4.07–4.15 (1 H, m), 7.08–7.67 (4 H, m); MS m/z 189 (M^+), 173, 159, 145, 133; HRMS, calcd for $C_{13}H_{16}O$ 188.1200, found 188.1210.

Registry No. **1a**, 100461-72-1; **1b**, 119695-44-2; **1c**, 10504-65-1; **1d**, 119695-46-4; **1e**, 100569-75-3; **1f**, 100461-68-5; **1g**, 100461-70-9; **1h**, 119695-48-6; **1i**, 119785-62-5; (*R*)-**1j**, 100461-74-3; (*R*)-**1k**, 100569-99-1; (*R*)-**1l**, 119816-10-3; (*S*)-**1m**, 119695-50-0; (*S*)-**1n**, 51210-64-1; (*S*)-**1o**, 113083-01-5; (*S*)-**1p**, 119785-64-7; **,2**, 22955-77-7; **2**·K, 119742-72-2; **3**, 72181-95-4; (*R*)-(+)-**3**, 100461-82-3; (*S*)-(−)-**3**, 100461-84-5; **3b**, 119785-60-3; (*S*)-(−)-**4**, 100461-83-4; (*R*)-(+)-**4**, 100461-85-6; **4f**, 119695-41-9; **4g**, 53110-84-2; **4h**, 119695-42-0; **5a**, 100461-78-7; **5b**, 100461-79-8; **6f**, 100461-80-1; **6g**, 100461-81-2; (*R*)-(+)-**7**, 35188-22-8; (*R*)-(+)-**8**, 51207-25-1; **9**, 41302-34-5; **10**, 7500-91-6; (*R*)-(−)-**10**, 89656-82-6; (*S*)-(+)-**10**, 89656-83-7; (*S*)-(+)-**11**, 100461-86-7; (*R*)-(−)-**11**, 119695-51-1; (±)-**11**, 119785-65-8; **13a** (isomer 1), 119785-67-0; **13a** (isomer 2), 119785-76-1; **13b** (isomer 1), 119785-72-7; **13b** (isomer 2), 119785-80-7; (−)-**14a**, 111170-63-9; (+)-**14a**, 111170-60-6; **14b** (isomer 1), 119695-52-2; **14b** (isomer 2), 119695-54-4; (−)-**15a** (isomer 1), 119785-68-1; (−)-**15a** (isomer 2), 119785-77-2; **15b** (isomer 1), 119785-73-8; **15b** (isomer 2), 119785-81-8; **16a**, 5978-55-2; **16b**, 5787-33-7; (−)-**17a**, 111189-00-5; (+)-**17a**, 111170-62-8; **17b** (isomer 1), 119695-53-3; **17b** (isomer 2), 119720-83-1; (+)-**18a** (isomer 1), 119785-69-2; (+)-**18a** (isomer 2), 119785-78-3; **18b** (isomer 1), 119785-74-9; **18b** (isomer 2), 119785-82-9; ethyl phenyl sulfide, 622-38-8; (*S*)-(+)-2-octanol, 6169-06-8; thiophenol, 108-98-5; (*S*)-(+)-2-octylphenyl sulfide, 111265-18-0; (*S*)-(+)-2-butanol, 4221-99-2; (*S*)-(+)-2-butylphenyl sulfide, 119785-70-5.

Alkylmetal Asymmetric Reduction. 20.[1] A Reinvestigation on the Stereochemistry of Ketone Reductions by Optically Active Alkylmetal Compounds

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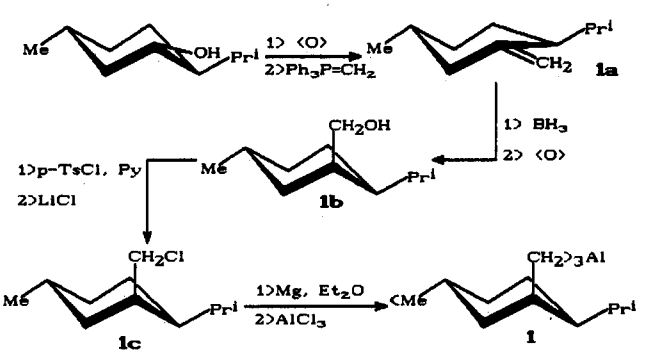
New chiral organometallic reagents, derived from (−)-menthol, tris[[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]methyl]aluminum, and from (+)-camphor, [[(1*R*,3*R*)-2,2-dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium chloride and bis[[(1*R*,3*R*)-2,2-dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium, have been devised as reducing agents. These compounds exhibit a good enantioface-differentiating ability in the reduction of prochiral ketones. The stereochemical results are discussed in the light of additional data on the reduction of ketones by other alkylmetal compounds. The mechanism proposed is consistent with previous reports, and the overall results have shown that, when alicyclic organometallic derivatives are involved in this kind of reduction, the interpretation of the stereochemistry of the processes should include consideration of the particular conformational freedom of each system.

In recent years, a variety of approaches to enantioselective reduction of carbonyl compounds have resulted in systems showing high enantiomeric purities in the reaction products.[2] In this context we have employed a number of chiral organometallic species, especially alkylaluminum compounds, derived from naturally occurring terpenoids, for asymmetric reduction of ketones with varying degrees of enantioselectivity.[3–5] Although some systems have been described that provide useful enantioselectivity,[3,5] our knowledge of reagent structure and mode of reduction has remained at a primitive level, limiting both application and further development. However, in earlier reports,[6,7] we have drawn a simple rule that seemed useful for prediction of the absolute configuration of the carbinol products. In an effort to obtain a greater understanding of the stereochemical outcome of this kind of alkylmetal enantioselective reduction and to confirm the stereochemical model proposed, we have undertaken a thorough investigation of the stereochemical outcome of the reduction of prochiral ketones by some chiral organometallic compounds having alkyl groups of different conformational homogeneity. Therefore we report here the results obtained by using tris[[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]-methyl]aluminum and some rigid, highly hindered, organometallic reagents of beryllium and magnesium.

