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ASYMMETRIC GRIGNARD AND MEERWEIN-PONNDORF-VERLEY REDUCTIONS LONG RANGE ASYMMETRIC SYNTHESIS AND THE REDUCTION OF PERFLUOROALKYL CARBONYL COMPOUNDS

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ASYMMETRIC GRIGNARD AND MEERWEIN-PONNDORF-VERLEY REDUCTIONS. LONG RANGE ASYMMETRIC SYNTHESIS AND THE REDUCTION OF PERFLUOROALKYL CARBONYL COMPOUNDS

by

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The author wishes to dedicate this thesis to his wife whose unfailing support and patience over nine years have made the completion of both his undergraduate education and this work possible and to his son who has been a constant source of joy and wonder since his birth.

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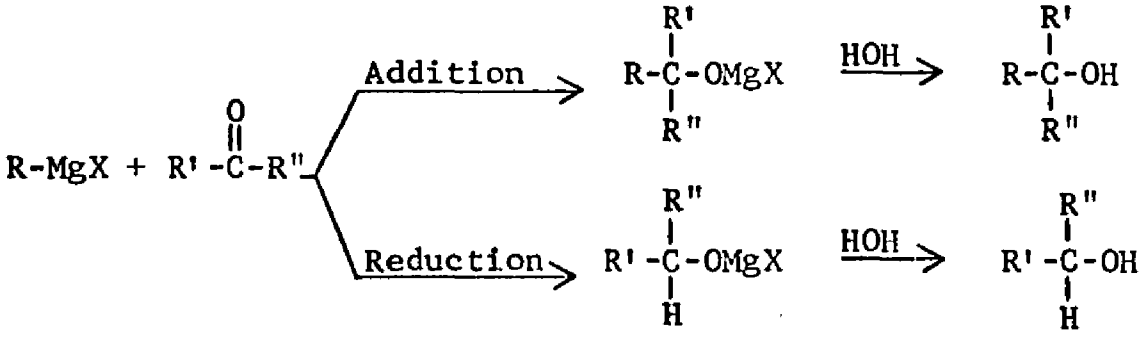
INTRODUCTION

Grignard Reduction Reactions

In his pioneering studies of the reactions of organomagnesium reagents, Grignard noted[1] that carbonyl compounds could react *via* several pathways. These less familiar reactions, notably the enolization and reduction of aldehydes and ketones, have been reviewed.[2] The reduction reaction, under which the proper conditions can become the major or

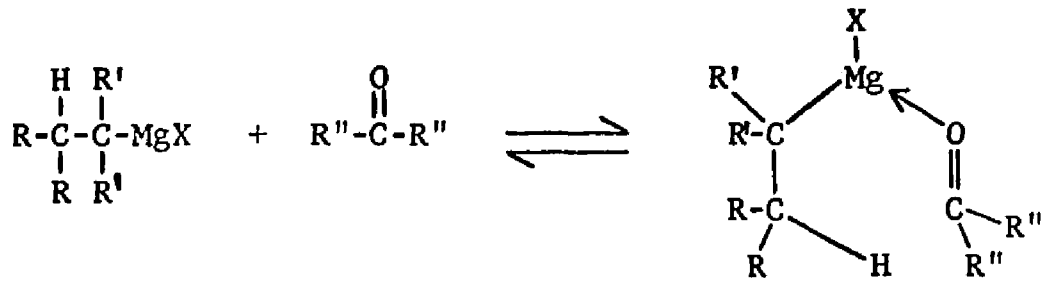


(eq. 1)

even exclusive pathway, has been the object of considerable study. The following empirical observations are pertinent to the elucidation of the mechanism of this reduction reaction:

1) True Grignard reductions produce equimolar quantities of alcoholate and an olefin arising from the Grignard reagent. 2) Increased branching, *i.e.*, steric hindrance, of groups on both the carbonyl compound and the Grignard reagent generally increases the amount of reduction relative to addition.[3] 3) Only reagents bearing hydrogens on the carbon β- to magnesium, behave as reducing agents.[4] 4) The amount of reduction relative to addition generally

increases as the number of hydrogens on the β-carbon(s) increases. On the basis of these observations Whitmore[5] proposed that the reduction proceeded by a pathway, (eq. 2), whose most important and novel feature was the six-membered, cyclic transition state 2 generated from an intermediate complex 1. In this mechanism the rate determining step involved the transfer of a "hydride-like" hydrogen from the β-carbon on the reducing agent to the carbonyl carbon of the substrate.



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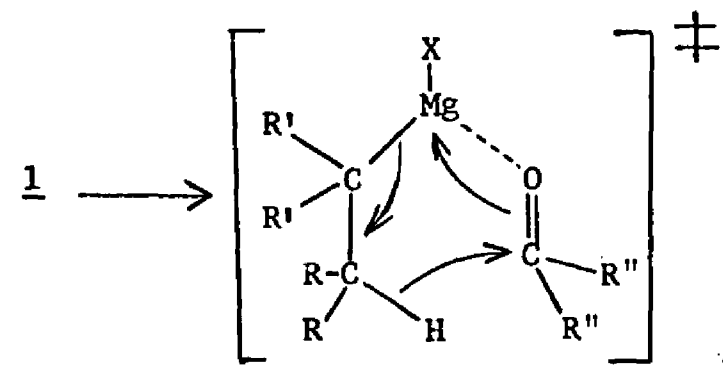
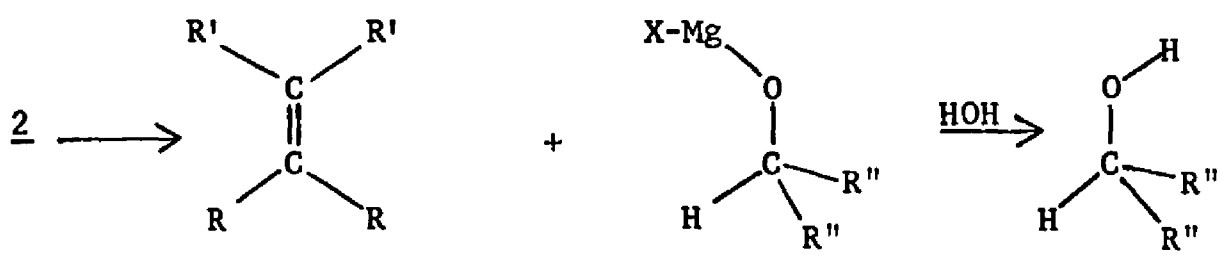


