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Chiral Carbenoids: Their Formation and Reactions

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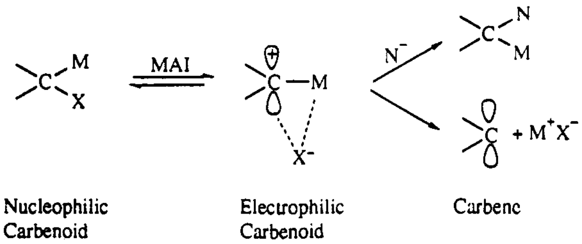
Carbenoids, generated by metalation or halogen–metal exchange reactions, have been prepared from chiral vinyl and cyclopropyl halides. The reactivity and stereochemistry observed in the reaction of these carbenoids has been interpreted as being due to metal-assisted ionization (MAI).

Introduction

During the course of our study of chiral vinyllithium reagents[1] we frequently witnessed the formation of byproducts which could be rationalized as resulting from a nucleophilic-type substitution on a vinylidene carbenoid. Several studies have been undertaken to elucidate the mechanism of these interesting reactions. The results of our initial investigations have been published, in part, in the form of short communications.[2-4] When the substrates were optically active we always observed that the products formed were also optically active, with remarkable preservation of optical activity and usually with inversion of configuration. We suggested that carbenoids were best viewed as cationic intermediates (electrophiles) in which the metal is assisting in the ionization of the carbon–halogen bond, thus forming a carbon cation–halogen anion tight ion pair which is then attacked by a nucleophile from the face opposite the halogen. Using stereochemistry as a probe enabled us to unambiguously show that the substitution products were formed by direct attack of the nucleophile on the carbenoid and not by trapping of the carbene by the nucleophile.

By definition carbenoids are species bearing a metal atom and a halogen atom on the same carbon. Their chemistry has been thoroughly reviewed.[5] Closs and Moss suggested the appellation "carbenoid" to the species and also that it is this intermediate that is responsible for electrophilic reactions and not carbene intermediates.[6] In fact, carbenoids are capable of undergoing ambiphilic reactions[7-9] depending on the temperature. At very low temperatures, ~−110 °C, where the carbon–metal bond is mainly covalent, carbenoids behave as ordinary nucleophiles and as such they react with different electrophiles to give the normal products of alkylation, acylation, etc. At higher temperatures, ~−80 °C, due to metal-assisted ionization (MAI),[2] they behave as electrophiles and at still higher temperatures they undergo α-elimination and are converted to carbenes. The exact temperature range for these transitions will, of course, depend on the substituents attached to the carbenoid carbon, the metal, the halogen, as well as the solvent.



The effect of metal is very pronounced; potassium and sodium carbenoids are very unstable and the lithium derivatives can only be prepared at very low temperature. When one moves, however, to other metals much more stable species can be obtained.[11] Some of these, for example, tin carbenoids, can be isolated and even distilled in vacuo.[12] The covalent nature of the carbon–tin bond is obviously responsible for this stability. For the alkali metals lithium and sodium, ab initio calculations performed by Schleyer[13] for lithio- and sodiofluoromethylenes showed large stabilization by fluorine (4 kcal/mol) due to the favorable Li–F interaction whereas fluorine stabilization in the sodio derivative is similar to that found in the "naked anion"[14] thus indicating that sodium is only an "ionic spectator".[13] At higher temperatures they undergo α-elimination[10] to produce carbenes.

The electrophilic nature of carbenoids is perhaps their most intriguing property. It implies that a partial positive

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charge is located (or developed) at the carbenoid carbon atom. Seebach and co-workers[15] have provided compelling ^{13}C-NMR experimental evidence to support the idea that carbenoids are electron deficient at carbon. They observed large deshielding (50–100 ppm) upon replacing a proton by lithium, $\Delta\delta$(H, Li), on vinyl and cyclopropyl carbons. Therefore, these carbenoids would be expected to react with an excess of organolithium reagent (external nucleophile) to form substitution products.[8a,c,16,17] Known also are numerous examples where the nucleophile is transferred intramolecularly from the coordination sphere of the metal to the carbenoid carbon. Such substitutions have been accomplished with zinc,[18] boron,[19] copper,[20] zirconium,[21] and other derivatives.[22] Only occasionally has the stereochemistry of those substitutions been inferred.[8d,9c]

There are, however, several other types of reactions where the intermediacy of carbenes has been postulated, such as in the extensive investigations of the reactions of haloforms with organolithiums and trapping the intermediates with olefins. Both carbene and carbenoid mechanisms have been suggested[5b,10] for these reactions since it is difficult to distinguish between them. As we mentioned earlier stereochemistry could be such a tool since carbene intermediates are achiral whereas carbenoids, depending on their stability, can be chiral. This may well be the case for lithium carbenoids if the carbon–lithium bond is sufficiently covalent. Nucleophilic substitution on a chiral carbenoid would lead to a chiral product whereas α-addition of a nucleophile to a carbene would give racemic product.

The vinyl and cyclopropyl systems selected for study have two important features. One is that the increase in s-character of the cyclopropyl (sp$^{2.28}$) and vinyl (sp^2) carbon atoms will produce a more covalent carbon–lithium bond and the other is that cyclopropyl and vinyl halides solvolyze extremely slowly.[23] However, when a lithium atom is attached to the halogen-bearing carbon atom (carbenoid) then solvolysis occurs rapidly even at very low temperatures and we attribute this phenomenon to metal-assisted ionization (MAI).[2]

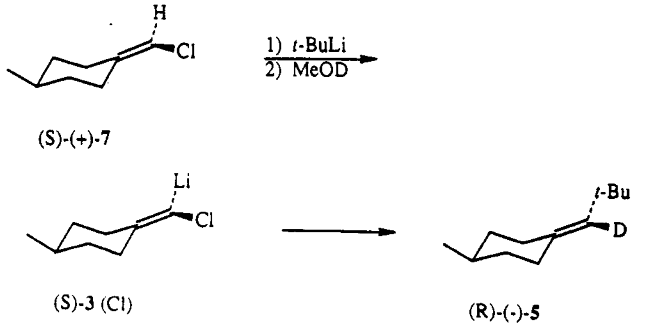
Two general methods exist to generate carbenoids: metal–halogen exchange between an organometallic (usually organolithium) reagent and a gem-dihalo derivative[24] and α-metalation of an organic halide (hydrogen–lithium exchange).[25] The former method is usually considered preferable since the reaction is cleaner and may frequently be conducted at lower temperature thus enabling preparation of the desired carbenoid at a temperature at which it is stable. The latter approach may in principle be only applied to alkyl chlorides and fluorides which do not undergo the lithium–halogen exchange reaction at significant rates and hence metalation can occur. This method of generating carbenoids is still often used mainly due to the greater availability of the starting halide compared with that of the corresponding dihalo compound. The reaction, however, is plagued by side reactions, especially β-eliminations.

In this paper we wish to report the results of our research on the mechanism and stereochemistry of reactions of chiral carbenoids with nucleophiles.

Results and Discussion

Treatment of (*S*)-(+)-(4-methylcyclohexylidene)bromomethane (1) of known absolute configuration and optical purity[1a,26] in ether at −90 °C with 2 equiv of *t*-BuLi followed by deuteriolysis yielded (*S*)-(−)-(4-methylcyclohexylidene)deuteriomethane (4), (*R*)-(−)-(4-methylcyclohexylidene)-1′-deuterio-2′,2′-dimethylpropane (5), and (*S*)-(−)-bis(4-methylcyclohexylidene)-2′-deuterioethane (6) with 1.0 equiv of deuterium in each compound. Compound 4 is the major product and is the result of the usual halogen–metal exchange reaction, whereas compounds 5 and 6 are derived from carbenoid 3(Br). Interestingly enough the formation of the carbenoid 3(Br) and the products derived from it could be almost completely supressed by carrying out the reaction in THF since this solvent promotes halogen–metal exchange.

Since vinyl chlorides undergo the metalation reaction at a much faster rate than the chlorine–lithium exchange with *tert*-butyllithium this would diminish the formation of products derived from chiral vinyllithium 2 and would largely result in the formation of the carbenoid intermediate 3(Cl) to produce 5 as a main product. Chiral (*S*)-(+)-(4-methylcyclohexylidene)chloromethane (7) was prepared, in 60% yield, with retention of configuration from (*S*)-(+)-1 by treating the latter with *tert*-butyllithium followed by reaction with benzenesulfonyl chloride. Chiral vinyl chloride 7 was reacted with *tert*-butyllithium to give, as expected, mainly (*R*)-(−)-5 and only traces of 4 and no detectable amount of 6. The results are summarized in Table I.