Scheme I



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(1) Part 19: Falorni, M.; Lardicci, L.; Uccello-Barretta, G.; Giacomelli, G. *Gazz. Chim. Ital.* **1988**, *118*, 495.

(2) See, for representative examples: (a) Noyory, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709. (b) Noyory, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *Ibid.* **1984**, *106*, 6717. (c) Midland, M. M.; McLaughlin, J. *J. Org. Chem.* **1984**, *49*, 4101. (d) Brown, H. C.; Pai, G. G. *Ibid.* **1985**, *50*, 1384. (e) ApSimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157. (f) Imai, T.; Tamura, T.; Yamamuro, A. *J. Am. Chem. Soc.* **1986**, *108*, 7402.

(3) Giacomelli, G.; Lardicci, L.; Palla, F. *J. Org. Chem.* **1984**, *49*, 310.

(4) Giacomelli, G.; Lardicci, L.; Palla, F.; Caporusso, A. M. *J. Org. Chem.* **1984**, *49*, 1725.

(5) Falorni, M.; Lardicci, L.; Rosini, C.; Giacomelli, G. *J. Org. Chem.* **1986**, *51*, 2030.

0022-3263/89/1954-2383$01.50/0

Table I. Reduction of Ketones by Tris[[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]methyl]aluminum (1)[a]

run	ketone	optically active carbinol: conv,[b] %	optically active carbinol: $[\alpha]^{25}_D$, deg (*c*, solvent)	optically active carbinol: % ee
1	ethyl phenyl ketone	66	+8.6 (neat)	30 (*R*)
2	isopropyl phenyl ketone	57	+24.3 (6.2, ether)	51 (*R*)
3	*tert*-butyl phenyl ketone	46	+4.0 (1.5, ether)	11 (*R*)
4	2-methyl-4-nonyn-3-one	88	−7.5 (neat, *l* = 1)	92 (*S*)
5	2,2-dimethyl-4-nonyn-3-one	75	−9.7 (14.2, hexane)	72 (*S*)

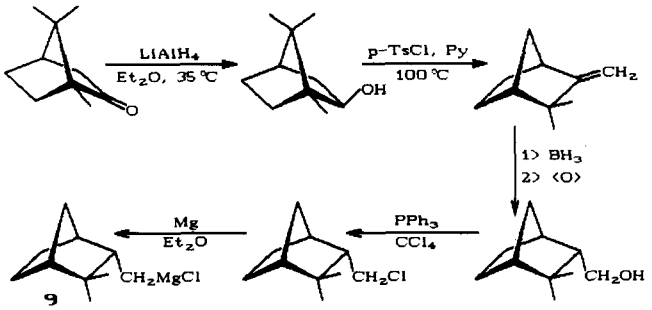
[a] Reactions were carried out in ether at 20 °C for 22 h. [b] GLC yields on the crude products.

Results and Discussion

The preparation of the optically active organoaluminum derivative **1** was carried out by following the sequences outlined in Scheme I. Hence, commercial (−)-menthol was converted into [(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]methanol (**1b**) via a recently published procedure.[1] The diastereomeric purity of the alcohol was determined by ^1H and ^{13}C NMR analysis, and it was found that **1b** contained less than 5% of the 1*R* isomer. By the standard *p*-TsCl/pyridine procedure, **1b** was converted into the tosyl ester, which was then reacted at 90–95 °C with LiCl in DMF to yield **1c**. Conversion of the chloride **1c** into the corresponding Grignard reagent, followed by treatment with anhydrous $AlCl_3$, gave tris[[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]methyl]aluminum (**1**) in 92% yield. The organoaluminum compound was not distilled in order to avoid any possible epimerization at the C1 center. The stereochemistry of **1** was, however, checked by oxidizing a sample: the alcohol recovered showed the same spectral features as the starting **1b**, further confirming that no isomerization took place during the preparation and isolation of **1**.[3,5]

The reductions were carried out in ethereal solvent by following previously published procedures[3] and using a slight excess (about 10%) of **1** with respect to the carbonyl compound. The results obtained are summarized in Table I. Contrary to that observed with a structurally similar organoaluminum compound, tri-*cis*-(1*S*)-myrtanylaluminum,[5] the reactions are relatively slow, and high conversions can be obtained only after 22 h in the case of α-acetylenic ketones (runs 4 and 5). In the case of hindered ketones, the rate drops noticeably, with less than 50% with *tert*-butyl phenyl ketone (run 3). In all the cases investigated, the reduced, optically active carbinol, which was purified by "flash chromatography", was the only product formed. As it can be seen by inspection of Table I, the sense and the degree of the asymmetric induction are highly dependent on the nature of the carbonyl substrate and, surprisingly, comparison with the results related to tri-*cis*-(1*S*)-myrtanylaluminum[5] shows that a reversal in the chirality of the products has occurred by changing the R group in the ketone from phenyl to α-acetylenic. Moreover, and contrary to the cited case,[5] the enantioface discrimination is significantly enhanced on passing from phenyl to α-alkynyl substrates (cf. runs 2 and 4). In these last cases (runs 4 and 5), the extent of enantioselectivity is of the same order of magnitude as reported for those methods employing more readily accessible complex metal hydrides.[2b]

Scheme II



Another problem arises, however, with these aluminum reagents, as demonstrated by considering the relative configurations of the alkyl groups bound to the metal atom in tri-*cis*-(1*S*)-myrtanylaluminum[5] and in compound **1**. Although the β-carbon atom has the opposite configuration with respect to the aluminum atom, the two organoaluminum compounds behave differently in the reduction of alkyl phenyl ketones, giving opposite enantioselectivity. This discrepancy in the differentiation might be due, in principle, to the different conformational requirements of the alkyl groups bound to the metal atom. We were, therefore, interested in determining the stereochemical trend of the reductions using more rigid and structurally similar alkylaluminum compounds, such as those derived from camphanyl chloride.