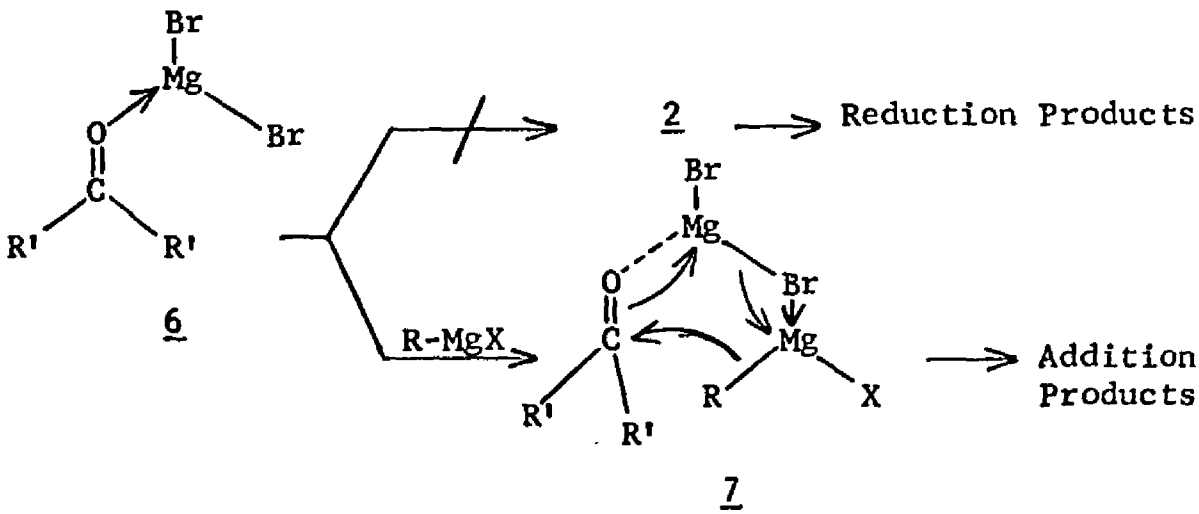
2

(eq. 2)



3 4 5

This mechanism has become generally accepted on the basis of its simplicity and ability to accommodate experimental observations obtained both prior to and after its proposal. Further evidence bearing on the mechanism of these reductions has included the observation that treatment of ketones with magnesium bromide prior to addition of Grignard reagents greatly increases the yield of addition products at the expense of reduction.[6] This observation appears to support the Whitmore mechanism since a magnesium bromide-ketone complex 6 could not undergo an intracomplex reduction via 2 but could participate in the termolecular transition state 7 generally accepted for the addition reaction.



However, perfluoroalkyl carbonyl compounds which do not form detectable amounts of complex with magnesium bromide[7] still showed increased yields of addition products when magnesium bromide was added prior to the Grignard reagent.[8]

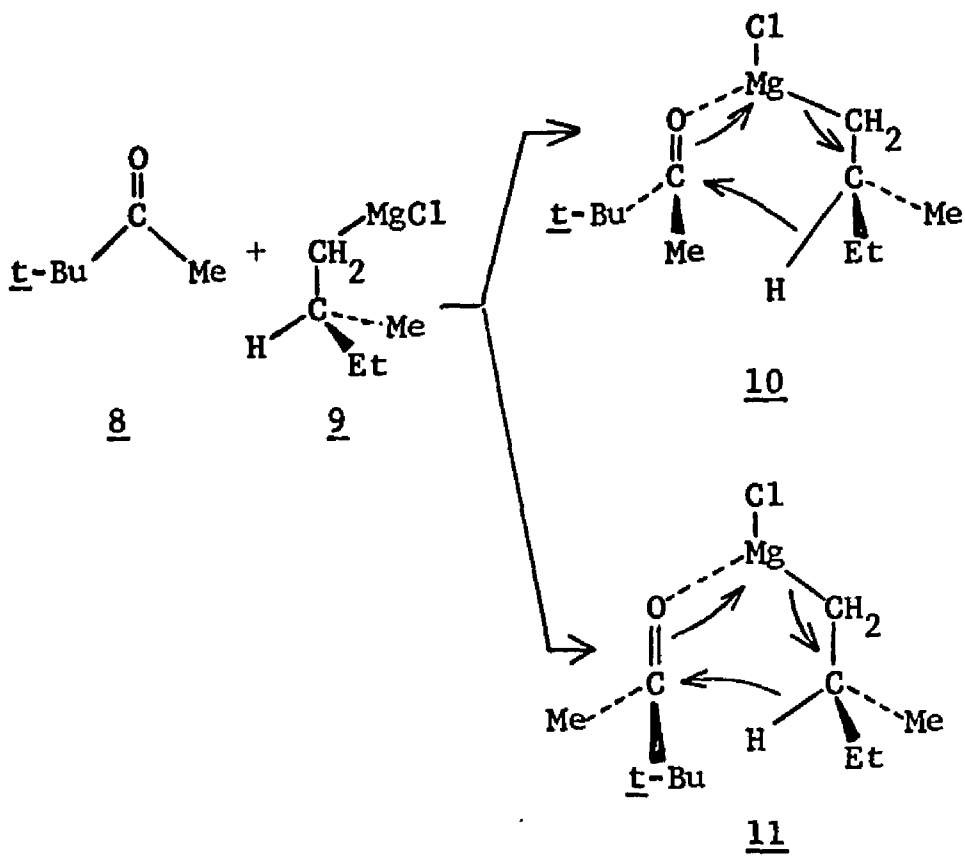
Dunn and Warkentin[9] demonstrated using deuterium labeling experiments that hydrogen was transferred only from the β-carbon during the reduction of benzophenone with isobutylmagnesium bromide. The kinetic isotope effect, k_H/k_D 2.0

to 2.2, observed at the β-hydrogen in these studies strongly indicates that the rate-determining step, at least in this one reaction, involves transfer of the β-hydrogen.

