a similar behavior.

As can be seen from Table III, representative examples of different classes of organic halides have been tested. In connection with the effect of surface it has been demon-

(16) (a) Alnajjar, M. S.; Kuivila, H. G. *J. Org. Chem.* **1981**, *46*, 1053. (b) Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833. (c) Ashby, E. C.; DePriest, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 6144.

(17) Ashby, E. C.; Oswald, J. *J. Org. Chem.* **1988**, *53*, 6068.

(18) (a) Boche, G.; Schneider, D. R. *Tetrahedron Lett.* **1978**, 2327. (b) Boche, G.; Schneider, D. R.; Wintermayr, H. *J. Am. Chem. Soc.* **1980**, *102*, 5697. (c) Walborsky, H. M.; Pierce, J. B. *J. Org. Chem.* **1968**, *33*, 4102.

(19) (a) Walborsky, H. M.; Aronoff, M. S. *J. Organomet. Chem.* **1973**, *51*, 55. (b) Walborsky, H. M.; Ollman, J.; Hamdouchi, C.; Topolski, M. *Tetrahedron Lett.* **1992**, 761.

(20) (a) Walborsky, H. M.; Chen, C. J. *J. Am. Chem. Soc.* **1971**, *93*, 671. (b) Walborsky, H. M.; Chen, C. J.; Webb, J. L. *Tetrahedron Lett.* **1964**, 3551. (c) Walborsky, H. M.; Topolski, M. *J. Org. Chem.* **1992**, *57*, 370. (d) Walborsky, H. M.; Topolski, M.; Hamdouchi, C.; Pankowski, J. *J. Org. Chem.* **1992**, *57*, 6188. (e) Walborsky, H. M.; Hamdouchi, C. *J. Org. Chem.* **1993**, *58*, 1187.

strated that magnesium clusters are more reactive toward alkyl halides than isolated magnesium atoms,[21] and the larger the cluster the greater is the reactivity.

In our proposed mechanism (Scheme I) pathway 1,4 involves the formation of a radical anion–radical cation tight ion pair on the surface which leads to retention of configuration. On the basis of the available literature it seems highly unlikely that relatively stable anion radicals could be formed from simple alkyl halides. According to experimental data[22] and theoretical calculations[23] single-electron transfer into a carbon–halogen bond is either purely dissociative (pathway 2) or proceeds via extremely short-lived species.[24] Saveant concludes[22b] that the reductive cleavage of the carbon halogen bond in aliphatic halides, either by direct electrochemical reduction at an inert electrode under heterogeneous conditions or by electrochemical reduction mediated by aromatic anion radicals, involves a concerted electron transfer–bond breaking mechanism where the origin of the driving force is the standard potential of the $RX/R^{\bullet} + X^{-}$ and not $RX/RX^{\bullet-}$ couple. According to Garst,[24] if anion radical intermediates exist their lifetimes would be extremely short (10^{-10} s). Ab initio (gas-phase) studies of the insertion reaction of magnesium into the carbon halogen bond do not predict formation of anion radicals with aliphatic[25a] or vinyl[25b] halides.

One concludes from these studies that the surface radical anion–radical cation ion pair (pathway 1, Scheme I) is most likely a transition state rather than an intermediate.[26] If, indeed, it is a transition state formed on the surface then its collapse on the surface would yield chiral Grignard reagent with retention of configuration (pathway 1,4), and pathway 3 would not be involved in the reaction. If the electron transfer is dissociative (pathway 2) then the tight radical pair formed can either combine to form largely racemic Grignard reagent (pathway 5) or the radicals can, on the surface, form dimeric product, disproportionation products (pathway 6), and some few of the radicals may leave the surface and go into solution. If they do not travel too far from the surface a few, ~1% in the case of (*S*)-(+)-1,[19a] may return to form Grignard reagent. However, while some halogen compounds may give rise to anion radicals that are intermediates and not transition states,[26] if these intermediates collapse at a rate of 10^{-10} s then for all intents and purposes what we concluded for the transition states holds for the intermediate as well. Grignard reagent formation is essentially a surface reaction.

There is no experimental evidence to believe that the cyclopropyl systems investigated by us or others[27,28] behave "atypically". Our mechanism of Grignard reagent formation, which is based on experiments involving stereochemistry, product distribution, and the results of radical trapping, has found general acceptance.[21d,29–34] We have also provided experimental proof that the basic assumption of the D-model that all the radicals leave the surface and diffuse freely in solution at all times is untenable.

Experimental Section

All reagents were purchased from Aldrich, unless stated otherwise. THF and ether were dried by reflux and distillation from sodium–potassium alloy. All experiments were conducted in a dry argon atmosphere. All melting points and boiling points are given uncorrected.

IR spectra were taken on Perkin-Elmer 257 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 300 MHz with $CDCl_3$ as solvent and with tetramethylsilane as an internal standard. Mass spectra and GC–MS analyses were performed using a Finnigan 4500 automated gas chromatograph/EI-CI mass spectrometer equipped with a DB-5 fused silica capillary column (J&W Scientific). Preparative gas chromatography separations were performed on Varian Aerograph Model 700 gas chromatograph with 15% SF-96 on chromosorb W as a stationary phase.

Microanalyses were performed by Beller Laboratories, Göttingen, Germany. High-resolution mass spectra[35] were taken on a Finnigan MAT95Q mass spectrometer in the electron impact mode at 70 eV.