The most important observation about these reactions is that product 5 is optically active and of inverted

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Scheme I

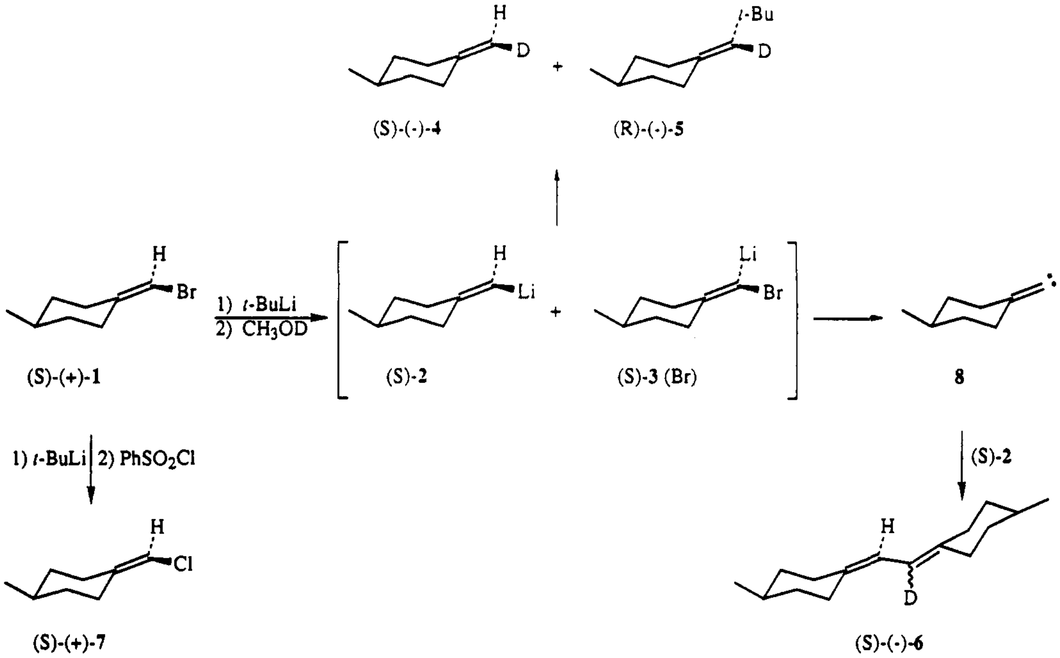


Table I. Reactions of (*S*)-(+)-(4-Methylcyclohexylidene)bromo- and chloromethanes with *tert*-Butyllithium[2]

halide	solvent	*T*, °C	**4** % yield (% OP)	**5** % yield (% OP)[a]	**6** % yield (% OP)[b]
Br	ether	-90	58 (100)	17 (39)	0.5 (58)
	THF	-90	90 (100)	5 (53)	5 (50)
Cl	ether	-75		36 (31)	
	THF	-75		70 (39)	

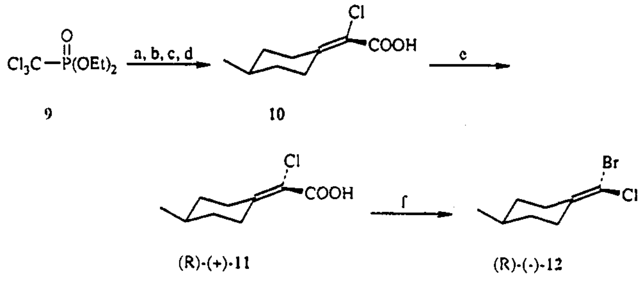
[a] Based on optically pure **5** $[\alpha]^{27}_{\mathrm{Hg}}$ + 9.68 (*c* = 1.0, chloroform). [b] Based on optically pure **6** $[\alpha]^{27}_{\mathrm{Hg}}$ +40.3 (*c* = 0.63, ethanol).[1b]

configuration. The optical purities found were remarkably high (31–53%), which indicates that the product was formed by a nucleophilic type substitution on the vinylidene carbenoid and not by trapping of the carbene by the nucleophile. The achiral carbene would have given rise to a completely racemic product (Scheme III).

That inversion did occur was proved by synthesizing an authentic sample of **5**. Thus (*S*)-(+)-**1** was reacted with di-*tert*-butylcuprate to give (*S*)-(+)-**5**. Since this reaction is known to proceed with complete retention of configuration,[27] the absolute configuration and optical purity of **5** has therefore been established.

The formation of the other carbenoid derived product **6** can be explained simply as the result of the addition of the optically stable vinyllithium **2**[1] to achiral carbene **8**. This would account not only for the retention of configuration but for the observed ~50% optical purity as well. Moreover **6** is formed only when the vinyl bromide **1** is used in full agreement with our mechanism. The structure of (*S*)-(−)-**6** as well as its absolute configuration and optical purity has been previously established.[1b]

Scheme II[a]



[a] Key: (a) 2*n*-BuLi/−80 °C; (b) ClCOOMe/−125 °C; (c)  /−60 °C; (d) KOH, H_3O^+; (e) resolution/quinine; (f) Br_2/Na_2CO_3.

Since carbenoid **3**(Cl) could not be effectively prepared from **7** by metalation at temperatures below −75 °C, we sought another method for its formation. Since the lithium–halogen exchange reaction is known to proceed rapidly at low temperatures (<100 °C) and with complete retention of configuration at carbon,[28] this became the method of choice. To this end we prepared (4-methylcyclohexylidene)bromochloromethane (**12**), the synthesis of which is depicted in Scheme II.

Thus, diethyl trichloromethanephosphonate (**9**) was converted to the ester **10** in a one-pot synthesis by sequential treatment of **9** with 2 equiv of *n*-butyllithium at −90 °C, methyl chloroformate at −125 °C, and 4-methylcyclohexanone at −60 °C.[29] The crude ester **10** was then saponified to give (4-methylcyclohexylidene)chloroacetic acid (**11**) in 59% overall yield. The racemic acid was converted by brominative-decarboxylation to either the racemic olefin **12** or, after resolution of **11** with quinine, to the optically active (*R*)-(−) olefin. The reaction with bromine and sodium carbonate (brominative-decarboxylation) had previously been shown to proceed with complete inversion of configuration.[1a] The optical purity of **11** was determined by NMR using diastereomeric amides with (*R*)-(+)-methylbenzylamine and was found to have ee = 90%. A sample of diastereomerically pure amide was subsequently obtained by recrystallization from

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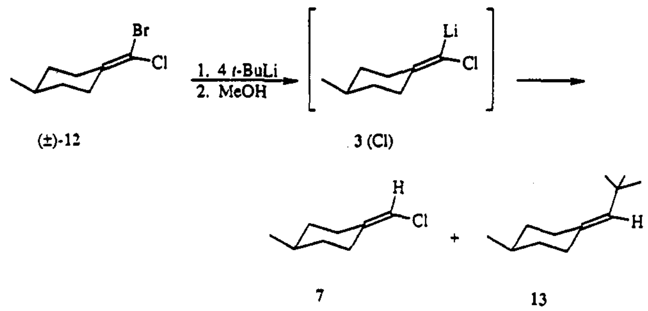
Table II. Reaction of (±)-(4-Methylcyclohexylidene)bromochloromethane (12) with *tert*-Butyllithium in THF

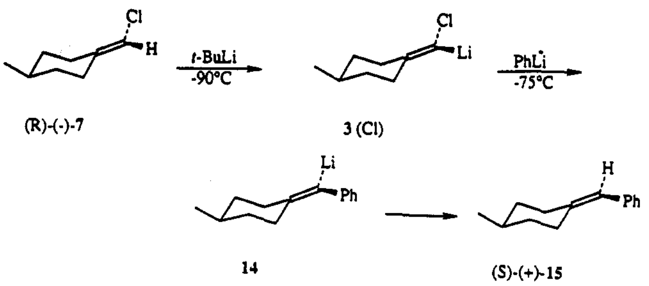


expt	time, h	T, °C	% yield of 7	% yield of 13
1	0.5	-100	45	35
2	3	-100	15	60
3	8	-100	8	64
4	3	-70	7	60

hexane and was used to grow a single crystal for X-ray analysis which established the absolute configuration of the acid 11 as (*R*)-(+); hence, its derivative 12 is assigned the (*R*)-(−) configuration.

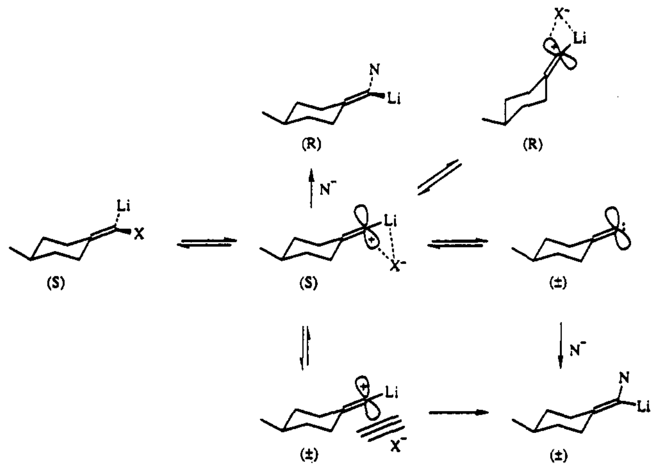
Initially racemic (4-methylcyclohexylidene)bromochloromethane (12) was treated with an excess of *tert*-butyllithium in order to investigate the product distribution under different reaction conditions and to determine the stability of 3(Cl). The results are presented in Table II.

The most important finding is that carbenoid 3(Cl), when generated at sufficiently low temperature, is quite stable. The yields of 7 (protonated carbenoid) are quite high, indicating that the substitution reaction, even at −70 °C, is not complete. The same reaction was finally carried out with optically active (*R*)-(−)-12 by generating the carbenoid at −100 °C (where it is quite stable) and allowing it to react with an excess of *tert*-butyllithium for 3 h at −70 °C. Product 13 was again found to be optically active with 38% net inversion of configuration. Finally, we were able to show that the nucleophile which reacts with the carbenoid need not be the same one used to generate the carbenoid. Thus, optically active (*R*)-(−)-7 was treated with 1 equiv of *tert*-butyllithium at −90 °C, and the resulting carbenoid was reacted with an excess of phenyllithium at −75 °C for 5 h. The expected product 15[30] was obtained in 70% yield and with 13% inversion of configuration. We suspect that the low optical purity is probably due to the limited configurational stability of the intermediate phenyl substituted vinyllithium 14.