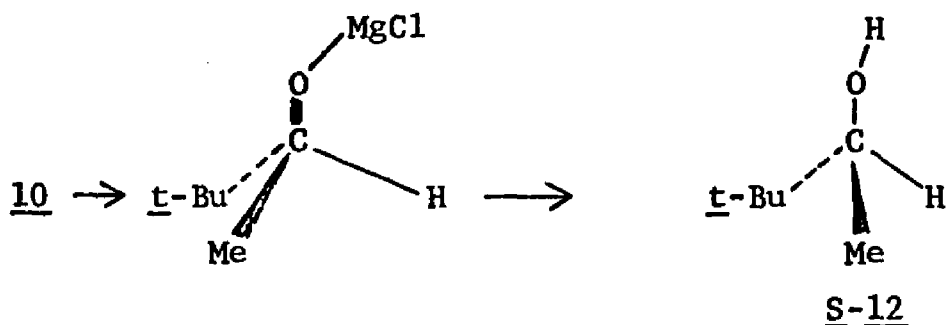
Regrettably, a recent report of the first kinetic study of a Grignard reduction reaction has provided results open to a variety of interpretations and has left unanswered several questions about the detailed nature of these reactions.[10]

Additional evidence which has been cited as favoring the Whitmore mechanism includes the observation of asymmetric reduction by optically active Grignard reagents and the utility of the presumed mechanism in rationalizing the stereochemistry of these reductions. Vavon and coworkers reported in 1946 and 1947[11] that treatment of phenyl alkyl ketones with the Grignard reagent prepared from optically active isobornyl chloride provided optically active phenylalkylcarbinols. These authors did not elaborate on their results other than to point out a relationship between the steric bulk of the ketone reduced and the amount of asymmetric synthesis achieved.[11b] In 1950 Mosher and LaCombe[12] published the first of a series of papers dealing with reductions of unsymmetrical carbonyl compounds with chiral Grignard reagents containing an asymmetric center at the carbon β- to magnesium. The initial investigation was designed to test a prediction based on the Whitmore mechanism that the reductions would provide optically active products and that the configurations of the products could be related to those of the reducing agents by a simple model. The model used was based on a planar, or nearly planar, conformation of Whitmore's cyclic transition state 2 in which the "sizes" of the groups on the Grignard reagent and the ketone could be classified as large and small, i.e., R_s or R_L and

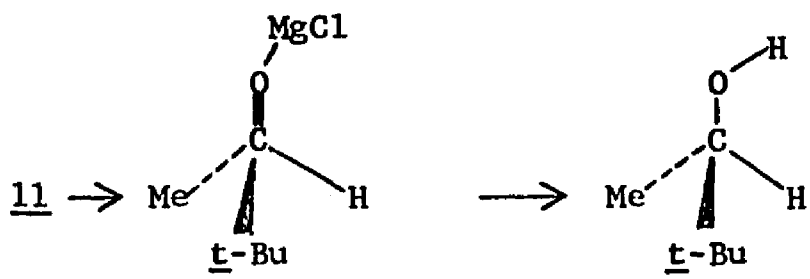
R'_S and R'_L, respectively, using well known steric and electronic factors. Models of the two diastereomeric transition states 10 and 11 are demonstrated (eq. 3) for the reduction



8 9 10 11 (eq. 3)



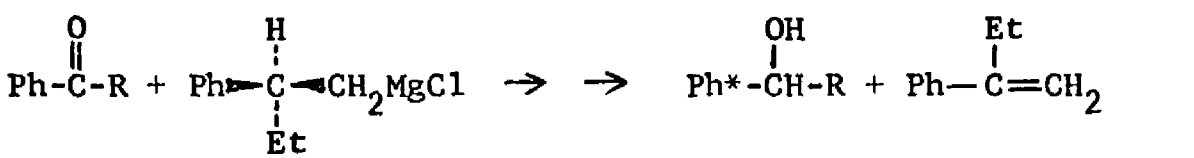
S-12



R-12

of methyl t-butyl ketone (8) with the Grignard reagent 9 from S-(+)-1-chloro-2-methylbutane. It was predicted that the transition state with the lower energy would be 10 in which the large group on one center opposes the small group on the other center to provide a better steric fit. Or, from another view, the less favorable transition state would be 11 in which the two large groups were on the same side of the ring. This expectation was experimentally verified when the methyl-t-butylcarbinol obtained from the reaction was found to contain a 14% excess of the S-(+)-enantiomer, S-12. In other papers in this series Mosher and coworkers have reported the reduction of a number of t-butyl alkyl[13], cyclohexyl alkyl[14], and phenyl alkyl ketones.[15,16]

More recently it has been found[17,18] that in some cases the amount of asymmetric synthesis obtained in β-asymmetric Grignard reductions is dramatically increased when both of the reactants contain aromatic groups. Thus the reduction of a series of phenyl alkyl ketones (13) with the Grignard reagent prepared from S-(+)-1-chloro-2-phenylbutane (15), (eq. 4), provided phenylalkylcarbinols (14)

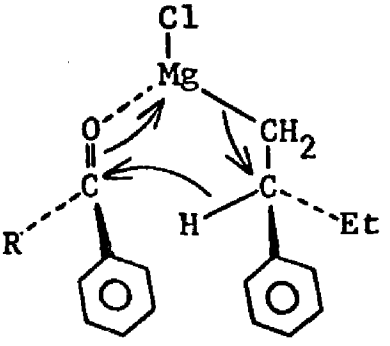


13 15 14 (eq. 4)