Methyl Cyclohexylideneacetate (7). Potassium *tert*-butoxide (106.4 g, 0.95 mol; Kodak) was added portionwise, with mechanical stirring, to a solution of methyl (diethoxyphosphoryl)-acetate (210 g, 1 mol) in methylene chloride (1000 mL) at −70 °C. The reaction mixture was stirred at this temperature until a completely clear solution was obtained (about 1 h), and cyclohexanone (98 g, 1 mol, 103 mL) was added. The reaction mixture was allowed to reach room temperature and was stirred overnight. When the reaction was completed the solution was washed with water (3 × 500 mL) and dried over anhyd sodium sulfate. The solvent was subsequently removed in vacuum, and the residue was distilled to give 138 g (90%) of the desired product: bp 55 °C/2 mmHg (lit.[7] bp 97.5–98.5 °C/18 mmHg); ^1H NMR δ 1.50–1.65 (m, 6H), 2.12–2.18 (m, 2H), 2.75–2.83 (m, 2H), 3.63 (s, 3H), 5.59 (s, 1H).

Methyl α-Bromocyclohexylideneacetate (8). Bromine (43.5 mL, 0.85 mol) was added dropwise with stirring to a solution of methyl cyclohexylideneacetate (7) (130 g, 0.85 mol) in methylene chloride (700 mL) at −70 °C. The reaction mixture was allowed to reach room temperature, and the solvent was removed under reduced pressure. The crude dibromo derivative was added to a solution of sodium methoxide (0.85 mol) in methanol (1000 mL), and the reaction mixture was stirred overnight at room temperature. The solvent was evaported under reduced pressure, and the residue was dissolved in ether (300 mL) and washed with water. The organic phase was dried with anhyd magnesium sulfate, the solvent was evaporated, and the residue was distilled under reduced pressure. Methyl cylochexylidenebromoacetate (8; 178 g, 79%) was obtained: bp 85 °C/2

(21) (a) Skell, P. S.; Girard, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 5518. (b) Ault, B. S. *J. Am. Chem. Soc.* **1980**, *102*, 3480. (c) Klabunde, K. J.; Whetten, L. *J. Am. Chem. Soc.* **1986**, *108*, 6529. (d) Sergeev, G. B.; Zagorsky, V. V.; Badaev, F. Z. *J. Organomet. Chem.* **1983**, *243*, 123.

(22) (a) Andrieux, C. P.; Gallardo, L.; Saveant, J. M.; Su, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 638. (b) Saveant, J. M. *Adv. Phys. Org. Chem.* **1990**, *26*, 1.

(23) (a) Symons, M. C. R. *J. Chem. Res., Synop.* **1978**, 360. (b) Clark, T. *J. Chem. Soc., Chem. Commun.* **1984**, 93. (c) Clark, T.; Illing, G. *J. Chem. Soc., Chem. Commun.* **1985**, 529.

(24) Garst, J. F.; Roberts, R. D.; Pacifici, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 3528.

(25) (a) Davis, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 4145. (b) Liu, L.; Davis, S. R. *J. Phys. Chem.* **1991**, *95*, 8619.

(26) Experimental evidence bearing on this question will be presented in a forthcoming publication whose manuscript is in preparation.

(27) Richey, H. G., Jr.; Moses, L. M. *J. Org. Chem.* **1983**, *48*, 4013.

(28) Kirmse, W.; Rode, J.; Rode, K. *Chem. Ber.* **1986**, *119*, 3672.

(29) Kharasch, M. S.; Reinmuth, C. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall, Inc.: New York, 1954.

(30) Vogler, E. A.; Stein, R. L.; Hayes, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3163.

(31) (a) Dubois, J. E.; Molle, G.; Tourillon, G.; Bauer, P. *Tetrahedron Lett.* **1979**, 5069. (b) Molle, G.; Bauer, P.; Dubois, J. E. *J. Org. Chem.* **1982**, *47*, 4120.

(32) Yurachenko, A. G.; Fedorenko, T. V.; Rodionov, U. N. *Zh. Org. Chem.* **1985**, *21*, 1673.

(33) (a) Schaart, B. J.; Blomberg, C.; Akkerman, O. S.; Bickelhaupt, F. *Can. J. Chem.* **1990**, *58*, 932. (b) Bodewitz, H. W. H. J.; Schaart, B. S.; Van der Niet, J. D.; Blomberg, C.; Bickelhaupt, F.; der Hollander, J. A. *Tetrahedron* **1978**, *34*, 2523. (c) Bodewitz, H. W. H. J.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron Lett.* **1975**, 2003; (d) *Tetrahedron* **1975**, *31*, 1053; (e) *Tetrahedron* **1973**, *29*, 719; (f) *Tetrahedron Lett.* **1972**, 281. (g) Grootveldt, H. H.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron Lett.* **1971**, 1999.

(34) Buske, G. R.; Ford, W. T. *J. Org. Chem.* **1976**, *41*, 1998.

(35) We thank Dr. David Powell, Chemistry Department, University of Florida, for the HRMS spectra.

mmHg (lit.[7] bp 65–75 °C (1.2 mmHg)); IR (film) 1720, 1638 cm^{-1}; ^1H NMR δ 1.50–1.70 (m, 6H), 2.42–2.55 (m, 4H), 3.79 (s, 3H).