On the basis of the experimental data presented so far we propose the mechanism shown in Scheme III below.

Scheme III. Metal-Assisted Ionization



In this mechanism we assume that at a temperature characteristic for each particular carbenoid a weakening of the carbon–halogen bond takes place and that this process is assisted by the lithium atom attached to the same carbon. We call this process metal-assisted ionization (MAI). The result is that the nature of the carbenoid is changed from a nucleophilic organometallic-like reagent to an electrophilic species. During the ionization process the carbenoid carbon undergoes rehybridization placing the developing positive charge in a p-orbital and producing a tight ion pair.[31] Lithium is now colinear with the two unsaturated carbon atoms and the leaving halide is still blocking one enantioface of the substrate. This view is consistent with the ^{13}C-NMR results of Seebach[17] who showed that carbenoids like 3 are electron deficient at carbon. The incoming nucleophile would therefore attack from the opposite face leading to inversion of configuration. There are several possible modes of racemization: firstly, when the leaving halide becomes solvent separated the substrate is linear and achiral, secondly, when the achiral carbene is produced (when α-elimination is completed), and thirdly, occurring within the solvent cage, the lithium atom behaves as a pivotal point about which the halogen can migrate from one face to the other. The final result is net inversion of configuration with some racemization, the process being reminescent of the solvolysis of chiral halides.[32] However, it is metal-assisted ionization that provides the driving force to permit vinyl halides to undergo solvolysis even at very low temperatures.

We suggest that our mechanism can also be applied to the Fritsch–Buttenburg–Wiechell rearrangement for which it has been shown that the migrating group has a trans relationship to the leaving group.[33] Finally, we would like to point out that our mechanism not only accounts for nucleophilic substitution on carbenoids but also represents our view of the α-elimination reaction, in that it is the halide which leaves first followed by the metal.

Since fluorides solvolyze roughly 10^6–10^7 slower than chlorides it was of interest to determine whether MAI would still be operative when the halogen is fluoride. To

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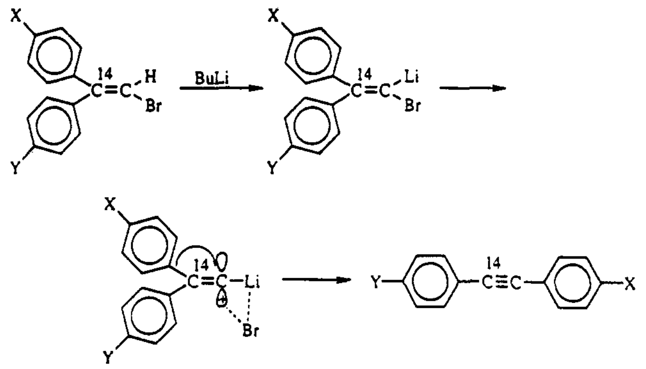
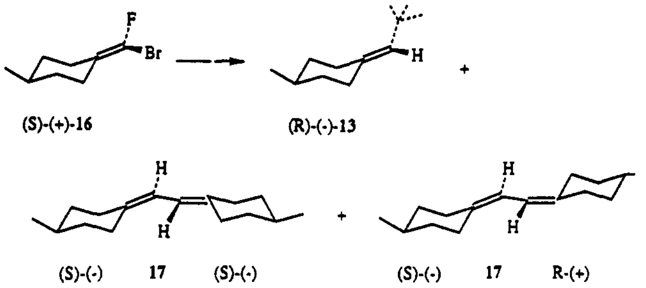


this end the previously synthesized (*S*)-(+)-(4-methylcyclohexylidene)bromofluoromethane (**16**) was prepared.[4,34] This was treated with 3 equiv of *tert*-butyllithium in ether at −100 °C for 5 min to give, after protonolysis with methanol, 40% of (*R*)-**13**, $[\alpha]^{22}_{\mathrm{Hg}}$ −9.7 (c = 1.1, chloroform), along with 30% of (*S*)-(−)-1,2-bis(4-methylcyclohexylidene)ethane (**17**), $[\alpha]^{22}_{\mathrm{Hg}}$ −10.9 (c = 1.0, ethanol). The latter was shown by NMR to be a mixture, in equal amounts, of two diastereoisomers, chiral (*S*)-(−)-(**17**) and meso **17**.



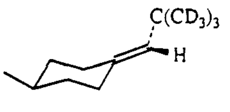
(S)-(+)-16 (R)-(-)-13

(S)-(-) 17 (S)-(-) (S)-(-) 17 R-(+)

These results are quite interesting. It seems that the fluorocarbenoid **18** is much less stable (more reactive) than its chloro counterpart. But the most surprising observation is that **13** is virtually optically pure and moreover that it is obtained with retention rather than the expected inversion of configuration. Apparently fluorine, due to its high electronegativity, not only participates in metal-assisted ionization very effectively but also plays a unique role in directing the incoming nucleophile. Finally, formation of **17** is surprising. This product as not observed in detectable amounts in the reactions of the chlorocarbenoid precursors **7** or **12**. It was only found in the reaction of the bromide **1** where it resulted from the reaction of the intermediate vinyllithium **2** with carbene **8**. Obviously, vinyllithium **2** must somehow have been produced in the reaction of **16** with *tert*-butyllithium.

To account for all the experimental observations we postulate that the highly electronegative fluorine plays a crucial role in the mechanism of the reaction. After carbenoid **18** is formed by the reaction of **16** with *tert*-butyllithium and MAI commences, a second *tert*-butyllithium molecule coordinates with the ionizing fluoride, thus directing the *tert*-butyl nucleophile to enter from the side of fluoride and leading to retention of configuration. This pathway is somewhat similar to an $S_{\mathrm{N}}i$ mechanism (path a, Scheme IV). Additionally there is another possible pathway (path b, Scheme IV), which accounts for the formation of **17**. As the carbenoid intermediate becomes more of a loose ion pair and the positive charge on the vinyl carbon develops it can then become a good hydride abstractor[35] and remove a hydride anion from the *tert*-butyl group to produce **2** and isobutylene. Vinyllithium **2**, thus formed, may then add to carbene to give, after protonation, an equal mixture of chiral and meso **17**.

If this postulate is correct then the use of perdeuterio-*tert*-butyllithium should give rise to **19** which possesses a perdeuterio-*tert*-butyl group and to **6** containing one deuterium per molecule. This is precisely what is observed.



19

In order to further test our concept of metal-assisted ionization another unreactive halide was sought.[3] It has been shown that cyclopropyl tosylate solvolyzes 10^6 times more slowy than cyclohexyl tosylate in acetic acid and that cyclopropyl chloride solvolysis is even slower.[25] The cyclopropyl system also creates another possibility for checking our mechanism. If, as we postulate, carbenoids are cationic intermediates then we should encounter usual and facile cyclopropyl to allyl cation rearrangement.[25,36]

The chiral system selected for this study was 1-chloro-2,2-diphenylcyclopropane (**20**). This compound had previously been prepared in our laboratory in connection with other studies.[37,38] Two stereospecific routes to this molecule were selected. The first giving (*S*)-(+)-**20** is based on Haller–Bauer cleavage of (*S*)-(+)-1-benzoyl-1-chloro-2,2-diphenylcyclopropane[37] and the second starts with (*S*)-(+)-1-chloro-2,2-diphenylcyclopropanecarboxaldehyde which is decarboxylated by tris(triphenylphosphine)-rhodium chloride and also yields (*S*)-(+)-**20**.[38] Both reactions proceed with retention of configuration.

Treatment of the enantiomeric (*R*)-(−)-1-chloro-2,2-diphenylcyclopropane (**20**) *n*-butyllithium at −25 °C gave rise to four major products. As expected based on our MAI mechanism (*S*)-(+)-1-*n*-butyl-2,2-diphenylcyclopropane (**21**) was obtained in 20% yield and with 51% inversion of configuration. However, another optically active compound was isolated as the major product in 50% yield and shown to be (*S*)-(+)-1-(1′,2′-diphenyl-2′-propynyl)-2,2-diphenylcyclopropane (**22**) with 90% inversion of configuration (vide infra). Additionally, we were able to isolate 9% of 1,1-diphenylcyclopropane (**23**) and 5% of 1,1-diphenylallene (**24**). In Scheme V we present an elaborated version of the MAI mechanism which explains the formation of all the products.

Thus, carbenoid **25** reacts with an excess of *n*-butyllithium to give the substitution product **21** with inversion of configuration. But the carbenoid, being a cationic intermediate, can also undergo electrocyclic ring opening and yield the allene **24**. In the presence of an excess of

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[34] Gedanken, A.; Duraisamy, M.; Huang, J.; Rachon, J.; Walborsky, H. M. *J. Am. Chem. Soc.* **1988**, *110*, 4593.