13 and 14: R = a, Me; b, Et; c, Pr; d, iBu; e, tBu; f, CF_3

containing up to 91% of the S-enantiomer, i.e., alcohols of up to 82% optical purity.[17] This last result, obtained with 13-c is unusually high for such a simple system and approaches

the absolute asymmetric synthesis of enzymatic reductions for which these reactions have been considered models.[19] The explanation offered for the unusually high values in these cases involved electronic repulsions between the aromatic rings in a transition state such as 16 which made it even more disfavored relative to 17 than would be predicted on a purely steric basis.[17]



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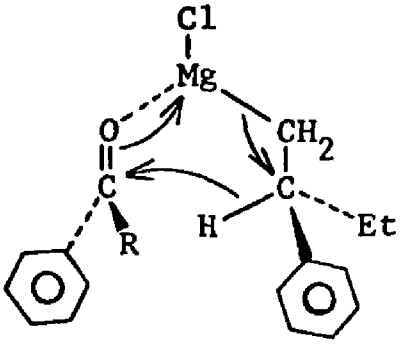
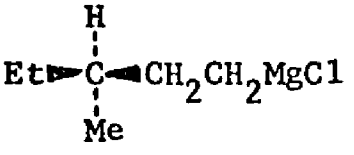


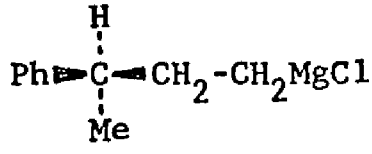
17

In one of the earliest studies of asymmetric Grignard reductions Mosher and LaCombe[20] reacted methyl t-butyl ketone (8) with the γ-asymmetric Grignard reagent (18) prepared from S-(+)-1-chloro-3-methylpentane and obtained racemic carbinol. This result has been interpreted as evidence that only transfer of hydrogen from an asymmetric center could produce observable asymmetric reduction, i.e., only β-asymmetric Grignard reagents could give asymmetric reduction.



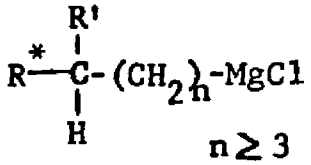
18

Kharasch and Reinmuth[22], however, pointed out that Vavon's "isobornylmagnesium chloride" transferred hydrogen from a nonasymmetric center although in this somewhat unusual case the α-carbon bearing magnesium could be considered asymmetric. It is now recognized that the only necessary conditions for kinetically controlled asymmetric syntheses, such as those under discussion, are that one of the reactants be chiral and nonracemic, and that two diastereomeric transition states lead to enantiomeric products. Thus, in theory at least,



19

reductions by γ-asymmetric Grignard reagents such as 18 should provide asymmetric syntheses although the optical rotation of the products might not be experimentally observable. This conclusion was recently verified by Morrison and coworkers[23] who reduced isopropyl phenyl ketone (13-c) with the Grignard reagent (19) prepared from R-(-)-1-chloro-3-phenylbutane. This experiment provided isopropylphenylcarbinol (14-c), containing a 25% excess of the R-(+)-enantiomer, a surprisingly high value in the face of the earlier study with 18. This initial result raised questions about the generality of γ-asymmetric Grignard reductions, their relation to reductions of similar series of ketones by β-asymmetric reagents and the possibility of obtaining "long range" asymmetric synthesis from reductions utilizing reagents such as 20 in which the methylene chain was extended even further.



$n \geq 3$

20

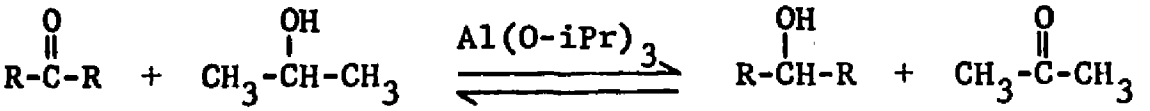
Another interesting aspect of γ-asymmetric Grignard reductions was the fact that the hydrogens transferred from the β-carbon of reagents such as 18 and 19 were diastereotopic and therefore, their rates of reaction should, in theory at least, differ. Morrison and coworkers[23] predicted on the basis of a planar transition state model and the observed product configuration that in the reduction of 13-c with R-19 the pro-S hydrogen on the β-carbon would be transferred more rapidly than the pro-R hydrogen.

This research was initiated to investigate long range asymmetric reductions in general and the various aspects of γ-asymmetric Grignard reductions discussed above in particular. However, during the course of these investigations two new areas which were either directly involved or were closely related to Grignard reduction reactions were taken under study. These areas, Meerwein-Ponndorf-Verley (MPV) reductions and the reductions of perfluoroalkyl carbonyl compounds by both Grignard and Meerwein-Ponndorf-Verley reagents, are discussed separately in the introduction although the similarities of these three areas of investigation will be emphasized in other portions of the thesis.

Meerwein-Ponndorf-Verley Reductions

The reduction of aldehydes by primary metal alcoholates was discovered independently in 1925 by Verley[24] and Meerwein and Schmidt.[25] Ponndorf[26] extended the reduction to ketones by using a secondary alcoholate, aluminum isopropoxide, as

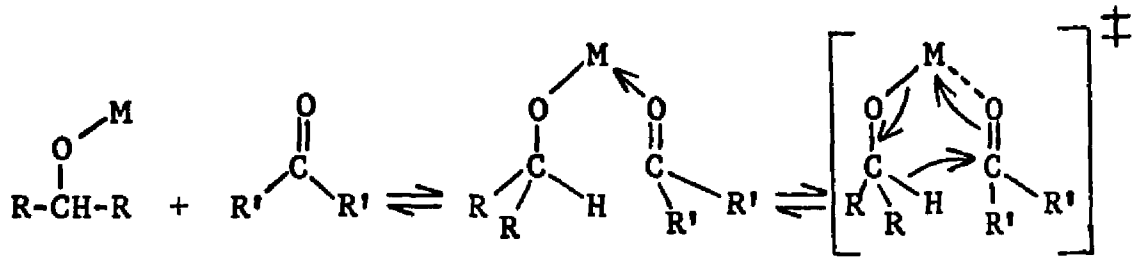
the reducing agent. In 1937, Oppenhauer[27] developed practical conditions for the reverse reaction, the alcoholate-catalysed oxidation of alcohols to carbonyl compounds.