Methyl 1-Bromospiro[2.5]octanecarboxylate (9). Trimethylsuloxonium iodide (110 g, 0.5 mol) was added portionwise to a slurry of sodium hydride (13.2 g, 0.55 mol) in DMSO (1500 mL). The mixture was stirred at room temperature until a completely clear solution was obtained. Methyl α-bromocyclohexylideneacetate (8) (100 g, 0.429 mol) was added dropwise, and the temperature was controlled by occasional cooling. The reaction mixture was then stirred overnight at room temperature and poured onto crushed ice (5 kg). The oily product was extracted with pentane (500 mL), and the pentane solution was washed thoroughly with water (5 × 500 mL). The organic phase was dried over anhyd magnesium sulfate, and the solvent was removed in vaccum. The residue was distilled to give 75 g (71%) of the desired product, bp 75–80 °C/1 mmHg which was sufficiently pure for further transformations. An analytical sample was obtained by using preparative gas chromatography: IR (film) 1719 cm^{-1}; ^1H NMR δ 0.98 (d, J = 6 Hz, 1H), 1.38–1.70 (m, 10H), 1.70 (d, J = Hz, 1H), 3.74 (s, 3H). Anal. Calcd for $C_{10}H_{15}BrO_2$: C, 48.59; H, 6.13. Found: C, 48.72; H, 6.03.

(±)-1-Bromospiro[2.5]octanecarboxylic Acid (10). Potassium hydroxide (19.6 g, 0.35 mol) was added to a solution of methyl 1-bromospiro[2,5]octanecarboxylate (9) (75 g, 0.3 mol) in 70% alcohol, and the reaction mixture was refluxed overnight. The solvent was evaporated under reduced pressure, and the residue was extracted with ether (3 × 50 mL). The water phase was acidified with 6 N hydrochloric acid and the product extracted with ether (3 × 50 mL). The ether phase was dried over anhyd magnesium sulfate and evaporated to dryness to leave an oily product which solidified on standing: yield 54 g, 78%; mp 130 °C (hexane); IR (nujol) 2500–3200, 1675 cm^{-1}; ^1H NMR δ 1.05 (d, J = 6 Hz, 1H), 1.42–1.74 (m, 10H), 1.75 (d, J = 6 Hz, 1H); ^{13}C NMR δ 24.93, 25.06, 25.53, 28.75, 29.89, 34.20, 35.37, 38.65, 175.56. Anal. Calcd for $C_9H_{13}BrO_2$: C, 46.36; H, 5.63. Found: C, 46.48; H, 5.72.

(±)-1-Bromo-1-(hydroxymethyl)spiro[2.5]octane (11). Lithium aluminum hydride (75 mL, 75 mmoles of a 1 M solution in THF) was added dropwise with stirring and external cooling to a solution of (±)-1-bromospiro[2.5]octanecarboxylic acid (10) (23.3 g, 100 mmol) in ether (200 mL). The reaction mixture was stirred for 1 h at room temperature, quenched with saturated ammonium chloride solution, and filtered, and the filtrate was washed with water (3 × 50 mL), dried over anhyd sodium sulfate, and evaporated to dryness. The oily residue was distilled to give 15.3 g (70%) of the desired alcohol 11: bp 80–85 °C/0.4 mmHg; IR (film) 3360 cm^{-1}; ^1H NMR δ 0.80 (d, J = 6 Hz, 1H), 0.90 (d, J = 6 Hz, 1H), 1.35–1.70 (m, 11), 3.75 (d, J = 13.2 Hz, 1H), 3.91 (d, J = 13.2 Hz, 1H). Anal. Cacld for $C_9H_{15}BrO$: C, 49.32; H, 6.91. Found: C, 49.34; H, 7.09.

(±)-1-Bromo-1-[(tosyloxy)methyl]spiro[2.5]octane (12). Tosyl chloride (11.4 g, 60 mmol) was added portionwise with external cooling to a solution of (±)-1-bromo-1-(hydroxymethyl)-spiro[2.5]octane (11) (10.1 g, 50 mmol) in pyridine (100 mL). The reaction mixture was stirred overnight at room temperature and poured onto crushed ice. The solid product was filtered and washed thoroughly with water. Recrystallization from petroleum ether gave 14.4 g (77%) of the desired product: mp 80 °C; IR (KBr) 1356, 1185, 1172 cm^{-1}; ^1H NMR δ 0.85 (d, J = 6.6 Hz, 1H), 0.88 (d, J = 6.6 Hz, 1H), 1.30–1.70 (m, 10H), 2.41 (s, 3H), 4.19 (d, J = 11.4 Hz, 1H), 4.38 (d, J = 11.4 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H). Anal. Calcd for $C_{16}H_{21}BrO_3S$: C, 51.47; H, 5.68. Found: C, 51.54; H, 5.62.