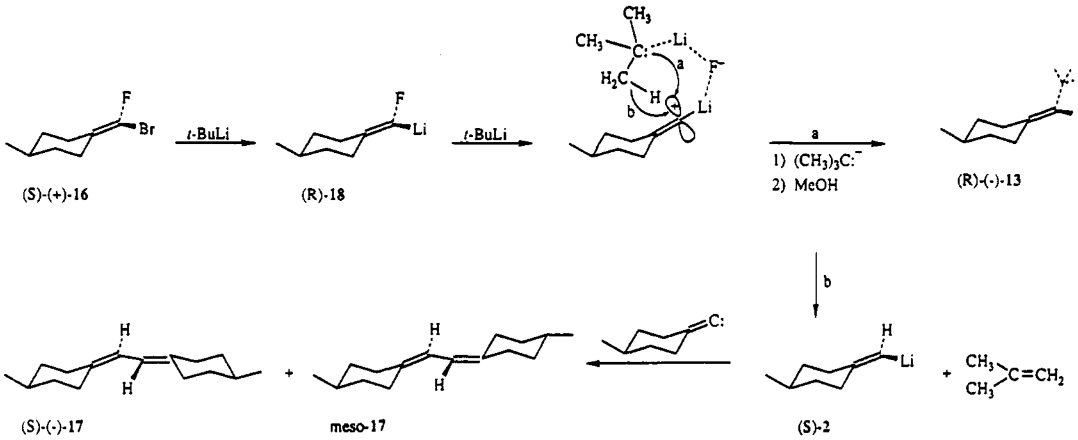
[35] Other examples of hydride abstraction by carbenoids have been reported: (a) Ritter, R. H.; Cohen, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 3718. (b) Harada, T.; Maeda, H.; Oku, A. *Tetrahedron Lett.* **1985**, *26*, 6489.

[36] Boche, G.; Walborsky, H. M. In *Cyclopropane-Derived Reactive Intermediates*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons: Chichester, New York, Brisbane, Toronto, Singapore, 1990; pp 117–174.

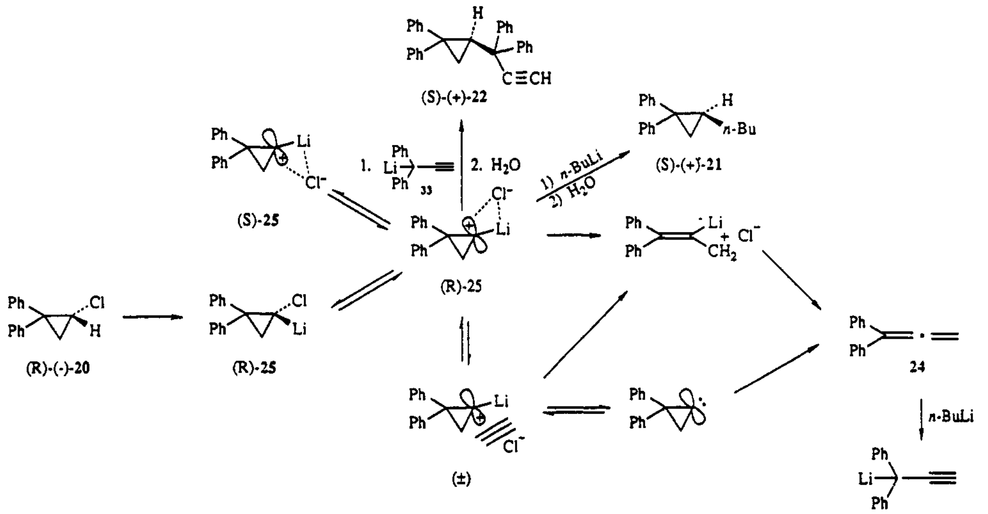
[37] Walborsky, H. M.; Allen, L. E.; Traenkner, H. J.; Powers, E. J. *J. Org. Chem.* **1971**, *36*, 2937.

[38] Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465.

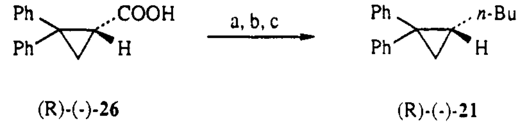
Scheme IV



Scheme V



Scheme VI[a]



[a] Key: (a) LiAlH$_4$; (b) TsCl; (c) (n-Pr)$_2$CuLi.

base (n-butyllithium) the allene is easily metalated (which accounts for its low isolated yield) to form the highly nucleophilic **33** which reacts with electrophilic **25** to produce **22** in a highly stereoselective manner (90% inversion of configuration). The small amount of **23** obtained in the reaction is either the result of lithium–chlorine exchange followed by protonolysis or hydride abstraction by electrophilic **25** from n-butyllithium.

In order to establish the absolute configuration and optical purity of **21** we prepared this compound independently as shown in Scheme VI. (R)-(−)-2,2-Diphenylcyclopropanecarboxylic acid (**26**) of known absolute configuration and optical purity[39] was converted to (R)-(−)-**21** by a well-known series of reactions not involving the chiral center.

It was also necessary to determine the optical purity and absolute configuration of **22**. This was achieved in the following manner. The dextrotatory product of the reaction $[\alpha]^{25}{}_{Hg}$ +120° (c 0.3, chloroform) was recrystallized from ether–hexane which increased the rotation to the value of $[\alpha]^{25}{}_{Hg}$ +150° (c 0.3, chloroform). This sample was treated with (R)-Mosher acid to give ynone **28** which was shown to be diastereomerically pure by NMR.

It was still necessary to establish that the other diastereoisomer of the ynone **28** showed different chemical shifts in the NMR spectrum. When racemic alkyne **22** (obtained from the reaction of racemic chloride **20** with n-butyllithium) was reacted with (R)-Mosher acid chloride a mixture of diastereoisomers was obtained from which the desired "other" diastereoisomer of the ynone could be obtained pure by crystallization. It had a distinctively different NMR spectrum from that of the first diastereoisomer. In this manner we were able to prove that the alkyne having the rotation of $[\alpha]^{25}{}_{Hg}$ +150° (c 0.3, chloroform) was optically pure and that the sample obtained from the carbenoid reaction, $[\alpha]^{25}{}_{Hg}$ +120° (c 0.3, chloroform), was 80% optically pure or the result of 90% inversion of configuration.

Unfortunately, we were not able to grow a single crystal of either diastereoisomer of ynone **28** for X-ray analysis and we therefore turned to chiroptical methods.[40] (S)-(+)-1-Diphenylhydroxymethyl-2,2-diphenylcyclopropane **29** was prepared, and its chiroptical properties were compared with those of the dextrotatory alkyne **22**. On the basis of the data in Table III we ascribe the (S)-(+) configuration to compound **22**.

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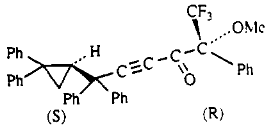
[39] Walborsky, H. M.; Barash, L.; Young, A. E.; Impastato, F. *J. Am. Chem. Soc.* **1961**, *83*, 2517.

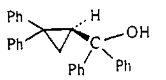
[40] Legrand, M.; Rougier, M. J. In *Stereochemistry. Fundamentals and Methods*; Kagan, H. B., Ed.; George Thieme: Stuttgart, 1977.

Table III. CD and UV Data for Compounds 22 and 29

22	29
^1L_b Band	^1L_b Band
$\Delta\epsilon$ = +1.05 (271), +1.28 (264), +0.92 (258)	$\Delta\epsilon$ = +1.08 (270), +1.44 (263), 1.16 (257)
ϵ = 1180 (258)	ϵ = 2320 (257)
^1L_a Band	^1L_a Band
$\Delta\epsilon$ = +12.8 (225)	$\Delta\epsilon$ = +16.7 (217)
ϵ = 23 000 (218)	ϵ = 23 000 (217)

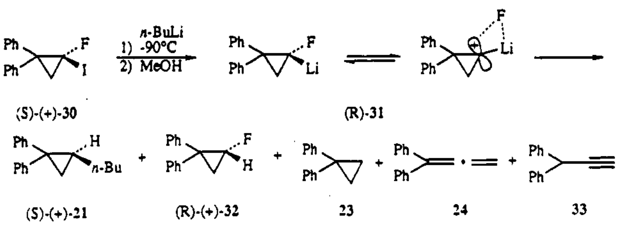


28



(S)-(+)-29

Finally, we generated the chiral fluorocyclopropyl carbenoid **31** by treating (*S*)-(+)-1-fluoro-1-iodo-2,2-diphenylcyclopropane (**30**)[41] with *n*-butyllithium at −90 °C. The choice of this substrate and this method allowed us to produce the carbenoid in a fast reaction and at a temperature lower than in the case of the chlorocarbenoid.



Again fluorine proved to be quite unpredictable. 12% of optically pure (*R*)-(+)-**32** was isolated, which means that this fluorocarbenoid unlike its vinyl counterpart persists at −90 °C and that moreover it perfectly maintains its configuration. Furthermore, the substitution product **21** was obtained in only low optical purity and, again unlike in the vinyl case, with inversion rather than retention of configuration. Other products can be rationalized similarly to the previously described examples. The 1,1-diphenylcyclopropane **23** must have been produced by the hydride-transfer reaction we postulated in the case of the vinyl fluorocarbenoid **18**.

It is not clear at this time why product **21** is obtained with inversion instead of retention of configuration. Inspection of the molecular models suggests that a steric effect due to the β-phenyl preventing the coordination of *n*-butyllithium with the fluoride in **31** might be responsible.