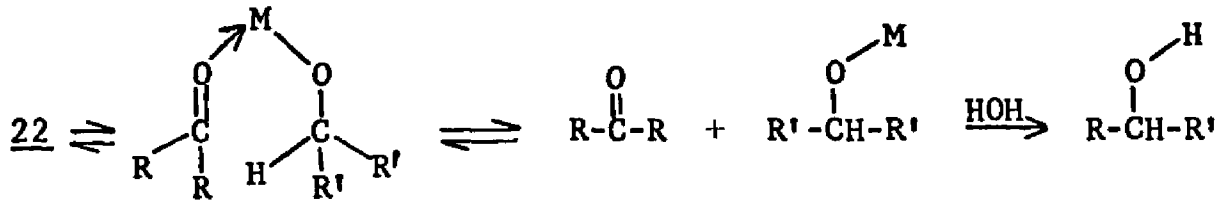
(eq. 5)

Although aluminum alcoholates are generally associated with the Meerwein-Ponndorf-Verley reduction, a variety of metals have been utilized to prepare the reducing agents[28] and the entire range of these systems is included under the term "Meerwein-Ponndorf-Verley (MPV)-type reductions", for simplicity of discussion. MPV reductions have been used extensively as a mild and selective method of reducing ketones and aldehydes in the presence of other sensitive or reducible functions, and the literature has been reviewed from a synthetic standpoint.[28]

The generally accepted mechanism for MPV-type reductions was first suggested by Woodward[9] and later elaborated upon by Jackman and Mills.[30] Comparison of the cyclic transition state for these reactions (22) with that proposed earlier by Whitmore[5] for the Grignard reduction (2) emphasizes the great similarity between the mechanisms of the two reactions. A major difference, however, lies in the well documented[31] reversibility of MPV-type reductions as compared to the essentially irreversible Grignard reductions. This difference leads to thermodynamically controlled product mixtures for most MPV reductions, whereas Grignard reductions lead to kinetically controlled products.



21 22



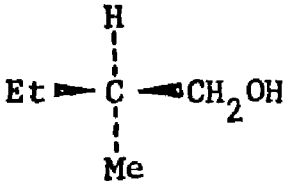
23

Evidence for the mechanism of MPV-type reductions is quite similar to that presented earlier for Grignard reductions. The exclusive transfer of the carbinol hydrogen has been demonstrated by deuterium labeling[32,33] experiments. Reduction was found to be hindered by bases such as amines[29,31-b], which form stable complexes with aluminum salts and presumably inhibit the formation of 21. Studies involving Hammett-type treatments of the reduction of aryl methyl[34] and aryl phenyl ketones[35] demonstrated that the reactions were facilitated by increasing positive charge on the carbonyl carbon. These observations were in accordance with the assumed "hydride-like" nature of the hydrogen transferred during reduction. As with Grignard reductions the observation of asymmetric synthesis during MPV-type reductions with chiral alcoholates has been widely cited as evidence for a transition state such as 22.

In 1949, Jackman and Mills[30] briefly discussed the stereochemical consequences of a cyclic transition state for

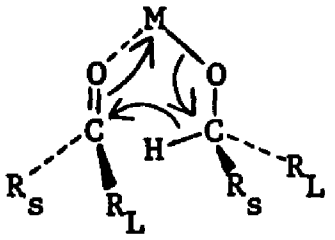
MPV reductions of substituted cyclohexanones. In a subsequent paper these authors[36] elaborated upon the idea of a cyclic, planar transition state to justify experimental observations. At about the same time Baker and Linn[37] reported unsuccessful attempts at asymmetric MPV reductions based upon a cyclic model. These three papers all predated that[12] in which a similar model was suggested for Grignard reductions and represented the first use of principles such as "steric size" to explain or predict stereochemical results on the basis of simple transition state models.

The first example of an asymmetric MPV reduction was reported in 1947 by Doering and Aschner[38], but regrettably this result never appeared in the formal literature other than as a footnote.[39] Phenyl isopropyl ketone (13-c) was reduced with the sodium salt of S-(-)-2-methyl-1-butanol (24) to provide 14-c containing a 2% excess of the S-(-)-enantiomer. In 1950. Doering and Young[39], Vavon and Antonini[40], and Jackman, Mills and Shannon[47] all reported asymmetric MPV-type reductions of unsymmetrical ketones using



24

alcoholates prepared from optically active secondary alcohols. These results as well as almost all obtained since that time were found to be in accordance with the planar cyclic transition state model in which the preferred transition state was 25, with the two "large" groups on opposite sides of the ring, rather than 26. However, Cervinka and coworkers[42] have



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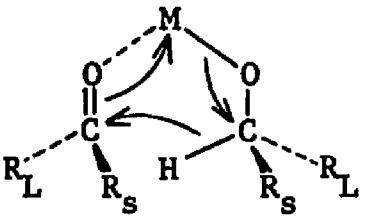
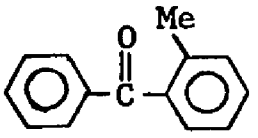


26

reported two cases in which the reduction of phenyl aryl ketones 27 and 28 with S-1-phenylethoxypotassium appears to proceed with 26 preferred.