Thus, commercial (+)-(1*R*)-camphor was reduced ($LiAlH_4$) to (−)-isoborneol, followed by pyrolysis of the corresponding tosylate in pyridine at 100 °C to give (+)-(1*R*)-camphene in good yield.[8] The in situ hydroboration of the olefin afforded *endo*-camphanol, containing the exo isomer (10%),[8] which was then converted by treatment with triphenylphosphine and carbon tetrachloride to *endo*-camphanyl chloride (exo 20%) (Scheme II).

Unfortunately, the camphanylaluminum dichloride did not react, under comparable reaction conditions, with alkyl phenyl ketones even after prolonged reaction times (4 days at room temperature). In this light, we, therefore, prepared [[(1*R*,3*R*)-2,2-dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium chloride (**2**) and bis[[(1*R*,3*R*)-2,2-dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium (**3**), taking into account the similarities of their chemical behavior to that of the organoalanes and their greater reactivity.[5,6] These compounds were prepared by the addition of anhydrous $BeCl_2$ to the Grignard reagent **9**, obtained from (1*R*)-camphanyl chloride (endo to exo ratio 80:20). After purification, the compounds **2** and **3** were characterized by ^1H NMR spectroscopy as diethyl etherates. Both **2** and **3** were employed in ethereal solvent at 20 °C, a slight excess being used, as compared to the carbonyl substrates. In order to obtain reliable values of enantioselectivity, samples of **2** and **3** were oxidized to the corresponding (1*R*)-camphanol, the diastereomeric purity of which confirmed the absence of any epimerization phenomena during preparation and purification of the organoberyllium compounds.

As shown in Table II, both compounds **2** and **3** reduced, asymmetrically, phenyl and α-alkynyl ketones to the corresponding carbinols. The reactions were very slow in the case of the reduction of alkyl phenyl ketones by compound **2**, although the reduction rate is increased when acetylenic ketones are involved (runs 9 and 10). Moreover,

(6) Giacomelli, G.; Menicagli, R.; Lardicci, L. *J. Org. Chem.* **1973**, *38*, 2370.
(7) Giacomelli, G.; Menicagli, R.; Lardicci, L. *J. Am. Chem. Soc.* **1975**, *97*, 4009.
(8) Falorni, M.; Lardicci, L.; Giacomelli, G. *J. Org. Chem.* **1986**, *51*, 5291.

Table II. Reduction of Ketones by [[(1*R*,3*R*)-2,2-Dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium Chloride (2) and Bis[[(1*R*,3*R*)-2,2-dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium (3)[a]

run	compound	ketone	optically active carbinol		
			conv, %	$[\alpha]^{25}_D$, deg (c, solvent)	% ee
6	2	ethyl phenyl ketone	39[b]	−7.8 (neat)	27 (*S*)
7		isopropyl phenyl ketone	34[b]	−29.4 (6.8, ether)	62 (*S*)
8		*tert*-butyl phenyl ketone	28[b]	−5.5 (7.5, ether)	15 (*S*)
9		4-nonyn-3-one	100[c]	−4.1 (13.0, hexane)	26 (*S*)
10		2-methyl-4-nonyn-3-one	75[c]	−0.3 (7.2, hexane)	4 (*S*)
11	3	ethyl phenyl ketone	100[d]	−5.7 (neat)	20 (*S*)
12		isopropyl phenyl ketone	95[d]	−24.4 (7.9, ether)	51 (*S*)
13		*tert*-butyl phenyl ketone	86[d]	−6.2 (3.5, ether)	17 (*S*)
14		4-nonyn-3-one	100[d]	−12.1 (7.2, hexane)	78 (*S*)
15		2-methyl-4-nonyn-3-one	98[d]	−2.2 (neat)	27 (*S*)
16		2,2-dimethyl-4-nonyn-3-one	100[d]	−0.8 (neat)	5 (*S*)

[a] Reactions were carried out in ether at 20 °C. [b] For 48 h. [c] For 2 h. [d] For 1 h.

in agreement with that previously observed in analogous cases, the reduction rate increased significantly on passing from RBeCl to R_2Be.[5,9] In these cases, the reaction tends toward reduction, in some cases, negligible formation of the addition product being observed (less than 1%). The data reported shows that compound **2** has roughly the same capability of enantioface differentiation as compound **3**, when alkyl phenyl ketones are reduced. This result dismisses the possibility of the influence of the second chiral group bound to the beryllium atom in compound **3** on the enantioselectivity. In these cases, the asymmetric induction is moderate to low, in particular for the reduction of *tert*-butyl phenyl ketone (runs 8 and 13). The reduction of α-alkynyl ketones occurs with higher enantioselectivity with compound **3**; however, the optical yields decrease sharply as the bulkiness of R increases (runs 14–16), thus emphasizing that steric effects play a significant role on the stereochemical outcome of this type of reaction.