Summary

Chiral carbenoids have been generated in vinyl and cyclopropyl systems and reacted with nucleophiles (organolithium reagents) to give substitution products with preservation (inversion or retention) of optical activity. By using stereochemistry as a probe we have been able to clearly distinguish between the carbenoid and carbene mechanisms. The latter would have inevitably led to complete racemization.

In order to explain the stereochemical results of the substitution reaction on carbenoid species we introduced the concept of metal-assisted ionization (MAI). We postulate that the presence of a metal, which can be considered as an α-substituent, greatly accelerates the solvolysis of organic halides. Thus, unreactive halides like vinyl and cyclopropyl chlorides and fluorides solvolyze very rapidly and at very low temperatures. Our concept suggests that it is the halide (not the metal!) which is the leaving group, thus leading to development of positive charge on carbon. With the halide still blocking one enantioface the carbenoid is attacked from the backside by the nucleophile and the substitution product is obtained with overall inversion of configuration. Retention was observed only in the case of a vinyl fluorocarbenoid due both to the specific properties of fluorine and spatial feasibility. The whole process of nucleophilic substitution is reminiscent of S_N1 substitutions of chiral halides, to which mechanistic class carbenoid reactions belong.

Experimental Section

All melting points and boiling points are uncorrected. ^{1}H NMR spectra were recorded at 200, 270, or 300 MHz using $CDCl_3$ as solvent unless noted otherwise, with Me_4Si and $CHCl_3$ (7.26 ppm) as internal standards. 13-C NMR spectra were recorded at 75 MHz.

Optical rotations were measured at the 546.1-nm mercury line on a Bendix-Ericson Model 987 ETL/NPL polarimeter equipped with a Bendix Model DR-1 digital display. The cell length was 0.4 dm, and the accuracy was ±0.002°. Ultraviolet (UV) spectra were recorded with a Cary 219 spectrophotometer. IR spectra were taken on Perkin-Elmer 257 spectrometer. Mass spectra were obtained from a Finnigan 4500 mass spectrometer.

Column chromatography was carried out by using either silica gel (70–230 mesh) (Merck) or activated alumina F-20 (80–200 mesh). Radial chromatography separations were performed with Merck silica gel 60 PF_{254}. High-pressure liquid chromatography (HPLC) was performed on (4.6-mm × 25-cm) Ultrasphere-Si and Pirkle covalent phenylglycine columns using 2-propanol–heptane solvent mixtures with a flow rate of 1 mL/min and a variable-wavelength detector. Preparative gas chromatography separations were performed on Varian Aerograph Model 700 gas chromatograph with 15% SF-96 on chromosorb W as a stationary phase. All bulk solvents were distilled before use. Diethyl ether, dimethoxyethane, and THF were dried by refluxing and distilling from sodium benzophenone dianion.

Microanalyses were performed by Beller Laboratories, Göttingen, Germany.

(*R*)-(−)-(4-Methylcyclohexylidene)chloromethane (7). *tert*-Butyllithium (22 mmol, 14.7 mL of a 1.5 M solution in pentane) was added at −90 °C to a solution of optically pure (*R*)-(−)-(4-methylcyclohexylidene)bromomethane[1a] (1) (10 mmol, 1.9 g) in THF. The reaction mixture was stirred for 1 h, a solution of benzenesulfonyl chloride (15 mmol, 2.4 g) in THF was added, and the reaction mixture was allowed to reach room temperature and then quenched with methanol. It was subsequently diluted with pentane and washed with water. The organic layer was dried over magnesium sulfate, the solvent was removed in vacuo, and the residue was purified by radial chromatography (elution with pentane) to give the desired product (0.86 g, 60% yield): bp 96 °C/50 mmHg; $[\alpha]^{25}_{Hg}$ −57.0° (*c* 1.2, ethanol); IR (film) 1640 cm^{-1}; ^{1}H NMR δ 0.88 (d, *J* = 6 Hz, 3 H), 0.90–1.02 (m, 2 H), 1.40–1.60 (m, 1 H), 1.68–1.80 (m, 3 H), 1.90–2.05 (m, 2 H), 2.18–2.28 (m, 1 H), 2.78–2.88 (m, 1 H), 5.75 (s, 1 H). Anal. Calcd for $C_8H_{13}Cl$: C, 66.43; H, 9.06. Found: C, 66.52; H, 9.13.

Reactions of (*S*)-(+)-(4-Methylcyclohexylidene)halomethanes 1 and 7 with *tert*-Butyllithium. A solution of *tert*-butyllithium in pentane (65.6 mmol, 41 mL of a 1.60 M solution) was added dropwise at −90 °C to a solution of (*S*)-(+)-(4-methylcyclohexylidene)bromomethane (1) (6.19 g, 32.8 mmol, ee = 82%) or (*S*)-(+)-(4-methylcyclohexylidene)chloromethane (7) (4.72 g, 32.8 mmol, ee = 82%) in ether or THF (90 mL). After the addition had been completed the solution was maintained at −90 °C for 1 h. The reaction mixture was quenched with methanol-*O-d* (4 mL; 99+% D), and after an additional 10 min it was poured onto water. The organic layer was separated and dried over magnesium sulfate, and the solvent was removed using a spinning-band distillation column. The crude reaction mixture was chromatographed over silica gel, eluting with pentane. The

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[41] Gawronska, K.; Gawronski, J.; Walborsky, H. M. *J. Org. Chem.* 1991, *56*, 2193.

following products were obtained (yields and optical activities corrected for the optically pure starting materials are given in Table I).

(*R*)-(−)-1-(4-Methylcyclohexylidene)-1-deuterio-2,2-dimethylpropane (5): bp 107 °C/53 mmHg: IR (neat) 2220, 1650 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 0.93 (d, *J* = 6 Hz, 3 H), 1.13 (s, 9 H), 1.13–2.30 (m, 8 H), 2.75–2.85 (m, 1 H). This product was shown to be identical by GC with an authentic sample (see below).

(*S*)-(−)-(4-Methylcyclohexylidene)deuteriomethane (4): bp 57 °C/90 mmHg; IR (neat) 3025 (vinyl CH), 2275 (vinyl CD), 1635 cm^{-1}; ^{1}H NMR δ 0.92 (d, *J* = 6 Hz, 3 H), 0.92–2.50 (m, 9 H), 4.70 (s, 1 H). This product was shown to be identical by GC with an authentic sample.[34]

1,2-Bis(4-methylcyclohexylidene)-1-deuterioethane (6): IR (film) 2500, 1620 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.88 (d, *J* = 6 Hz, 3 H), 0.89 (d, *J* = 6 Hz, 3 H), 0.8–2.30 (m, 16 H), 2.7–2.85 (m, 2 H), 5.98 (s, 2 H). This product was identical by GC with an authentic sample.[1b]

Reaction of Optically Active (4-Methylcyclohexylidene)-chloromethane (7) with *tert*-Butyllithium and Phenyllithium. Trapping of the Chiral Carbenoid by a Nucleophile. *tert*-Butyllithium (2 mmol, 1.35 mL of a 1.5 M solution in pentane) was injected to a solution of (*R*)-(−)-(4-methylcyclohexylidene)-chloromethane (7) (ee = 92%) in THF (15 mL) at 90 °C. The reaction mixture was stirred for 30 min during which time the temperature was allowed to rise to −75 °C. At this point phenyllithium (10 mmol, 5 mL of 2.0 M solution in cyclohexane/diethyl ether) was syringed into the reaction mixture, and stirring was continued for 5 h at −75 °C. The reaction mixture was quenched with methanol (2 mL), diluted with pentane (20 mL), and washed with water. The organic phase was separated and dried over sodium sulfate, solvent removed under reduced pressure, and the oily residue was purified by radial chromatography (pentane–methylene chloride) to give 275 mg (70%) of (*S*)-(+)-(4-methylcyclohexylidene)phenylmethane (15): $[\alpha]^{25}_{D}$ +7.4° (*c* 0.4, ethanol, ee = 12%) [lit.[30] $[\alpha]^{25}_{D}$ +60° (ethanol)]. Taking into account the optical purity of the starting material this result indicates a 13% net inversion of configuration: ^{1}H NMR δ 0.90 (d, *J* = 6 Hz, 3 H), 0.98–1.20 (m, 2 H), 1.50–1.68 (m, 1 H), 1.70–2.00 (m, 3 H), 2.16–2.30 (m, 1 H), 2.30–2.38 (m, 1 H), 2.80–2.88 (m, 1 H), 6.22 (s, 1 H), 7.15–7.37 (m, 5 H).

Preparation of (*S*)-(+)-1-(4-Methylcyclohexylidene)-2,2-dimethylpropane (13) of Known Absolute Configuration. To a stirred slurry of dry cuprous iodide (6.48 g, 34 mmol) in THF (80 mL) at −75 °C was added *tert*-butyllithium (68 mmol, 45.3 mL of a 1.5 M solution in pentane) over a period of 15 min to obtain a dark slurry. After 30 min a solution of (*S*)-(+)-(4-methylcyclohexylidene)bromomethane (1) (8.5 mmol, 1.60 g; ee = 82%) in THF (5 mL) was added and stirring continued at 0 °C for 90 min. The mixture was cooled to −75 °C, and a stream of oxygen was passed through for a period of 60 min. The reaction mixture was poured onto water and extracted with pentane. The pentane solution was washed with Na$_2$S$_2$O$_3$ and then with water. Evaporation of the solvent provided a light yellow liquid which was purified by column chromatography (silica gel, pentane) to yield 0.15 g (11%)[42] of 13: $[\alpha]^{25}_{Hg}$ +7.94 (*c* 1.0, chloroform) corrected value for the optically pure compound $[\alpha]^{25}_{Hg}$ +9.68 (*c* 1.0, chloroform); ^{1}H NMR δ 0.84 (d, *J* = 6 Hz, 3 H), 0.88–1.12 (m, 2 H), 1.05 (s, 9 H), 1.40–1.54 (m, 1 H), 1.64–1.80 (m, 3 H), 1.88–2.05 (m, 2 H), 2.69–2.79 (m, 1 H), 5.10 (s, 1 H); ^{13}C NMR δ 21.73, 28.76, 31.22, 31.26, 32.34, 35.69, 36.95, 37.76, 132.20, 139.04.