(±)-1-Bromo-1-methylspiro[2.5]octane (13). (±)-1-Bromo-1-[(toxyloxy)methyl]spiro[2.5]octane (12) (3.73 g, 10 mmol) was added to a commercially available solution of L-Selectride in THF (30 mL, 30 mmol). The reaction mixture was stirred for 3 h at room temperature and quenched with water (2 mL). Sodium hydroxide (10 mL of 30% solution) was added followed by 5 mL of a 30% solution of hydrogen peroxide. When the vigorous reaction had subsided, the reaction mixture was extracted with pentane (30 mL), the organic layer was separated, washed with water (3 × 30 mL), and dried over magnesium sulfate, and the solvent was removed under reduced pressure. The oily residue was purified by using flash chromatography with pentane as an eluent to yield 1.9 g (95%) of product: ^1H NMR δ 0.56 (d, J = 6 Hz, 1H), 0.83 (d, J = 6 Hz, 1H), 1.33–1.69 (m, 10H), 1.81 (s, 3H); ^{13}C NMR δ 25.32, 25.46, 25.81, 26.25, 28.13, 28.54, 31.24, 36.72, 44.20. Anal. Calcd for $C_9H_{15}Br$: C, 53.61; H, 7.46. Found: C, 53.77; H, 7.46.

(±)-1-Methylspiro[2.5]octane (15). *tert*-Butyllithium (10 mmol, 6.7 mL of 1.5 molar solution) was added dropwise with stirring to a solution of (±)-1-bromo-1-methylspiro[2.5]octane (13) (1.01 g; 5 mmol) in THF (20 mL) at −70 °C, and the reaction mixture was stirred for 1 h, quenched with methanol (2 mL), diluted with pentane (25 mL), and washed with water (3 × 25 mL). The organic phase was dried over anhyd magnesium sulfate and the solvent removed by distillation using a spinning band column. The residue was distilled in a Kugelrohr apparatus to afford the desired hydrocarbon: bp 135 °C; yield 0.43 g, 70%; ^1H NMR δ 0.23 (dd, J = 4.8, 4.2 Hz, 1H), 0.28 (dd, J = 4.2, 8.4 Hz, 1H), 0.40–0.52 (m, 1H), 1.00 (d, J = 6.0 Hz, 3H), 1.12–1.48 (m, 10H). Anal. Calcd for C_9H_{16}: C, 86.99; H, 13.01. Found: C, 86.97; H, 13.05.

Reaction of (±)-Bromide 13 with Mg in Ether. Product Distribution. (±)-1-Bromo-1-methylspiro[2.5]octane (13) (2.03 g, 10 mmol) was added to a suspension of Rieke magnesium (720 mg, 30 mmol) in ether (25 mL) containing *tert*-butyl alcohol-*O*-*d*[4b] (40 mmol). The reaction started immediately and was over within minutes, but stirring was continued for 1 h at room temperature. The excess of Rieke magnesium was then cautiously decomposed with saturated ammonium chloride solution, the organic phase was separated, washed with water, dried over anhyd sodium sulfate, and the ether was removed by distillation using a spinning band column. The residue was analyzed by GC–MS techniques, and the products were isolated by using preparative GC.

The following compounds were found:

2,3-Diethoxybutane (16)[12] (diethyl ether dimer) as a 1:1 mixture of meso and (±) isomers; 3%: ^1H NMR δ 1.00–1.30 (m, 12H), 3.35–3.40 (m, 2H), 3.40–3.60 (m, 4H); MS (EI) M^+ 146 (1), 73 (100).

(±)-1-Methylspiro[2.5]octane (15): yield 70%; ^1H NMR δ 0.23 (dd, J = 4.8, 4.2 Hz, 1H), 0.28 (dd, J = 4.2, 8.4 Hz, 1H), 0.40–0.52 (m, 1H), 1.00 (d, J = 6.0 Hz, 3H), 1.12–1.48 (m, 10H); MS (EI) M^+ 124. This product was 33% deuterated as determined by NMR which equates to a 23% yield of Grignard reagent.

Bi-1,1′-methylspiro[2.5]oct-1-yl (17) as a 1:1 mixture of diastereoisomers: yield 3%; ^1H NMR δ 0.08 (d, J = 4.5 Hz, 2H), 0.17 (d, J = 4.5 Hz, 2H), 1.06 (s, 6H), 1.19–1.63 (m, 20H); MS (EI) M^+ 246 (27), 163 (100); HRMS calcd for $C_{18}H_{30}$ 246.2348, found 246.2343.

Polymeric material (320 g) containing aliphatic protons and ether moieties: ^1H NMR δ 0.8–2.0 (broad multiplet), 3.8–3.95 broad multiplet.

1-Methylenespiro[2.5]octane (18). (±)-1-Bromo-1-[(tosyloxy)methyl]spiro[2.5]octane (12) (373 mg, 1 mmol) was added to a slurry of Zinc powder (260 mg, 4 mmol) in DMF (10 mL). The reaction mixture was stirred at 100 °C for 2 h, cooled, and filtered. The filtrate was diluted with pentane (25 mL), washed thoroughly with water (5 × 50 mL), and dried over anhyd sodium sulfate and the solvent evaporated. The residue was purified by flash chromatography (pentane) to give the desired olefin: yield 73 mg, 60%; IR (film) 1619 cm^{-1}; ^1H NMR δ 1.22–1.67 (m, 6H), 1.87–1.95 (m, 2H), 1.98–2.07 (m, 2H), 3.03 (s, 2H), 5.44 (d, J = 1.2 Hz, 1H), 5.59 (J = 1.2 Hz); HRMS calcd for C_9H_{14} 122.1096, found 122.1096.