In all the cases, the absolute configuration of the carbinol recovered is *S*. In fact, on the simple suggestion that by size phenyl > alkyl and alkyl > α-alkynyl, the reduction of α-alkynyl ketones occurs with opposite stereochemical course with respect to that of alkyl phenyl ketones, since priorities[10] of the groups are in the order of phenyl > alkyl, α-alkynyl > alkyl in the two different series of ketones. The *S* configuration of the products (Table II) is therefore a consequence of a change in the mode of attack on passing from alkyl phenyl to α-alkynyl ketones. Such a reversal of stereochemistry does not occur with compound **1**, with (alkylbutyl)aluminum derivatives,[4] and with *B*-(*cis*-10-pinanyl)-9-borabicyclo[3.3.1]nonane.[2c]

Further contribution to the rationalization of the stereochemical trend of these reactions can be supported by the data concerning the asymmetric reductions of ketones by the Grignard reagents **4–9**, as outlined in Table III.

As previously reported,[1] in the cases of compound **7–9**, no addition product was observed, although compounds **4–6** did give rise to significant amounts of the addition products, at least with alkyl phenyl ketones.[11] The optical yields are low to moderately high (up to ca. 65%, runs 23, 27, 30, 36), and the enantioface discrimination generally drops on passing from alkyl phenyl to α-alkynyl ketones, with the exception of those reactions carried out with compound **8** (runs 37 and 38). The sense and extent of the asymmetric induction are highly dependent on the structure of the R group in the Grignard reagent. With respect to the alkyl phenyl ketones, it is interesting to note that, even in this case, a reversal of the absolute configuration of the products has occurred with use of the Grignard reagent [(3*S*)-menthylmethyl]magnesium chloride (**7**).[1]

Table III. Asymmetric Reduction of Some Ketones by Optically Active Grignard Reagents[a]

run	Grignard reagent	ketone	% ee
17	(*S*)-2-methylbutyl **4**	ethyl phenyl ketone	6 (*S*)[b]
18		isopropyl phenyl ketone	24 (*S*)[b]
19		*tert*-butyl phenyl ketone	16 (*S*)[b]
20		4-nonyn-3-one	7 (*R*)[c]
21		2-methyl-4-nonyn-3-one	18 (*R*)[c]
22	(*S*)-2,3-dimethylbutyl **5**	ethyl phenyl ketone	14 (*S*)[b]
23		isopropyl phenyl ketone	67 (*S*)[b]
24		*tert*-butyl phenyl ketone	2 (*R*)[b]
25		2,2-dimethyl-4-nonyn-3-one	32 (*R*)
26	(*S*)-2,3,3-trimethylbutyl **6**	ethyl phenyl ketone	25 (*S*)[b]
27		isopropyl phenyl ketone	65 (*S*)[b]
28		*tert*-butyl phenyl ketone	36 (*S*)[b]
29		2,2-dimethyl-4-nonyn-3-one	24 (*R*)
30	(3*S*)-menthylmethyl **7**	isopropyl phenyl ketone	66 (*R*)[c]
31		*tert*-butyl phenyl ketone	40 (*R*)[c]
32		2,2-dimethyl-4-nonyn-3-one	21 (*S*)[c]
33	*cis*-(1*S*)-myrtanyl **8**	isopropyl phenyl ketone	38 (*R*)[c]
34		*tert*-butyl phenyl ketone	34 (*R*)
35		1-acetonaphthone	42 (*R*)
36		2-acetonaphthone	65 (*R*)
37		4-nonyn-3-one	56 (*R*)[c]
38		2-methyl-4-nonyn-3-one	47 (*R*)
39	*endo*-(1*R*)-camphanyl **9**	ethyl phenyl ketone	10 (*S*)
40		isopropyl phenyl ketone	39 (*S*)
41		4-nonyn-3-one	13 (*S*)
42		2-methyl-4-nonyn-3-one	27 (*S*)

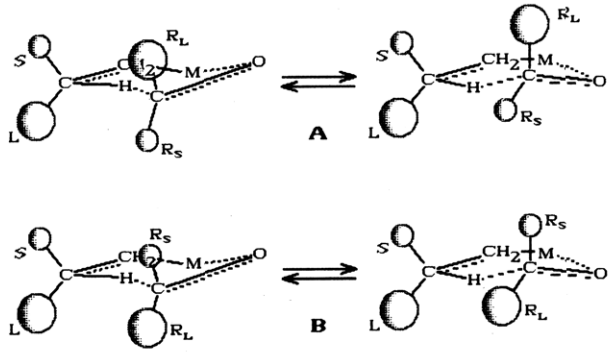
[a] Reactions were carried out in ether at 20 °C for 1 h. [b] From ref 11. [c] From ref 1.

It is worth pointing out that in all the cases examined, the direction of enantioselectivity is not metal dependent. It appears to be strictly related to the absolute configuration of the β-carbon atom with respect to the metal atom. In the case of the menthylmethyl derivatives **1** and **7**, a reversal of stereochemistry was observed.

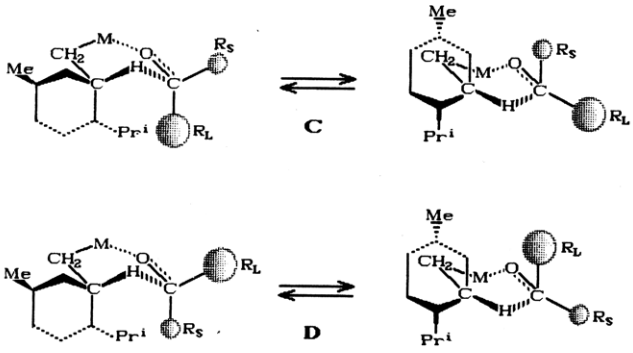
As to the origin of enantioselection, steric approach has customarily been considered to play a decisive role. Among a number of observations that deserve comment, the most important and empirical rule for the orientation in the asymmetric induction of simple prochiral carbonyl substrates is that aryl and alkynyl groups exert qualitatively the same electronic directing influence on the direction of the stereochemistry, and therefore, any differentiation depends primarily on the difference in the steric requirements. However, it is not easy to present a unifying view

(9) Giacomelli, G.; Falorni, M.; Lardicci, L. *Gazz. Chim. Ital.* **1985**, *115*, 289.
(10) IUPAC tentative rules for the nomenclature of organic chemistry: *J. Org. Chem.* **1970**, *35*, 2849.
(11) Giacomelli, G.; Lardicci, L.; Caporusso, A. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1795.