A very useful extension of asymmetric MPV reductions has been the preparation of optically active primary alcohols (29) owing their asymmetry to deuterium labeling.[33a,43] Recently, reductions of this type were used to assign the



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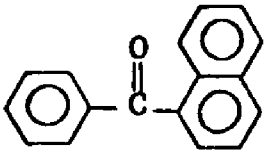

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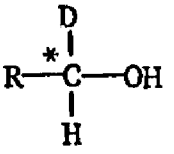


29

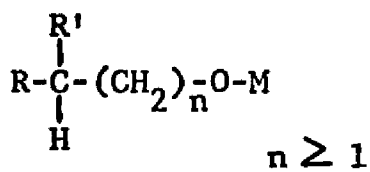
absolute configurations of two compounds of the type 29.[44,45]

Mislow and coworkers have used the partial reduction of racemic mixtures of chiral ketones in the biphenyl series with optically active alcoholates to assign the absolute configurations of several series of biphenyl compounds.[46]

Although asymmetric MPV reductions have been widely studied and used in the assignment of absolute configurations, very little has been done to study the effect of the alcoholate, ketone, solvent and other variables on the degree of asymmetric synthesis obtained in these reactions. This has been due largely to the reversible nature of MPV

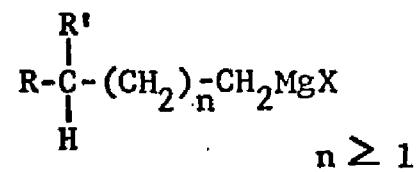
reductions, which generally renders any correlation of the optical purity of products and differences in transition state energies unreliable. Also, there appears to have been little or no attempt made by different workers to standardize either the systems or conditions used in these reductions, so that the available results are not necessarily comparable.

The great similarity between Grignard and MPV reductions suggested that it would be worthwhile to study MPV reductions by primary optically active alcoholates 30, as an extension of our studies of long range Grignard reductions. Reductions by primary alkoxymagnesium halides 30, M = MgX, seemed especially attractive because the reagents and transition states for these reactions would be expected to be very similar to those involved in Grignard reductions with 31.



$n \geq 1$

30



$n \geq 1$

31

In view of the failure of the γ-asymmetric Grignard reagent 18 to provide measurable asymmetric synthesis[20], it was somewhat surprising that the first asymmetric MPV-type reduction[38] reported involved the structurally analogous

alcoholate* the sodium salt of 24. More recently three examples of asymmetric reduction by aluminum salts of 24 were reported[47] while earlier attempts by Baker and Linn[37] had been unsuccessful.

Thus our initial interest in this area involved extending studies of long range asymmetric reductions to MPV-type systems. However, during initial investigations it became apparent that reductions of 13-f by alkoxymagnesium halides provided 14-f of appreciable optical purity in high yield under conditions that were both mild and reproducible. More important, it was found that under the conditions employed the reaction was essentially irreversible. Thus the optical purities of the products obtained could be related directly to transition state energy differences and utilized to study variables influencing these differences.

---

* Difficulty is encountered in comparing obviously similar reagents such as 30 and 31 if the Greek letter designations commonly used for asymmetric Grignard reduction are extended to MPV type reductions. Thus the γ-asymmetric Grignard reagent 18 was prepared from a γ-asymmetric chloride but the corresponding alcoholates are prepared from the β-asymmetric alcohol 24. To resolve this difficulty all comparisons between the two types of reagents will be designated "1,n-asymmetric inductions", following the terminology of Cram and coworkers.[48] In this system "1" and "n" refer to the relative positions of the inducing and incipient asymmetric centers in the transition states. Using this convention reductions by Grignard reagents such as 9 or 15 and those by secondary alcoholates prepared from optically active alcohols such as 14 are both 1,3-asymmetric reductions since in the transition states the inducing and incipient asymmetric centers are separated by the hydrogen transferred. Reductions by both 30 and 31 would be 1,4-asymmetric for n = 1; 1,5-asymmetric for n = 2; and so on.

Reductions of Perfluoroalkyl Carbonyl Compounds

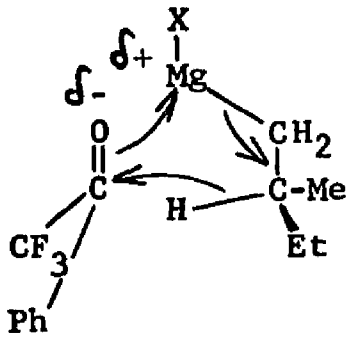
The unusual behavior of carbonyl groups adjacent to perfluoroalkyl groups relative to that of "normal" carbonyl groups has been known for some time and has been discussed in a review by Braendlin and McBee.[19] Most, if not all, of this unusual behavior may be attributed to the electron-withdrawing inductive effect of the strongly electronegative perfluoroalkyl groups. Thus the carbonyl carbon in these compounds is much more susceptible to attack by nucleophilic species, while the carbonyl oxygen is a weaker Lewis base than usual.

Among the consequences of increasing the positive character of the carbonyl group is the great ease with which it is reduced by a variety of methods including the use of metal hydrides and catalytic hydrogenation. This ease of reduction becomes quite striking in cases where there are two reaction pathways available, one of which is reduction. One such instance is the competative addition to and reduction of carbonyl compounds by Grignard reagents containing β-hydrogens. In all cases where the results may be compared, the relative yield of Grignard reduction products has been much greater for perfluoroalkyl carbonyl compounds than with corresponding "normal" compounds of similar steric size.[49]