Grignard Reaction in Ether in the Presence of 1-Methylenespiro[2.5]octane (18). (±)-1-Bromo-1-methylspiro[2.5]-octane (13) (406 mg, 2 mmol) and 1-methylenespiro[2.5]octane (18) (61 mg (0.5 mmol) were added to the slurry of Rieke magnesium (144 mg, 6 mmol) in ether (10 mL). The reaction mixture was stirred for 1 h at room temperature and worked up as in the product distribution experiment described above. The crude product was analyzed by chromatography and NMR, and no olefin 18 could be found. Upon removal of all the volatile components the previously described polymeric material was isolated in substantive amounts (140 mg).

Grignard Reaction of (±)-13 in Ether in the Presence of DCPD. (±)-1-Bromo-1-methylspiro[2.5]octane (13) (203 mg, 1 mmol) was added to a suspension of Rieke magnesium (120 mg, 5 mmol) in ether (15 mL) containing deuterated dicyclohex-

ylphosphine (2.0 g, 10 mmol). The reaction mixture was stirred for 1 h at room temperature and quenched with *tert*-butyl alcohol. The excess of Rieke magnesium was then cautiously decomposed with saturated ammonium chloride solution, the organic phase was separated, washed with water, and dried over anhyd sodium sulfate, and the ether was removed by distillation using a spinning band column. The residue was analyzed by GC–MS techniques. The deuterium incorporation into the main product, 1-methylspiro[2.5]octane (**15**), was found to be 6% (calculation based on molecular ion, M^+ 124).

Grignard Reaction in Perdeuterated Diethyl Ether. (±)-1-Bromo-1-methylspiro[2.5]octane (**13**) (203 mg, 1 mmol) was added to a flask containing magnesium turnings (36 mg, 1.5 mmol; mechanically activated[13]) in perdeuterated ether (2 mL; Cambridge Isotope Laboratories, 99% D). The reaction was initiated by the addition of a small amount of ethylene bromide. The reaction mixture was refluxed for 2 h, cooled to room temperature, and quenched with methanol (1 mL). Usual workup afforded the product mixture which was further analyzed by NMR in order to assess the extent of deuterium incorporation into the main product, 1-methylspiro[2.5]octane (**15**) (70% of the total yield). Integration of the methyl signals corresponding to the deuterated and nondeuterated compound showed that the hydrocarbon is 18% deuterated. Taking into account the total yield of hydrocarbon this result equates to 13% of the radicals being trapped by the solvent.

Resolution of (±)-1-Bromospiro[2.5]octanecarboxylic Acid (10). Commercial dehydroabietylamine (250 g, 60%) in 42 mL of toluene was added, at 75 °C, to a solution of 58 g of acetic acid in 140 mL of toluene. The solution was stored at ambient temperature for 4 h. The salt was collected, washed with cold toluene and pentane, and recrystallized twice from 350 mL of toluene to give after air drying 90 g (60%) of colorless solid: mp 139 °C, $[\alpha]^{25}_D$ +33° (*c* 1, methanol),[36] 141–143 °C, $[\alpha]^{25}_D$ +30°.

The salt was added to a mixture of 300 mL of 20% NaOH/300 mL ether. The mixture was chilled, and the amine was extracted with 400 mL of ether. The ether solution was washed with 3 × 100 mL of 10% NaOH and water and dried over K_2CO_3. The solvent was removed under vacuo to give a colorless oil which crystallized after storage at ambient temperature: mp 46 °C; ^{1}H NMR δ 0.89 (s, 3H), 1.20 (d, 6H), 1.22 (s, 3H), 1.3–2.0 (m, 16H), 6.9 (s, 1H), 7.0 (d, J = 8.4 Hz, 1H), 7.2 (d, J = 8.4 Hz, 1H).

To a solution of (±)-1-bromospiro[2.5]octanecarboxylic acid (**10**) (22 g, 94 mmol) in 900 mL of ethyl acetate and heated under reflux was added dropwise a solution of dehydroabietylamine (13.4, 47 mmol) in 400 mL of ethyl acetate. The addition was maintained slowly over a 6-h period in order to avoid a rapid precipitation. After the addition was completed, the solution was allowed to cool to ambient temperature for 12 h. The white needles were collected and recrystallized once from 400 mL of a methanol/ethyl acetate (7:1) mixture and then three times from 150 mL of methanol to give 4.2 g of a sharp melting solid, mp 187 °C. The suspension of the salt in 150 mL of ether was added to a 150-mL cold solution of 10% NaOH. The mixture was shaken vigorously until all of the solid had dissolved. The ether layer was separated, and the aqueous solution was washed with ether and acidified with a solution of 30% HCl. After extraction with ether, the organic layers were combined, washed with saturated NaCl, and dried over anhyd $MgSO_4$, and the solvent was removed in vacuo to give 1.8 g of optically pure acid as a white solid: mp 87 °C, $[\alpha]^{25}_{Hg}$ −13° (*c* 0.9, $CHCl_3$); IR (Nujol) 3200, 1700, 1665 cm^{-1}; ^{1}H NMR spectrum identical with that of the racemic sample.