Scheme III



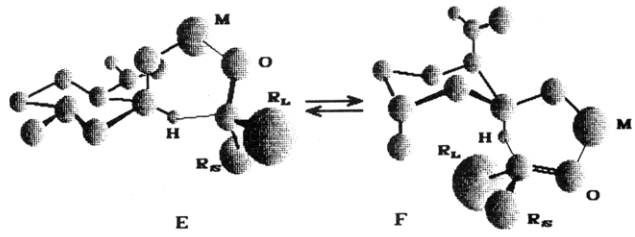
Scheme IV



of the mechanism by figuring a single transition state model. Nevertheless, the simple model, emphasizing the transition state, previously reported,[6,7] can be drawn to rationalize the stereochemical consequences on the basis of the Curtin–Hammett principle.[12] The reaction begins with the complexation of the metal atom to the oxygen atom of the ketone, activating the C=O group. The hydride transfer then occurs from the β-carbon with respect to the metal atom to the carbonyl carbon by way of a quasi-planar six-membered transition state (Scheme III) in which the coordinative bond between metal and oxygen atoms has to be relatively loose to permit the minimization of the steric compression among the groups. Thus, indicating as L the more substituted carbon attached to the chiral β-carbon atom of the alkyl metal compound and as S the less substituted, two types of chair-like transition states, A and B (Scheme III), are conceivable.[6] However, under the hypothesis that the steric interactions should be reduced when the substituent groups on the substrate and the reducing agent are facing larger–smaller and smaller–larger, respectively, structure B is highly unfavorable, as indicated by model inspection.[7] Therefore, according to this view (Scheme III), the reduced carbinol must have the *S* absolute configuration (in the case of phenyl alkyl ketones) when the β-carbon with respect to the metal atom has the configuration depicted.[13]

This mechanistic picture agrees with the data obtained for the aliphatic organometallic compounds **4–6** and for the reactions of alkyl phenyl ketones with compounds **2**, **3**, **8** and **9**. However, it fails in the rationalization of the data for compounds **1** and **7** (Tables I and III).

Scheme V



In these cases, the reductions take place via a cyclic boat-like transition state wherein the metal atom and the β-hydrogen may assume a planar orientation, which is favorable for the developing alkene double bond (Scheme IV). The selectivity of the reaction should be due, in these cases, to the prevalence of the transition state in which both the two small groups are in a 1,3-diaxial position. This model correctly predicts the proper stereochemistry of the carbinols obtained by using compounds **1** and **7**, but it cannot be used to rationalize all the other data. Moreover, it is difficult to believe that these reactions follow different mechanistic pathways by changing the structure of the reducing alkyl metal compound.

On the other hand, compounds **1** and **7** can assume a variety of cyclohexane conformations, and with the more stable cyclohexane chair-like conformer, having the methyl and isopropyl substituents in the equatorial position (structure E of the drawings in Scheme V), the stereochemical trend might be rationalized as being the same as that of the other reducing agents. Assembly E clearly cannot be the prevalent diastereomeric state since it predicts the wrong enantiomeric product. However, we can suppose that the other energetically unfavored chair-like conformation F (Scheme V), having methyl and isopropyl substituents in the axial position,[14] is more reactive than E, so determining the sense of differentiation. In the case of the *cis*-(1*S*)-myrtanyl and *endo*-(1*R*)-camphanyl derivatives, this conformation cannot occur and the stereochemical trend is analogous to that of the aliphatic derivatives. It should be noted that, in this last case, a reversal of the direction of enantioselectivity is observed on passing from alkyl phenyl to α-alkynyl ketones as the relative importance of the sizes of large and small groups is reversed. The particular conformational homogeneity of these reducing agents seems, in effect, to give valid support to this apparent discrepancy.

Experimental Section

Boiling points are uncorrected. ^{1}H NMR (60 MHz) and ^{13}C NMR (25.2 MHz) Fourier transform spectra were obtained with Varian T-60 and XL-100 spectrometers on $CDCl_3$ solutions with Me_4Si as internal standard. ^{1}H NMR spectra of organometallic compounds were performed on C_6D_6 solutions. Optical rotations were measured on a Perkin-Elmer 142 automatic polarimeter in a 1-dm tube; unless otherwise specified, rotations refer to those of pure liquids. GLC analyses (Perkin-Elmer 3920 B) were performed with Carbowax 20M (2 m) as a stationary phase and nitrogen as carrier gas. All new compounds gave satisfactory microanalyses for C, H and Cl (within ±0.3%). All solvents were reagent grade materials, purified by standard methods and redistilled just before their use. All reactions were carried out under an argon atmosphere. (+)-(*S*)-1-Chloro-2,3-dimethylbutane and (+)-(*S*)-1-chloro-2,3,3-trimethylbutane were obtained according to known procedures.[11] (−)-3-Methylenementhane[1] (**1a**), *endo*-(1*R*)-camphanyl chloride,[8] and *cis*-(1*S*)-myrtanyl chloride[3] were