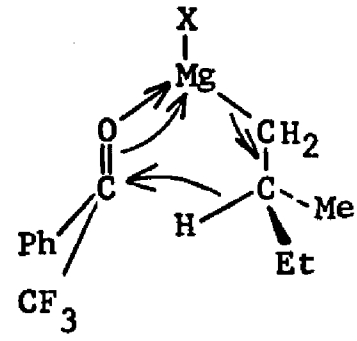
The unusual facility of Grignard reductions of perfluoroalkyl carbonyl compounds is in line with the generally accepted "hydride-like" character of the hydrogen transferred in these reactions. However, the decreased basicity of the carbonyl oxygen in the same compounds would be expected to decrease the stability of the Grignard reagent-ketone complexes 1 assumed to be precursors for both the reduction and addition reactions. This was experimentally demonstrated

by McBee and coworkers[7], who were unable to detect any complex formation between perfluoroalkyl carbonyl compounds and magnesium bromide, a stronger Lewis acid than Grignard reagents. On the basis of the ease of reduction and lack of observable complexation, McBee[7] proposed that the Grignard reduction of perfluoroalkyl carbonyls might proceed by an intermolecular transfer of hydrogen rather than by the intracomplex transfer proposed in the Whitmore mechanism. Confusing the issue was an observation that treatment of perfluoroalkyl carbonyls with magnesium bromide prior to adding a potentially reducing Grignard reagent greatly increased the relative amount of addition reaction at the expense of reduction.[7,50] As discussed in the introduction for Grignard reduction reactions, a similar observation with normal carbonyl compounds was interpreted as evidence for intracomplex hydrogen transfer[6] although alternative explanations have been offered in the perfluoroalkyl case.[7]

Mosher and coworkers[16], in an attempt to resolve this problem, reduced trifluoromethyl phenyl ketone (13-f) with the Grignard reagent from S-(+)-1-chloro-2-methylbutane (9). Trifluoromethylphenylcarbinol of "high optical rotation" was obtained as the only high-boiling product, although at the time this experiment was conducted neither the maximum rotation nor the absolute configuration of the product was known. On this basis the authors concluded that a highly oriented transition state, involving either intermolecular (32-a) or intracomplex (32-b) hydrogen transfer was required to explain the asymmetric synthesis. However, in theory a transition state such as 33 which has no particular orientation between the two molecules other than that required for the hydrogen transfer could provide the same result.

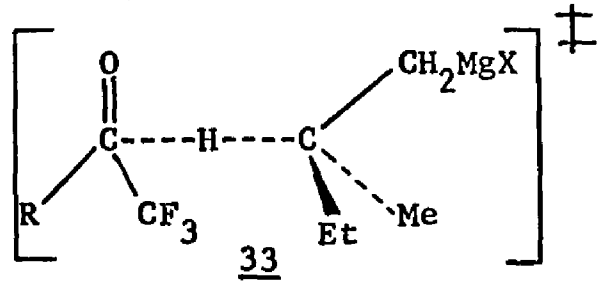


32-a



32-b

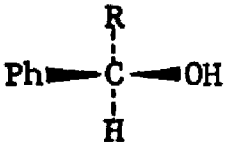
On the basis of the evidence available at that time three mechanistic possibilities were considered.[7,16,49] The first involved a scheme identical to that of the normal Grignard reduction mechanism, except that the amount of complex present at any one time was too small to be detected; i.e., the equilibrium between uncomplexed and complexed reactant heavily favored the uncomplexed form. The second involved a rate-determining complex formation step followed by a fast hydrogen transfer. The third possibility consisted of a nonoriented transition state such as 33 involving intermolecular hydrogen transfer. No experimental evidence has been presented which clearly distinguishes between these three alternatives.



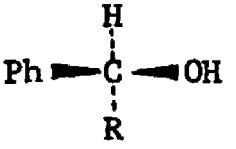
33

Recently the absolute configuration and maximum rotation were reported for trifluoromethylphenylcarbinol[51] (14-f) making it possible to determine that the product obtained earlier by Mosher and coworkers[16] had the configuration shown in 34 rather than that shown in 35 which was obtained on reducing a series of "normal" phenyl alkyl ketones with

the same reagent.[15] The result was also the opposite of



34



35

that predicted on the basis of the cyclic transition state model and points up the rather large unexplained differences in behavior between normal and perfluoroalkyl carbonyl compounds. In the meantime preliminary experiments conducted as part of this thesis also demonstrated anomalous behavior for trifluoromethyl phenyl ketone in asymmetric reductions.

Studies were initiated with the aim of defining the extent and the origin of this anomalous behavior and, hopefully of elucidating the details of the mechanism of reductions of perfluoroalkyl carbonyl compounds. At the same time, H. S. Mosher and his group have been conducting complimentary investigations[18] with 1,3-asymmetric Grignard reductions.

RESULTS AND DISCUSSION

General

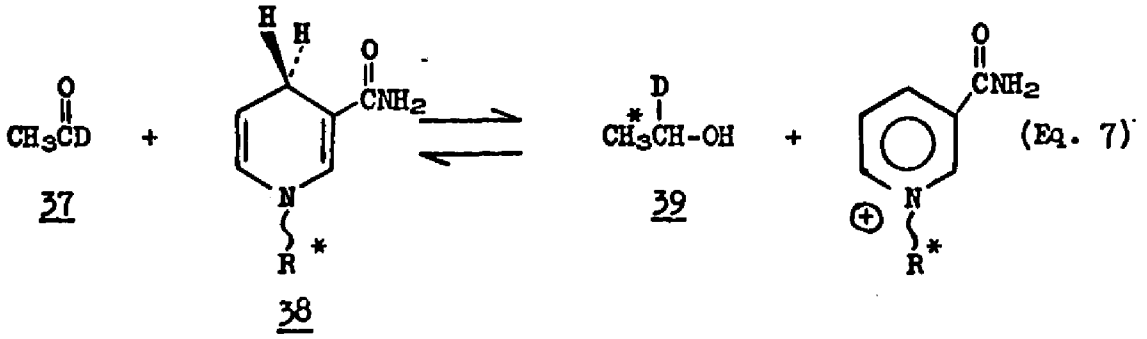
There has been a great deal of interest in asymmetric Grignard and Meerwein-Ponndorf-Verley (MPV) reductions in the 20 years since their discovery. The vast majority of studies have been concerned with 1,3-asymmetric reductions in which hydrogen was transferred from an asymmetric center on the reducing agent. A few examples of 1,4-asymmetric reductions of this type have been reported, but the reducing agents studied were either rather complex and not amenable to simple interpretation[11] or the results obtained could not be compared to those from other systems.[38,47] No examples of 1,5- (or greater) asymmetric Grignard or MPV reductions have been reported. An interesting feature of long range asymmetric reductions (1,4 or greater) is the possibility of studying two asymmetric processes simultaneously. Thus, in reducing agents such as 36 in which a hydrogen is transferred from a methylene group there should be a preference for transfer of one or