The mother liquors were combined and the solvents evaporated. The salt was decomposed with cold 10% NaOH, and the liberated amine was extracted with ether. The aqueous solution was washed with ether and acidified with cold 30% HCl, and the carboxylic acid was extracted into ether. The combined ether extracts were washed once with dilute HCl and twice with saturated NaCl and dried over anhyd $MgSO_4$. Removal of the solvent gave 17.5 g of the partially enriched with (+)-acid, mp 123 °C. The latter was dissolved in 150 mL of hot hexane, and the solution was seeded with a crystal of racemic acid. The resulting crystals were filtrated, and the mother liquors were concentrated and crystallized once more to yield 14.9 g of the racemic acid, mp 130 °C. The remaining filtrate was evaporated to give 2.2 g of (*R*)-(+)-acid: mp 85–86 °C; $[\alpha]^{25}_{Hg}$ +12° (*c* 0.8, $CHCl_3$); IR and ^{1}H NMR spectra were identical with those of (*S*)-(+)-acid.

Finally the recovered racemic acid was subjected to the same process of resolution described above to collect a total amount of 5.8 g of (*S*)-(−)- and 6.4 g of (*R*)-(+)-acid.

Determination of Optical Purities of (*R*)-(+)- and (*S*)-(−)-1-Bromospiro[2.5]octanecarboxylic Acid (10). A diastereoisomeric mixture of amides **14** was prepared from racemic 1-bromospiro[2.5]octanecarboxylic acid (**10**) and optically pure (*S*)-(−)-α-methylbenzylamine. To a solution of **10** (100 mg, 0.43 mmol) in 7 mL of dry CH_2Cl_2 was added a 2 M solution of oxalyl chloride in CH_2Cl_2 (0.7 mL) and a drop of DMF. After the solution was stirred for 0.5 h at room temperature, the solvent and the excess of oxalyl chloride were removed in vacuo and the residue dissolved in 4 mL CH_2Cl_2 and treated with 2 equiv of (*S*)-(−)-α-methylbenzylamine at 0 °C for 2 h. The solution was poured onto a mixture of ice and HCl and extracted with ether. The ether layers were combined and washed successively with 10% NaOH, 5% HCl, and saturated NaCl and dried over anhyd $MgSO_4$. The solvent was evaporated in vacuo to give a glassy solid: ^{1}H NMR showed a mixture of two diastereoisomers in a 1:1 ratio δ 0.92 (d, J = 6 Hz, 1H), 1.49 (d, J = 7.2 Hz, 3H of (*S*,*S*)-diast), 1.53 (d, J = 6.5 Hz, 3H of (*S*,*R*)-diast), 1.5–1.7 (m, 10H), 1.83 (d, J = 6 Hz, 1H of (*S*,*S*)-diast), 1.85 (d, J = 6 Hz, 1H of (*S*,*R*)-diast), 5.1 (m, 1H), 6.7 (m, 1H), 7.3 (m, 5H).

The same procedure was used to convert (*S*)-(−)-1-bromospiro-[2.5]octanecarboxylic acid (**10**) to the corresponding amide **14** by reaction with (*S*)-(−)-α-methylbenzylamine. The above isolation procedure gave in quantitative yield the (*S*,*S*)-(−)-amide **14** as a white solid: mp 126 °C; $[\alpha]^{25}_{Hg}$ −62° (*c* 0.5, $CHCl_3$); IR (KBr) 3290, 1640, 1524 cm^{-1}; found by ^{1}H NMR to be free of the (*S*,*R*)-diastereoisomer δ 0.92 (d, J = 6 Hz, 1H), 1.49 (d, J = 7.2 Hz, 3H), 1.5–1.7 (m, 10H), 1.83 (d, J = 6 Hz, 1H), 5.1 (m, 1H), 6.7 (m, 1H), 7.3 (m, 5H). Anal. Calcd for $C_{17}H_{22}ONBr$: C, 61.08; H, 6.65. Found: C, 60.76; H, 6.88.

In an identical manner the (*R*)-(+)-1-bromospiro[2.5]octanecarboxylic acid (**10**) was converted to the corresponding amide **14** with (*S*)-(−)-α-methylbenzylamine. The ^{1}H NMR showed an optical purity of 94% determined from the signals corresponding to one of the cyclopropyl protons and the methyl group δ 0.92 (d, J = 6 Hz, 1H), 1.53 (d, J = 6.5 Hz, 3H), 1.5–1.7 (m, 10H), 1.85 (d, J = 5.6 Hz, 1H), 5.1 (m, 1H), 6.7 (m, 1H), 7.3 (m, 5H).

X-ray Analysis of the (*S*,*S*)-(−)-Amide 14. Single crystals of (−)-amide **14** ($C_{18}H_{22}BrON$) made from (−)-acid **10** were grown by slow evaporation from a 2-propanol solution. The crystals were monoclinic, space group $P2_1$ with a = 11.733(3) Å, b = 9.892(6) Å, c = 14.313(5) Å and d_{calcd} = 1.42 g cm^{-3} for Z = 4 (M_r = 348.32). The intensity data were measured on a CAD4 Enraf Nonius diffractometer (Mo radiation, monochromated, θ − 2θ scans). The size of the crystal used for data collection was approximately 0.15 × 0.15 × 0.3 mm^3. No absorption correction was necessary (μ = 24.7). A total of 3219 reflections were measured for 2θ ≤ 50°, of which 1760 were considered to be observed [$I \geq 2\sigma(I)$]. The structure was solved by direct methods using MULTAN 78[1] and refined by full-matrix least-squares methods. In the final refinement, anisotropic thermal parameters were used for non-hydrogen atoms. Methyl hydrogen atoms where located from a difference Fourier map; the remaining hydrogen atoms parameters were calculated assuming idealized geometry. Hydrogen atom contributions were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were R = 5.8 and R_w = 5.4% for the 1760 observed reflections. The final difference Fourier map was essentially featureless with no peaks greater than 0.3 e A^{-3}. The absolute configuration of the (−) acid **10** was found to be (*S*)-(−). The author has deposited coordinates for (*S*,*S*)-(−)-**14** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(*R*)-(−)- and (*S*)-(+)-1-Bromo-1-(hydroxymethyl)spiro-[2.5]octane (11). The optically pure carbinols **11** were prepared