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(13) According to this model, as the steric requirements of the alkyl group in the ketone increase, the discrimination between R_L and R_S should decrease, resulting in decreased enantioselectivity. The data obtained show, on the contrary, that, in the alkyl phenyl series, the stereoselectivity is the highest when R is an isopropyl group. In this respect it is to be considered that as the alkyl groups in the ketone increase in bulk, the conformational mobility of the phenyl group may decrease, its size changing formally.[6,7]

(14) The inspection of molecular models indicates that this transition state has, however, a greater homogeneity than E.

prepared from (−)-(1*R*)-menthol [$[\alpha]^{20}_D$ −50° (*c*, 10 in EtOH)], (+)-(1*R*)-camphor [$[\alpha]^{20}_D$ +44.3 (*c*, 10 in EtOH)], and (−)-β-pinene [$[\alpha]^{23}_D$ −21.0], respectively, according to previously reported procedures. Alkyl aryl ketones were obtained by purification of commercial products; the α-alkynyl ketones were prepared according to known procedures.[15] Optical purity was determined in various ways. Direct comparison of optical rotation, when possible, was carefully done with the synthetic and authentic resolved materials. In some cases,[3,16] the alcoholic products were converted to the MTPA esters by using MTPACl; the ee was determined by ^{19}F NMR (94.1 MHz). The enantiomeric composition of alkylarylcarbinols was also evaluated by HPLC on csp as earlier reported:[5] the values of % ee obtained are in agreement (within ±3%) with those determined by optical rotations.

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-(hydroxymethyl)cyclohexane (1b).[1] To a well-stirred suspension of $NaBH_4$ (1.6 g, 41 mmol) and (2*S*,5*R*)-2-isopropyl-5-methyl-1-methylenecyclohexane [3-methylenementhane, **1a**, 15.3 g, 100 mmol, $[\alpha]^{25}_D$ −66.06° (*c*, 5.6 in hexane)] in dry diglyme (100 mL) was added dropwise (20 min), at 0 °C, $BF_3{\cdot}Et_2O$ (7.8 g, 55 mmol). After being stirred at room temperature for 3 h, the mixture was oxidized in the usual manner (1 h, 50–60 °C) by the addition of H_2O (10 mL) and NaOH (3 N, 10 mL) followed by H_2O_2 (36%, 10 mL). Workup by ether extraction and drying (Na_2SO_4), followed by distillation, yielded the alcohol **1b** (15.6 g, 91%), bp 84 °C (0.7 mm), containing the 1*R* isomer (20%, GLC). The epimeric purity of **1b** was raised to 90% by conversion into its acid phthalate[1] and slow recrystallization from light petroleum ether. After saponification of the acid phthalate, **1b** was recovered (60% overall yield from **1a**): bp 82–85 °C (0.3 mm); $[\alpha]^{25}_D$ +22.07° (*c*, 4.5 in EtOH); ^1H NMR δ 3.66 (d, 2 H), 2.21–0.69 (m, 20 H); ^{13}C NMR δ 59.5, 46.9, 37.9, 36.5, 35.8, 29.5, 26.2, 25.9, 22.8, 21.8, 20.9; MS *m/z* 170 (M^+).

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-(chloromethyl)cyclohexane (1c).[1] To a solution of **1b** (20.0 g, 120 mmol) in dry pyridine (60 mL) was added, at −10 °C, *p*-TsCl (25.0 g, 130 mmol) within 10 min. The resulting mixture was stirred at room temperature for 16 h, hydrolyzed with 10% HCl, extracted with $CHCl_3$, dried (Na_2SO_4), and worked up in the usual manner. The crude product was crystallized from ether to give the tosylate of **1b** (35.8 g, 92%): ^1H NMR δ 7.79–7.11 (dd, 4 H), 3.96 (d, 2 H), 2.43 (s, 3 H), 2.23–0.60 (m, 19 H).

A solution of the tosylate of **1b** (35.8 g, 110 mmol) in dry DMF (200 mL) was reacted at 90–95 °C with LiCl (5.4 g, 130 mmol) in DMF (100 mL). The mixture was stirred for 8 h at 90–95 °C, hydrolyzed with water, and extracted with ether. After distillation of dried (Na_2SO_4) ethereal extracts, **1c** was recovered (12.4 g, 60%): bp 80–86 °C (0.7 mm); $[\alpha]^{25}_D$ +14.53° (*c*, 3.3 in heptane); ^1H NMR δ 3.59–3.36 (m, 2 H), 2.36–0.69 (m, 19 H); ^{13}C NMR δ 47.7, 43.8, 39.5, 38.3, 36.5, 29.6, 25.9, 25.6, 22.5, 21.6, 20.6; MS *m/z* 188 (M^+); pure by GLC.

[(*S*)-2,3-Dimethylbutyl]magnesium Chloride (5),[11] **[(*S*)-2,3,3-Trimethylbutyl]magnesium Chloride (6),**[11] **[[(1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohex-1-yl]methyl]magnesium Chloride (7), [[(1*S*,2*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-yl]methyl]magnesium Chloride (8),**[3] **and [[(1*R*,3*S*)-2,2-Dimethylbicyclo[2.2.1]hept-3-yl]methyl]magnesium Chloride (9).** These compounds were prepared from (*S*)-1-chloro-2,3-dimethylbutane [$[\alpha]^{25}_D$ +4.84°], (*S*)-1-chloro-2,3,3-trimethylbutane [$[\alpha]^{25}_D$ +30.31], **1c**, *cis*-(1*S*)-myrtanyl chloride [$[\alpha]^{25}_D$ −10.31° (*c*, 2 in $CHCl_3$)], and *endo*-(1*R*)-camphanyl chloride [$[\alpha]^{25}_D$ −4.23° (*c*, 4 in benzene), containing the exo isomer (20%)], respectively, by following standard procedures.