(±)-(4-Methylcyclohexylidene)chloroacetic Acid (11). *n*-Butyllithium (110 mmol, 73 mL of a 1.5 M solution in hexane) was added at −90 °C to the stirred solution of diethyl trichloromethanephosphonate (9)[43] (50 mmol, 12.8 g) in a mixture of ether (100 mL) and THF (50 mL). The reaction mixture was stirred at this temperature for 30 min and cooled to −120 °C. Precipitation occurred at this temperature (presumably the excess of *n*-butyllithium crystallizes). Methyl chloroformate (3.85 mL, 50 mmol in 5 mL of THF) was injected with vigorous stirring and external cooling (liquid nitrogen). Freezing of the reaction mixture should be avoided. When the addition was complete (exotherm was observed) the reaction mixture was allowed to warm to −60 °C and 4-methylcyclohexanone (55 mmol, 6.8 mL) was injected. The reaction mixture was stirred overnight at room temperature, cooled to −20 °C, and decomposed with 50 mL of 2 N sulfuric acid. The organic phase was separated, washed with water (50 mL), saturated sodium carbonate solution (3 × 50 mL), and water, and dried over anhyd magnesium sulfate. The solvent was removed in vacuo, and the crude product was distilled (Kugelrohr), bp 95–110 °C/0.4 Torr. The distillate was dissolved in 70% alcohol (100 mL) containing potassium hydroxide (50 mmol, 2.8 g), and the reaction mixture was refluxed for 30 min. The alcohol solvent was then removed under reduced pressure, and remaining aqueous solution was extracted with ether (50 mL). The ether phase was discarded and the water phase was acidified with concentrated hydrochloric acid. A thick, heavy oil which had separated was extracted with ether (3 × 50 mL). The ether phase was dried over anhyd magnesium sulfate, the solvent was removed under reduced pressure, and the residue was distilled (Kugelrohr) to give 5.6 g (59% yield based on diethyl trichloromethanephosphonate) of the desired product: bp 135–140 °C/0.2 torr; IR (Nujol) 3500–2500 (OH) 1695 (C=O), 1605 (C=C) cm^{-1}; ^{1}H NMR δ 0.89 (d, *J* = 6 Hz, 3 H), 1.02–1.18 (m, 2 H), 1.55–1.70 (m, 1 H), 1.77–1.91 (m, 2 H), 1.97–2.12 (m, 2 H), 3.00–3.09 (m, 1 H), 3.42–3.51 (m, 1 H); ^{13}C NMR δ 20.94, 31.17, 31.61, 32.93, 34.92, 35.54, 114.68, 156.58, 169.39. Anal. Calcd for C$_9$H$_{13}$ClO$_2$: C, 57.29; H, 6.70. Found: C, 57.37; H, 6.79.

(±)-(4-Methylcyclohexylidene)bromochloromethane (12). Bromine (20 mmol, 3.2 g) was added at 0 °C to a solution of the chloro acid 11 (20 mmol, 3.78 g) in methylene chloride (50 mL). The reaction mixture was kept in a freezer for 1 day and subsequently steam distilled from a saturated aqueous solution of sodium carbonate. The distillate was extracted with methylene chloride (three times 50 mL), and the extract was dried over anhyd magnesium sulfate. The solvent was removed under reduced pressure, and the residue was distilled (Kugelrohr) to give 1.34 g (30%) of the desired product, bp 80–85 °C/0.5 mmHg; IR (film) 1602 (C=C) cm^{-1}; ^{1}H NMR δ 0.89 (d, *J* = 6 Hz, 3 H), 0.93–1.09 (m, 2 H), 1.44–1.58 (m, 1 H), 1.69–1.80 (m, 2 H), 1.82–1.99 (m, 2 H), 2.74–2.83 (m, 1 H), 2.86–2.94 (m, 1 H); ^{13}C NMR δ 20.91, 30.79, 31.41, 33.41, 34.21, 34.32, 97.12, 141.17. Anal. Calcd for C$_8$H$_{12}$BrCl: C, 42.98; H, 5.42. Found: C, 42.84; H, 5.40.

Resolution of (±)-(4-Methylcyclohexylidene)chloroacetic Acid (11) into Enantiomers. (±)-(4-Methylcyclohexylidene)-chloroacetic acid (50 mmol, 9.45 g) was dissolved in warm ethyl acetate (250 mL), and quinine (25 mmol, 8.1 g dissolved in small amount of chloroform) was added. The solid product was filtered and recrystallized three times from ethyl acetate. The salt, mp 189 °C, was subsequently decomposed with sodium hydroxide solution, quinine was removed by extraction with chloroform, and the alkaline phase was acidified with hydrochloric acid and extracted with ether (3 × 25 mL). The solvent was removed under reduced pressure, and the residue was distilled (Kugelrohr) to give 1.9 g (20%) of optically active material $[\alpha]^{25}_{Hg}$ +7.35° (*c* 1.04, chloroform). The optical purity of this sample has been found to be 90% (see below); hence, the corrected specific rotation for optically pure material is $[\alpha]^{25}_{Hg}$ +8.17° (*c* 1.04, chloroform).

Optical Purity Determination. Racemic chloro acid 11 (1 mmol, 189 mg) was dissolved in methylene chloride (5 mL), and oxalyl chloride (2 mmol, 2 mL of 1 M solution in methylene chloride) was added. The reaction mixture was stirred for 3 h at room temperature and evaporated to dryness. The residue was dissolved in methylene chloride (5 mL), and a solution of (*R*)-(+)-α-methylbenzylamine (1.5 mmol, 0.19 mL) and triethylamine (1.5 mmol, 0.21 mL) in methylene chloride (2 mL) was added. The reaction mixture was stirred for 1 h at room temperature and quenched with water. The organic phase was separated, washed with 1 N hydrochloric acid, water, saturated sodium carbonate solution, and water, and dried over anhyd magnesium sulfate. The solvent was removed under reduced pressure to give a mixture of diastereomeric amides in essentially quantitative yield. The ^{1}H NMR spectrum revealed, inter alia, two well-separated doublets at δ = 0.86 and 0.88 ppm corresponding to the ring methyl group. The integration of the signals indicated a 50:50 composition for this mixture.

When the sample of optically active acid was converted to the amide by the same procedure the NMR analysis showed that

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[42] Worm, A. T. dissertation, Purdue University, 1970.

[43] Kosolapoff, G. M. *J. Am. Chem. Soc.* **1947**, *69*, 1002.

enantiomeric purity of this acid was 90%. A pure sample of the amide, mp 83–84 °C, was obtained by recrystallization from hexane: ^{1}H NMR δ 0.88 (d, J = 6 Hz, 3 H), 0.97–1.14 (m, 2 H), 1.50 (d, J = 6 Hz, 3 H), 1.50–1.56 (m, 1 H), 1.72–1.86 (m, 2 H), 1.88–2.04 (m, 2 H), 2.86–2.96 (m, 1 H), 3.36–3.46 (m, 1 H), 5.04–5.15 (m, 1 H), 6.44 (s, broad, 1 H), 7.25–7.35 (m, 5 H). Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.96; H, 6.13. Found: 69.85; H, 6.03.

Preparation of Optically Active (*R*)-(−)-(4-Methylcyclohexylidene)bromochloromethane (12). The procedure described previously for the preparation of the racemic compound was followed exactly. The (*R*)-(−) compound obtained had a specific rotation of $[\alpha]^{25}_{\mathrm{Hg}}$ −.45° (c 1.3, $CHCl_3$). Assuming a complete inversion of configuration one may calculate the specific rotation of the optically pure material to be $[\alpha]^{25}_{\mathrm{Hg}}$ −5.0° (c 1.3, $CHCl_3$).

Reaction of (±)-(4-Methylcyclohexylidene)bromochloromethane with *tert*-Butyllithium. *tert*-Butyllithium (4 mmol, 2.66 mL of 1.5 M solution in pentane) was added dropwise, with stirring, to a solution of (4-methylcyclohexylidene)bromochloromethane (12) (1 mmol, 223 mg) in THF (15 mL) at −100 °C. The exact reaction conditions for each run are indicated in the Table II. The reaction mixture was quenched with methanol, diluted with pentane (20 mL), and washed with water (20 mL). The organic layer was separated and dried over anhyd magnesium sulfate, and the solvent was distilled using a spinning band column. The residues was then analyzed by GC, and two main products were found: (4-methylcyclohexylidene)chloromethane (7) and 1-(4-methylcyclohexylidene)-2,2-dimethylpropane (13) (the yields are given in the Table II). These products were isolated in pure form by using preparative gas chromatography and identified by comparison with authentic samples.