(36) Gottstein, W. J.; Cheney, L. C. *J. Org. Chem.* **1965**, *30*, 2072.

following the same precedure as for the racemic material. From acid having $[\alpha]^{25}_{Hg}$ −13° was obtained (*S*)-(+)-1-bromo-1-(hydroxymethyl)spiro[2.5]octane (**11**): $[\alpha]^{25}_{Hg}$ +39° (*c* 0.7, $CHCl_3$). Acid with $[\alpha]^{25}_{Hg}$ +12° gave (*R*)-(−)-carbinol **11** $[\alpha]^{25}_{Hg}$ −37° (*c* 1, $CHCl_3$). ^1H NMR were identical with that of the racemic compound.

(*R*)-(−)- and (*S*)-(+)-1-Bromo-1-[(tosyloxy)methyl]spiro[2.5]octane (12). Identical procedures as for the racemic material were used to prepare optically pure tosylates **12**. From (*S*)-(+)-carbinol **11** was prepared (*S*)-(+)-1-bromo-1-[(tosyloxy)methyl]-spiro[2.5]octane (**12**), mp 78 °C, $[\alpha]^{25}_{Hg}$ +17° (*c* 1, $CHCl_3$), and the carbinol **11** with $[\alpha]^{25}_{Hg}$ −37° (*c* 1, $CHCl_3$) gave (*R*)-(−)-tosylate **12**, mp 78 °C, $[\alpha]^{25}_{Hg}$ −16° (*c* 1.2, $CHCl_3$). ^1H NMR were identical with that of the racemic sample.

(*R*)-(−)- and (*S*)-(+)-1-Bromo-1-methylspiro[2.5]octane (13). The reductions of the optically pure tosylates with L-Selectride were conducted in a manner identical with that used for the racemic compound to yield from tosylate (*S*)-(+)-**12** having $[\alpha]^{25}_{Hg}$ +17°, (*S*)-(+)-1-bromo-1-methylspiro[2.5]octane (**13**), $[\alpha]^{25}_{Hg}$ +37° (*c* 1.2, $CHCl_3$). The tosylate with $[\alpha]^{25}_{Hg}$ −16° gave the (*R*)-(−)-**13** bromide, $[\alpha]^{25}_{Hg}$ −35° (*c* 0.8, $CHCl_3$). ^1H NMR were identical with that of the racemic compound.

Conversion of (*S*)-(+)-1-Bromo-1-methylspiro[2.5]octane (13) to (±)-1-Methylspiro[2.5]octanecarboxylic Acid (19) via Single-Electron Transfer from Li–Aromatic Anion Radical. To a solution of 128 mg (1 mmol) of naphthalene in 4 mL of dry THF was added lithium metal (7 mg, 1 mmol) under an argon atmosphere. The mixture was stirred at ambient temperature until the lithium was completely consumed (ca. 2 h). The green solution of lithium naphtalenide was transfered via a cannula into the solution of (*S*)-(+)-1-bromo-1-methylspiro[2.5]octane (**13**), $[\alpha]^{25}_{Hg}$ +26.5° (*c* 1.6, $CHCl_3$) (200 mg, 1 mmol), in 1 mL of dry THF. The reaction mixture was stirred for 15 min at ambient temperature and then carbonated by passing a stream of CO_2 through the solution at −30 °C. The mixture was allowed to reach ambient temperature, poured onto a mixture of ice and HCl, and extracted with ether. The acid was separated from the mixture by extraction with 10% NaOH. The aqueous layer was washed with ether and acidified with HCl. After extraction with ether, the organic layers were combined, washed with saturated NaCl, and dried over anhyd $MgSO_4$. Removal of the solvent in vacuo gave 36 mg (21%) of racemic acid **19**: mp 52–53 °C; IR (KBr) 3500–2300, 1672 cm^{-1}; ^1H NMR δ 0.47 (d, *J* = 4.8 Hz, 1H), 1.31 (d, *J* = 4.8 Hz, 1H), 1.36 (s, 3H), 1.42–1.58 (m, 10H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.60. Found: C, 71.52; H, 9.57.

Following the procedure described above (±)-1-methylspiro-[2.5]octanecarboxylic acid (**19**) was converted to the amide **20** with (*S*)-(−)-α-methylbenzylamine to give, after isolation, in quantitative yield, a mixture of two diastereoisomers in a 1:1 ratio: mp 65–80 °C; IR (KBr) 3319, 1619, 1523 cm^{-1}; ^1H NMR δ 0.28 (d, *J* = 4.8 Hz, 1H), 1.08 (d, *J* = 4.8 Hz, 1H of (*S*,*S*)-diast), 1.125 (d, *J* = 4.8 Hz, 1H of (*R*,*S*)-diast), 1.32 (s, 3H), 1.38–1.48 (m, 10H), 1.46 (d, *J* = 7.2 Hz, 3H of diast *RS*), 1.5 (d, *J* = 7.2 Hz, 1H of (*S*,*S*)-diast), 5.1 (m, 1H), 5.75 (m, 1H), 7.25 (m, 5H). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.67; H, 9.30. Found: C, 79.61; H, 9.34.