Tris-[[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]methyl]aluminum (1). To an ether solution (200 mL) of the Grignard reagent **7** obtained (82%) from **1c** (3.3 g, 17.5 mmol) was added anhydrous $AlCl_3$ (5.8 g, 43 mmol) in dry ether (200 mL) at 0 °C. The mixture was refluxed with stirring for 4 h and the upper liquid phase transferred under argon to a suitable container. After removal of the solvent under reduced pressure, the crude product was stirred at 0.005 mm for 4 h to eliminate any remaining volatile product. Chemically pure **1** (19.44 g, 92%) was recovered and stored under argon in anhydrous ether, at room temperature. A sample of **1** (3.4 g, 6.99 mmol) was oxidized according to published procedures[17] to yield 2.6 g (73%) of original **1b**: bp 85 °C (0.3 mm); $[\alpha]^{25}_D$ +22.10° (*c*, 7.5 in EtOH); ^1H NMR δ 3.66 (d, 2 H), 2.21–0.69 (m, 20 H).

[[(1*R*,3*R*)-2,2-Dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium Chloride (2). To an ether solution (200 mL) of the Grignard reagent **9** obtained (71%) from *endo*-(1*R*)-camphanyl chloride (15.53 g, 90 mmol) was added anhydrous $BeCl_2$ (5.19 g, 65 mmol) at 0 °C. The mixture was refluxed with stirring for 6 h and the upper liquid phase transferred under argon to a suitable container. After removal of the solvent under reduced pressure, the crude product was stirred at 0.01 mm for 4 h to eliminate any remaining volatile product. Diethyl etherate–**2** [16.3 g, 98%; ^1H NMR δ 4.26–3.77 (m, 4 H), 2.50–0.96 (m, 23 H)] was recovered and stored under argon in anhydrous ether, at room temperature. A sample of **2** (5 mmol) was treated with a stream of air according to published procedures.[17] A sample of *endo*-(1*R*)-camphanol was obtained:[8] bp 120 °C (20 mm); $[\alpha]^{25}_D$ −9.65° (*c*, 3.77 in benzene); ^1H NMR δ 3.62 (d, 2 H), 2.27 (m, 1 H), 1.80–1.08 (m, 9 H), 1.03 (s, 0.6 H), 1.00 (s, 2.4 H), 0.91 (s, 0.6 H), 0.85 (s, 2.4 H).

Bis[[(1*R*,3*R*-2,2-dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium (3). To an ether solution (200 mL) of the Grignard reagent **9** obtained (84%) from *endo*-camphanyl chloride (25.9 g, 150 mmol) was added anhydrous $BeCl_2$ (5.12 g, 64 mmol) at 0 °C. With the same workup as described for **2**, diethyl etherate–**3** [(22.9 g, 99%; ^1H NMR δ 3.93–3.47 (q, 4 H), 2.23–0.96 (m, 40 H)] was recovered and stored under argon in anhydrous ether, at room temperature. Compound **3**, upon oxidation, furnished, analogously to **2**, a sample of *endo*-(1*R*)-camphanol, $[\alpha]^{25}_D$ −9.73° (*c*, 4.03 in benzene).

Asymmetric Reduction of Ketones. The following procedures are representative of all the experiments with the same reducing agent.

(A) With Tris[[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]methyl]aluminum (1): Run 1. Ethyl phenyl ketone (1.07 g, 8 mmol) in anhydrous ether (10 mL) was added rapidly at room temperature to an ethereal solution of **1** (4.86 g, 10 mmol). A pale yellow coloration developed immediately and faded slowly. After 26 h, the resulting mixture was cautiously hydrolyzed with dilute H_2SO_4, extracted with ether, and dried (Na_2SO_4). Removal of the solvent and distillation of the residue, followed by flash chromatography[18] (80:20 light petroleum ether/ethyl acetate), afforded (+)-ethylphenylcarbinol: 0.50 g, 46%; $[\alpha]^{25}_D$ +8.6°; pure by GLC.

(B) With [[(1*R*,3*R*)-2,2-Dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium Chloride (2): Run 7. Isopropyl phenyl ketone (1.18 g, 8 mmol) in anhydrous ether (10 mL) was added rapidly at room temperature to an ethereal solution of **2** (11 mmol). An orange coloration developed immediately and faded slowly. After 48 h, the resulting mixture was submitted to the standard hydrolytic and extractive workup. Removal of the solvent and distillation of the residue, followed by flash chromatography[18] (80:20 light petroleum ether/ethyl acetate), afforded (−)-isopropylphenylcarbinol: 0.28 g, 25%; $[\alpha]^{25}_D$ −29.4° (*c*, 6.8 in ether); pure by GLC.

(C) With Bis[[(1*R*,3*R*)-2,2-dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium (3): Run 12. Isopropyl phenyl ketone (1.31 g, 8.8 mmol) in anhydrous ether (10 mL) was added rapidly at room temperature to an ethereal solution of **3** (12 mmol). An orange coloration developed immediately and faded slowly. After 16 h, the resulting mixture was submitted to the preceding hydrolytic and extractive workup. Removal of the solvent and distillation of the residue, followed by flash chromatography[18] (80:20 light petroleum ether/ethyl acetate) on a portion of the crude product, afforded (−)-isopropylphenylcarbinol: 0.35 g; $[\alpha]^{25}_D$ −24.4° (*c*, 7.9 in ether); pure by GLC.

(D) With Grignard Reagents 4–9. The following procedure is representative of runs 17–42.