(4-Methylcyclohexylidene)chloromethane (7): ^{1}H NMR δ 0.88 (d, J = 6 Hz, 3 H), 0.90–1.02 (m, 2 H), 1.40–1.60 (m, 1 H), 1.68–1.80 (m, 3 H), 1.90–2.05 (m, 2 H), 2.18–2.28 (m, 1 H), 2.78–2.88 (m, 1 H), 5.75 (s, 1 H).

1-(4-Methylcyclohexylidene)-2,2-dimethylpropane (13): ^{1}H NMR δ 0.84 (d, J = 6 Hz, 3 H), 0.88–1.12 (m, 2 H), 1.05 (s, 9 H), 1.40–1.54 (m, 1 H), 1.64–1.80 (m, 3 H), 1.88–2.05 (m, 2 H), 2.69–2.79 (m, 1 H), 5.10 (s, 1 H); ^{13}C NMR δ 21.73, 28.76, 31.22, 31.26, 32.34, 35.69, 36.95, 37.76, 132.20, 139.04.

Reaction of (*R*)-(−)-(4-Methylcyclohexylidene)bromochloromethane (12) with *tert*-Butyllithium. The carbenoid was generated from 1 mmol of (*R*)-(−)-(4-methylcyclohexylidene)bromochloromethane 12 (ee = 90%) and *tert*-butyllithium (4 mmol) at −100 °C in THF. The reaction mixture was stirred for 3 h at −70 °C and was worked up in the usual manner and followed by preparative GC to yield a sample of (*R*)-(−)-1-(4-methylcyclohexylidene)-2,2-dimethylpropane (13): $[\alpha]^{25}_{\mathrm{Hg}}$ −3.3° (c 0.72, chloroform), which corresponds to 34% optical purity (specific rotation of the optically pure product is $[\alpha]^{25}_{\mathrm{Hg}}$ −9.68 (c 1, chloroform). Taking into account 90% enantiomeric purity of the starting material the result of this reaction indicates 38% inversion of configuration.

Reaction of (*S*)-(+)-(4-Methylcyclohexylidene)bromofluoromethane (16) with *tert*-Butyllithium. To a solution of *tert*-butyllithium (22 mL of a 1.7 M solution in hexane, 0.0373 mol) in 50 mL of ether, cooled to −110 °C, was added 1.93 g (0.0093 mol) of (*S*)-(+)-(4-methylcyclohexylidene)bromofluoromethane (16) ($[\alpha]^{25}_{\mathrm{Hg}}$ +11.5° (c 1.1, ethanol)). The reaction mixture was stirred at −110 °C for 5 min, methanol (2.2 mL) was added, and the reaction mixture was allowed to come to ambient temperature. The reaction mixture was washed with water and dried over $MgSO_4$ and the solvent evaporated. The HPLC analysis (column, Varian MicroPak MCH-5 methanol 100%; flow rate 1 mL/min) showed 0.59 g (40%) of 1-(4-methylcyclohexylidene)-2,2-dimethylpropane (13) (t_R = 4.4 min) and 0.3 g (30%) of 1,2-bis(4-methylcyclohexylidene)ethane (17) (t_R = 5.68 min). The crude product was chromatographed using flash chromatography (silica gel) and eluting with pentane to yield two major products:

(*R*)-(−)-1-(4-Methylcyclohexylidene)-2,2-dimethylpropane (13): $[\alpha]^{25}_{\mathrm{Hg}}$ −9.7 ±0.3° (c 1.5 $CHCl_3$); optically pure; IR (film) 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 7 Hz, 3 H), 1.09 (s, 9 H), 0.86–2.15 and 2.7–2.82 (m, 9 H), 5.14 (s, 1 H).

1,2-Bis(4-methylcyclohexylidene)ethane (17): $[\alpha]^{25}_{\mathrm{Hg}}$ −10.9 ± 0.3° (c 1.0, ethanol); IR (film) 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6 Hz, 3 H), 0.89 (d, J = 6 Hz, 3 H), 0.8–2.30 (m, 16 H), 2.7–2.85 (m, 2 H), 5.98 (s, 2 H). The ^{1}H NMR spectrum shows that this compound is a mixture, in equal amounts, of two diastereomers (meso and racemic).

Reaction of (±)-(4-Methylcyclohexylidene)bromofluoromethane (16) with *tert*-butyllithium-*d*$_9$. To a solution of 1.035 g (0.005 mol) of (*R*,*S*)-(4-methylcyclohexylidene)bromofluoromethane (16) dissolved in 50 mL of ether and cooled to −110 °C was added 10.5 mL (1.7 M solution in pentane, 0.0175 mol) of *tert*-butyllithium-*d*$_9$. The reaction was stirred at −110 °C for 5 min, 2 mL of methanol was added, and the mixture was allowed to come to ambient temperature. The reaction mixture was diluted with 25 mL of pentane and washed with water, and dried over $MgSO_4$ and the solvent evaporated. HPLC analysis (column, Varian MicroPak MCH-5 methanol 100%; flow rate 1 mL/min) of the crude product showed 0.26 g (30%) of 1-(4-methylcyclohexylidene)-2,2-ditrideuteriomethyl-3,3,3-trideuteriopropane (19) (t_R = 4.4 min) and 1,2-bis(4-methylcyclohexylidene)-1-deuterioethane (6) 0.19 g (35%) (t_R = 5.68 min). The crude product was chromatographed using flash chromatography (silica gel, pentane) to give two major products:

1-(4-Methylcyclohexylidene)-2,2-ditrideuteriomethyl-3,3,3-trideuteriopropane (19): MS (CI) M + 1 = 176 for $C_{12}H_{13}D_9$; ^{1}H NMR δ 0.89 (d, J = 7 Hz, 3 H), 0.86–2.15 and 2.7–2.82 (m, 9 H), 5.53 (s, 1 H).

1,2-Bis(4-methylcyclohexylidene)-1-deuterioethane (6): IR (film) 1620, 2500 cm^{-1}; ^{1}H NMR δ 0.88 (d, J = 6 Hz, 3 H), 0.89 (d, J = 6 Hz, 3 H), 0.8–2.30 (m, 16 H), 2.7–2.85 (m, 2 H), 5.98 (s, 1 H).

Reaction of (*R*)-(−)-1-Chloro-2,2-diphenylcyclopropane (20) with *n*-Butyllithium. *n*-Butyllithium (7.3 mmol, 5.65 mL of 1.30 M solution in hexane) was added at −25 °C to a stirred solution of (*R*)-(−)-1-chloro-2,2-diphenylcyclopropane (20)[37,38] (3.7 mmol, 0.84 g, ee = 87.5%) in THF (50 mL). The resulting red solution was stirred at −25 °C for 2 h and then quenched with water. The reaction mixture was subsequently poured into water and extracted with hexane. The hexane solution was washed with water, dried over anhyd magnesium sulfate, and evaporated to obtain the crude product as a dark oil. The final separation was achieved by using radial chromatography (elution with pentane). The following products were obtained.

1,1-Diphenylcyclopropane (23): 64 mg, 9%;[44] ^{1}H NMR δ 1.29 (s, 4 H), 7.1–7.4 (m, 10 H).

1,1-Diphenylallene (24): 35 mg, 5%;[45] ^{1}H NMR δ 5.26 (s, 2 H), 7.1–7.4 (m, 10 H).

(*S*)-(+)-1-Butyl-2,2-diphenylcyclopropane (21): 185 mg, 20%; $[\alpha]^{25}_{\mathrm{Hg}}$ −85.3° (c = 0.6, chloroform), after correction for the optical purity of the starting material this value corresponds to 51% net inversion of configuration. Spectral and chromatographic properties were identical with those of an authentic sample (preparation, see below).

(*S*)-(+)-1-(1′,1′-Diphenyl-2′-propynyl)-2,2-diphenylcyclopropane (22): 0.36 g, 50%; mp 123–124 °C; $[\alpha]^{25}_{\mathrm{Hg}}$ +120° (c 0.3, chloroform, ee = 80%) (this value corresponds to 90% net inversion of configuration); recrystallization from ether–hexane increased the rotation to the value of $[\alpha]^{25}_{\mathrm{Hg}}$ +150° (c = 0.3, chloroform), which is the rotation of the optically pure compound (for proof see next experiment). The absolute configuration was elucidated from chirooptical properties (see Table III): ^{1}H NMR δ 1.60 (dd, J = 5.0, 8.7 Hz, 1 H), 2.05 (s, 1 H), 2.20 (dd, J = 5.0, 6.6 Hz, 1 H), 2.55 (dd, J = 6.6, 8.7 Hz, 1 H), 6.9–7.6 (m, 20 H); MS (EI, 15 eV) m/e 384 (M$^+$), 204 (100). Anal. Calcd for $C_{30}H_{24}$: C, 93.71; H, 6.29. Found: C, 93.57; H, 6.33.