Conversion of (*S*)-(+)-1-Bromo-1-methylspiro[2.5]octane (13) to (*S*)-(+)-1-Methylspiro[2.5]octanecarboxylic Acid (19) via Halogen–Metal Exchange. To a solution of (*S*)-(+)-1-bromo-1-methylspiro[2.5]octane (**13**) (268 mg, 1.3 mmol), $[\alpha]^{25}_{Hg}$ +37°, in 5 mL of dry ether, under argon at −78 °C, was added dropwise 1.9 mL (2.8 mmol) of a 1.5 M solution of *tert*-butyllithium in pentane. After complete addition the mixture was stirred at −78 °C for 30 min and then carbonated by passing a stream of CO_2 through the solution. The reaction mixture was allowed to reach ambient temperature, poured onto a mixture of ice and NaOH, and washed with pentane. The basic layer was neutralized with 10% HCl and extracted with ether. The etheral layers were combined, washed with saturated NaCl, and dried over anhyd $MgSO_4$. Removal of the solvent in vacuo gave 150 mg (69%) of (*S*)-(+)-1-methylspiro[2.5]octanecarboxylic acid (**19**): mp 49–50 °C; $[\alpha]^{25}_{Hg}$ +20° (*c* 0.97, $CHCl_3$). ^1H NMR identical with that of the racemic sample.

Conversion of the acid **19** to the amide **20** with (*S*)-(−)-α-methylbenzylamine following the procedure described above gave in quantitative yield the (*S*,*S*)-amide **20** which was found by ^1H NMR to be free of the (*S*,*R*)-diastereoisomer: ^1H NMR δ 0.28 (d, *J* = 4.8 Hz, 1H), 1.08 (d, *J* = 4.8 Hz, 1H), 1.32 (s, 3H), 1.38–1.48 (m, 10H), 1.5 (d, *J* = 7.2 Hz, 3H), 5.1 (m, 1H), 5.75 (m, 1H), 7.25 (m, 5H).

Preparation of Optically Active Grignard Reagent in THF from the Reaction of (*S*)-(+)-1-bromo-1-methylspiro-[2.5]octane (13) with Rieke Magnesium. (*S*)-(+)-1-Bromo-1-methylspiro[2.5]octane (**13**), $[\alpha]^{25}_{Hg}$ +37° (*c* 1.2, $CHCl_3$) (200 mg, 1 mmol), was injected neat into a suspension of Rieke magnesium (120 mg, 5 mmol) in 6 mL of THF at ambient temperature. After the reaction had been completed (2 h), the reaction mixture was carbonated by passing carefully dried carbon dioxide at −78 °C through the mixture. The reaction mixture was allowed to reach room temperature and then quenched with 10% HCl. The products were extracted with pentane, and the acid was subsequently separated from neutral products by extraction with 10% NaOH followed by acidification (HCl) and extraction with ether. The ether fraction was evaporated to give the desired acid, and neutral products were analyzed (GC and NMR) after evaporation of the original pentane solution. The following products were found:

1-Methylspiro[2.5]octane (15): yield 20%; racemic. ^1H NMR was identical with that of authentic sample.

1-Methylspiro[2.5]octanecarboxylic acid (19): 97 mg, 58%; mp 52 °C. IR and ^1H NMR identical to those described above. This sample showed a very low value of the optical rotation. Polarimetry was not relied upon to determine its optical purity and absolute configuration. Instead, an NMR method previously described was used.

After conversion of the acid **19** to the amide **20** with (*S*)-(−)-α-methylbenzylamine the optical activity and configuration were determined easily by ^1H NMR from the signals corresponding to the cyclopropyl protons. The integration showed 13% of retention of optical activity and configuration.

Preparation of Optically Active Grignard Reagent in Ether from the Reaction (*S*)-(+)-1-Bromo-1-methylspiro-[2.5]octane (13) with Rieke Magnesium. Rieke magnesium was first prepared in THF, and the THF was substituted by the desired amount of dry ether (6 mL). (*S*)-(+)-1-Bromo-1-methylspiro[2.5]octane (**13**) was subjected to the reaction with Rieke magnesium in an identical manner as in THF. After carbonation and workup, the mixture was submitted to the same procedure of isolation and analysis to show the following products:

1-Methylspiro[2.5]octane (15): yield 42%, racemic. ^1H NMR was identical with that of an authentic sample.

1-Methylspiro[2.5]octanecarboxylic acid (19): 42 mg, 25%. ^1H NMR was identical with that of an authentic sample.

The formation of the amide **20** with (*S*)-(−)-α-methylbenzylamine was conducted following the same procedure as previously described. After isolation, the crude product was analyzed by ^1H NMR and comparison with authentic samples to show from the integration of the signals corresponding to one of the cyclopropyl protons a 10% of retention of optical activity and configuration.

Acknowledgment. This work was supported by grants from the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, to whom we are grateful.