Run 40. Isopropyl phenyl ketone (1.63 g, 11 mmol) in anhydrous ether (10 mL) was added rapidly at room temperature to an ethereal solution of **9** (14.5 mmol). After 18 h, the resulting

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mixture was submitted to the previous hydrolytic and extractive workup. Removal of the solvent and distillation of the residue, followed by flash chromatography[18] (80:20 light petroleum ether/ethyl acetate) on a portion of the crude product, afforded (-)-isopropylphenylcarbinol: 0.53 g; $[\alpha]^{25}_D$ -18.5° (c, 3.4 in ether); pure by GLC. The ee% of the recovered isopropylphenylcarbinol was also evaluated by HPLC on csp.[5] The optical rotations of the carbinols are summarized as follows: 2,2-dimethyl-4-nonyn-3-ol, $[\alpha]^{25}_D$ +2.63° (c, 6.2 in hexane) (run 25); 2,2-dimethyl-4-nonyn-3-ol, $[\alpha]^{25}_D$ +1.98° (c, 3.4 in hexane) (run 29); 2-methyl-4-nonyn-3-ol, α^{25}_D +3.85° (l = 1) (run 38); ethylphenylcarbinol, $[\alpha]^{25}_D$ -3.0° (run 39); 4-nonyn-3-ol, α^{25}_D -2.1° (l = 1) (run 41); 2-methyl-4-nonyn-3-ol, α^{25}_D -2.2° (l = 1) (run 42).

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Titanium(IV) Chloride Catalyzed Cyclopropanations of Alkenes Using Zinc Dust, Copper(I) Chloride, and Dihalomethanes

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The addition of catalytic amounts of titanium(IV) chloride greatly facilitates the cyclopropanation reactions of alkenes with dibromomethane using zinc dust and copper(I) chloride in ether. The rates of reaction and yields of cyclopropane products obtained from alkenes not bearing Lewis acid sensitive functional groups are as good or better than those found by using dibromomethane with ultrasound promotion. They are also comparable to those obtained by using diiodomethane under various conditions.

Several years ago, we reported[1] that Simmons–Smith type cyclopropanations[2] of alkenes using the inexpensive, convenient to handle dibromomethane can be accomplished rapidly and with yields similar to those obtained with diiodomethane if the reactions are carried out under sonocation in an ultrasonic cleaning bath. In this ultrasound procedure, the method of Rawson and Harrison[3] employing zinc dust and copper(I) chloride for in situ generation of the necessary zinc–copper couple is used.

In the course of attempting to measure the rates of alkene cyclopropanation under both ultrasonic and nonultrasonic conditions, we were plagued with problems of poor reproducibility.[4] Thus, we undertook a search for possible reaction catalysts or inhibitors, which led to the discovery that the addition of catalytic amounts of titanium(IV) chloride strongly facilitates the reactions of alkenes with dibromomethane, zinc dust, and copper(I) chloride in ether. The rates of reaction and yields of cyclopropanation products are similar to those observed earlier by us under the less convenient sonocation conditions[1] and in several instances are somewhat better (see Table I). Only in the case of the Lewis acid sensitive vinyl ether 3,4-dihydro-2*H*-pyran and with crotyl alcohol is the yield significantly decreased by using titanium(IV) chloride instead of ultrasonic conditions. With 3,4-dihydro-2*H*-pyran and titanium(IV) chloride, large amounts of a high-boiling polymer are formed. Efforts to significantly increase the yields of the latter cyclopropanations by varying reaction conditions were unsuccessful.

Table I. Cyclopropanations of Various Alkenes Using Dibromomethane and Zinc Dust–Copper(I) Chloride in Ether

	yield,[a] %	
starting alkene	$TiCl_4$ promoted[b]	ultrasound promoted[c]
cyclohexene	58	60
cyclooctene	73	72
1-hexene	49	30
1-octene	50	28
α-pinene	55	40
β-pinene	77	50
crotyl alcohol	36	57
3,4-dihydro-2*H*-pyran	17	41

[a] Yield based on reacted alkene of distilled cyclopropanated product. [b] The $TiCl_4$-promoted reactions are generally carried out at 45–50 °C over a period of about 2 h with 0.2 mol of alkene, 0.6 mol of CH_2Br_2, 0.8 mol of zinc dust, 0.08 mol of CuCl, and 0.012 mol of $TiCl_4$ in 100 mL of ether. [c] The ultrasound promoted reactions[1] were generally carried out over a period of 2–4 h with 0.2:0.4:0.8:0.08 mol of the reactants in 100 mL of ether in a 150-W Bransonic cleaning bath at 45–50 °C.

In the early stages of this work, some investigations of the effects of varying the amount of titanium(IV) chloride on the rates and yields of cyclopropanation products were carried out. It was found that use of greater than 1–2 mol % of titanium(IV) chloride based on the dibromomethane employed resulted in reactions that went out of control. This was due both to the exothermicity of the rapid reactions and to rapid release of ethylene in a side reaction,[4] which made condensation of the refluxing ether difficult.

For the titanium(IV) chloride promoted cyclopropanations reported in Table I, the alkene to dibromomethane to zinc dust mole ratios used were all close to 1 to 3 to 4. However, in the ultrasound-promoted reactions the mole ratios were all close to 1 to 2 to 4. The higher dibromomethane to alkene mole ratios were employed in the present titanium(IV) chloride promoted cyclopropanations to overcome the side reaction of dibromomethane giving ethylene.[4] Even with the present 1 to 3 to 4 mole ratio, some unreacted alkene was still observed in several of the runs with slowly reacting alkenes such as 1-octene and α-pinene.

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