Reaction of (*S*)-(+)-1-(1′,1′-Diphenyl-2′-propynyl)-2,2-diphenylcyclopropane (22) with (*R*)-Mosher Acid Chloride. Determination of Optical Purity. To a solution of optically active (*S*)-(+)-1-(1′,1′-diphenyl-2′-propynyl)-2,2-diphenylcyclopropane (22) (192 mg, 0.5 mmol; $[\alpha]^{25}_{\mathrm{Hg}}$ +150° (c 0.3, chloroform)) in ether (4 mL) was added, at −70 °C, *n*-butyllithium (0.5 mL, 0.5 mmol of 1.0 M solution in hexane), and the solution was allowed to warm to ambient temperature. It was then syringed slowly into a solution of (*R*)-Mosher acid chloride (126 mg, 0.5

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mmol) in ether (2 mL) at −70 °C. After the addition had been completed the reaction mixture was allowed to reach room temperature, it was washed with water, aqueous sodium carbonate, and water, and dried over anhyd magnesium sulfate, and the solvent was evaporated. The crude product was purified by using radial chromatography to afford 45 mg (23%) of unreacted alkyne and 230 mg (quantitative yield based on unreacted alkyne) of the desired ynone **28**: $[\alpha]^{25}_{\mathrm{Hg}}$ +190 (c = 0.4 chloroform). Despite numerous efforts this diastereoisomer failed to crystallize: ^{1}H NMR (300 MHz) δ 1.49 (dd, J = 5.5, 9.0 Hz, 1 H), 1.91 (dd, J = 5.5 Hz, J = 6.0 Hz, 1 H), 2.57 (dd, J = 6.0, 9.0 Hz, 1 H), 3.28 (s, 3 H), 6.66 (d, J = 8.0 Hz, 2 H), 6.9–7.5 (m, 23 H). The diastereomeric purity of this material was assumed to be >98% since no signals belonging to the other diastereoisomer could be found.

Reaction of (±)-1-(1′,1′-Diphenyl-2′-propynyl)-2,2-diphenylcyclopropane (22) with (*R*)-Mosher Acid Chloride. The procedure described above was followed exactly starting with racemic alkyne **22**. The mixture of diastereoisomers was obtained from which the other diastereoisomer of the ynone **28** could be isolated by repeatedly crystallizing the mixture from ether–methanol: mp 151–152 °C; $[\alpha]^{25}_{\mathrm{Hg}}$ −128.5 (c = 0.5 chloroform); IR (Nujol) 2220, 1685 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.62 (dd, J = 5.5, 9.0 Hz, 1 H), 2.17 (dd, J = 5.5, 6.0 Hz, 1 H), 2.58 (dd, J = 6.0, 9.0 Hz, 1 H), 3.35 (s, 3 H), 6.82 (d, J = 8.0 Hz, 2 H), 6.9–7.5 (m, 23 H). Anal. Calcd for $C_{40}H_{31}F_3O_2$: C, 79.98; H, 5.20. Found: C, 79.61; H, 5.15.

Preparation of an Authentic Sample of (*R*)-1-Butyl-2,2-diphenylcyclopropane (21). To a stirred suspension of cuprous iodide (1.85 g, 4.85 mmol) in ether (75 mL) at −20 °C was added *n*-propyllithium (19.6 mmol, 15.1 mL of 1.30 M solution hexane) over a period of 10 min. During the addition the reaction mixture turned yellow, dark blue, and at the end a clear colorless solution was obtained. The solution was cooled to −75 °C, and a solution of (*R*)-[(2,2-diphenylcyclopropyl)carbinyl]-*p*-toluenesulfonate (**27**)[39] (1.85 g, 4.9 mmol; ee = 70%) in ether (15 mL) was syringed in. The reaction mixture was stirred at this temperature for 1 h, and then it was slowly warmed to 0 °C and stirred for one more h. The reaction mixture was worked up by pouring onto ice, washing with saturated ammonium chloride solution and water, and drying over sodium sulfate. The ether was then evaporated to give a pale yellow liquid which was purified by column chromatography (silica gel, hexane): yield 0.95 g, 78%, $[\alpha]^{25}_{\mathrm{Hg}}$ −134.9° (c 0.5, chloroform). This value corresponds to a corrected rotation of $[\alpha]^{25}_{\mathrm{Hg}}$ −193° (c 0.5, chloroform) for the optically pure sample which was shown to be homogenous by GC: ^{1}H NMR (300 MHz) δ 0.74 (dd, J = 8, 14.5 Hz, 1 H), 0.82 (t, J = Hz, 3 H), 1.19 (m, 2 H), 1.26 (m, 2 H), 1.40 (m, 3 H), 1.58 (m, 1 H), 7.1–7.4 (m, 10 H). Anal. Calcd for $C_{19}H_{22}$: C, 91.14; H, 8.86. Found: C, 91.17; H, 8.91.

Preparation of (*S*)-(+)-1-(Diphenylhydroxymethyl)-2,2-diphenylcyclopropane (29). A solution of methyl (*S*)-(+)-2,2-diphenylcyclopropanecarboxylate[39] (0.25 g, 1 mmol; ee = 90%) in ether (3 mL) was added to a solution of phenylmagnesium bromide (3 mmol, 3 mL of 1.0 M solution in ether) in ether (10 mL). After 3 h at room temperature aqueous ammonium chloride solution was added, the etheral solution was washed with water and dried over anhyd magnesium sulfate, and the solvent was evaporated. The crude product was purified by radial chromatography using hexane–methylene chloride as an eluent: yield 0.22 g (64%), $[\alpha]^{25}_{\mathrm{Hg}}$ +133.5° (c 0.9, chloroform), after correction for the optical purity of the starting material this value corresponds to the specific rotation of $[\alpha]^{25}_{\mathrm{Hg}}$ +148.3° (c 0.9, chloroform) for the optically pure compound. CD and UV data for this compound are given in the Table III: ^{1}H NMR (300 MHz) δ 1.20 (s, 1 H), 1.40 (dd, J = 4.8, 9.3 Hz), 2.13 (dd, J = 4.8, 6.6 Hz), 2.70 (dd, J = 6.6, 9.3 Hz, 1 H), 7.05–7.60 (m, 20 H). Anal. Calcd for $C_{28}H_{24}O$: C, 89.32; H, 6.42. Found: C, 89.42; H, 6.49.

Reaction of (*S*)-(+)-1-Fluoro-1-iodo-2,2-diphenylcyclopropane (30) with *n*-Butyllithium. A solution of (*S*)-(+)-1-fluoro-1-iodo-2,2-diphenylcyclopropane (**30**)[41] (338 mg, 1 mmol) in ether (10 mL) was treated at −90 °C with *n*-butyllithium (2.2 mmol, 1.4 mL of 1.6 M solution in hexane). The reaction mixture was stirred for 3 h at −90 °C and quenched with methanol, diluted with ethyl ether, washed with water and dried over anhyd magnesium sulfate. Evaporation of the solvent gave an oily mixture of products which was separated by radial chromatography (elution with hexane and hexane–methylene chloride (4:1)). The following products were isolated.

(*R*)-(+)-1-Fluoro-2,2-diphenylcyclopropane (**32**): 25 mg (12%), $[\alpha]^{25}_{\mathrm{Hg}}$ +20.7 (c 1.0, chloroform); optically pure, identical with an authentic sample;[41] ^{1}H NMR (300 MHz) δ 1.57 (dd, J = 6.3, 11.7 Hz, 1 H), 1.79 (ddd, J = 3.2, 7.0, 22.8 Hz, 1 H), 5.01 (ddd, J = 3.2, 6.3, 65.4 Hz, 1 H), 7.15–7.45 (m, 10 H).

1,1-Diphenylcyclopropane (**23**): 17 mg (9%);[44] ^{1}H NMR δ 1.29 (s, 4 H), 7.1–7.4 (m, 10 H).

(*S*)-(+)-1-Butyl-2,2-diphenylcyclopropane (**21**): 22 mg (9%), $[\alpha]^{25}_{\mathrm{Hg}}$ +42° (c = 0.14, chloroform, ee = 22%). Spectral and chromatographic properties were identical with those of an authentic sample.

1,1-Diphenylallene (**24**): 35 mg (18%);[45] ^{1}H NMR δ 5.26 (s, 2 H), 7.1–7.4 (m, 10 H).

3,3-Diphenyl-1-propyne (**33**): 19 mg (10%);[45] ^{1}H NMR (300 MHz) δ 2.47 (d, J = 3 Hz, 1 H), 5.00 (d, J = 3 Hz, 1 H) 7.1–7.4 (m, 10 H).

X-ray Analysis. Single crystals of the amide, $C_{17}H_{22}ClON$, were grown by slow evaporation of a hexane–ethyl acetate solution. The crystals were orthorhombic, space group $P2_12_12_1$ with a = 9.0456 (3) Å, b = 11.453 (3) Å, c = 14.991 (4) Å and d_{calc} = 1.195 g/cm^3 for Z = 4 ($M\gamma$ = 291.82). The intensity data were measured on a CAD4 Enraf Nonius diffractometer (Mo radiation, monochromated, θ–2θ scans). The size of the crystal used for collection was approximately 0.10 × 0.15 × 0.30 mm^3. No absorbtion correction was necessary (μ = 2.29). A total of 1670 reflections were measured for $\theta < 25°$, of which 975 were considered to be observed [$I > 2\sigma(I)$]. The structure was solved by direct methods using MULTAN 78 and refined by full-matrix least-squares methods.

The absolute configuration of the (4-methylcyclohexylidene)-chloroacetic acid (**11**) was found to be (*R*)-(+). The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crytallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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Supplementary Material Available: Crystal data and tables of interatomic distances, selected bond angles, selected torsional angles and positional and thermal parameters and their estimated standard deviations for $C_{17}H_{22}ClON$ and a table of structure factors F_{obsd} and F_{calcd} for $C_{17}H_{22}ClON$ (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.