36, Y = CH_2 or -O-

(Eq. 6)

the other diastereotopic hydrogen, while at the same time an optically active alcohol is formed (eq. 6). This stereochemical behavior is formally quite similar to that observed in enzymatic reductions involving NADH as a coenzyme. These reactions have been shown to be stereospecific with respect to both the transfer of the diastereotopic

hydrogens from the dihydropyridine moiety 38 of NADH and to the formation of optically active ethanol-1-d (39) if deuterated aldehydes such 37 are reduced (eq. 7).[52]



37 38 39 (Eq. 7)

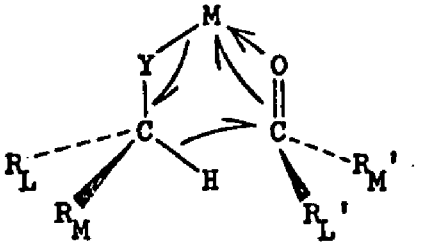
1,3-Asymmetric MPV and Grignard reductions have been discussed as models for NAD-NADH coenzyme redox systems.[19,53] The opportunity to study the relationship between the two forms of asymmetric reactions taking place in long range asymmetric Grignard and MPV reductions would presumably make these systems even better models for enzymatic reductions.

A series of long range asymmetric reductions was accomplished utilizing chiral alcoholates and Grignard reagents. These reductions included examples of 1,4-, 1,5- and 1,6-asymmetric reduction and, in the case of MPV reductions, the 1,3-asymmetric reductions for the sake of comparison. The effect of a number of structural variations in both substrate and reducing agents was studied. A series of reductions by both racemic and optically active stereospecifically deuterium labeled γ-asymmetric Grignard reagents was investigated to elucidate the behavior of the diastereotopic β-hydrogens transferred during

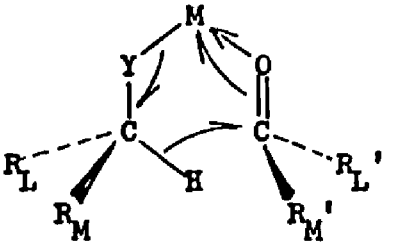
these reactions. The results of studies involving reducing agents prepared from optically active materials are summarized in Table 1 (Grignard reductions) and Tables 3 and 4 (MPV reductions). The results of the deuterium labeling experiments are summarized in Table 2.

In order to provide a frame of reference for the results to be discussed in this work, some general findings of earlier workers in the area will be presented. Basic to stereochemical studies with 1,3-asymmetric Grignard and MPV reductions has been the assumption that the configurations of products obtained from these reactions could be rationalized by the proper assignments of the relative sizes of groups in the two diastereomeric transition states 65 and 66 generated by one enantiomer of the reducing agents.

Y = $-CH_2-$ or $-O-$



65



66

The enantiomer formed in excess has been found to result from a transition state such as 65 rather than 66 in almost every case tested. The relative sizes of groups in these reactions have been determined empirically to be: Phenyl > t-butyl > cyclohexyl > isopropyl > ethyl > methyl.[13,18] Deuterium has also been tested and intuitively would be expected to be smaller than methyl.[18] The only result in the above series that might seem unusual is the fact that all alkyl groups

Table 1

Long Range Asymmetric Grignard Reductions

19, n = 1, X = Cl 13 14

44, n = 1, X = Br

48, n = 2, X = Cl

threo-80

Reducing Agent				Ketone	Yield, %		Phenylalkylcarbinol				
Reag.	Conf.	%e.e.	X	R	Addn.	Red.	[α]D (t°)	%e.e.[a]	Conf.	%A. I.[b]
19	S	53	Cl	Et	85	5	-2.76 (27)	9.7	S	18
19	S	53	Cl	tBu	52	48	-1.2 (24)	4.6	S	9
19	S	49	Cl	tBu	53	47	-1.1 (27)	4.2	S	9
44	R	90	Br	tBu	60	40	-0.42 (27)	1.6	S	2
19	S	49	Cl	CF_3	95	5	+0.60 (28)	1.9	S	4
44	R	90	Br	CF_3	90	10	-1.47 (28)	4.6	R	5
80	2R,3S	50	Cl	iPr	-	-	-2.3 (28)	9.3	S	19
80	2S,3R	91	Cl	tBu	-	-	0.0 (28)	0.0	-	0
80	2S,3R	91	Cl	CF_3	-	-	+2.05 (28)	6.5	S	7

Table 1 (Cont.)

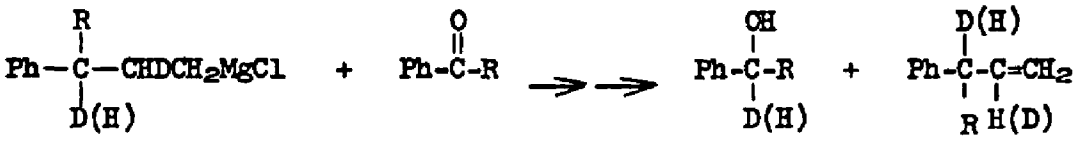
Reducing Agent				Ketone	Yield, %		Phenylalkylcarbinol				
Reag.	Conf.	%e.e.	X	R	Addn.	Red.	[α]D (t°)	%e.e.[a]	Conf.	%A. I.[b]	
48	R	89	Cl	tBu	10	90	-2.3 (30)	8.9	S	10	
48	R	89	Cl	CF_3	5	95	-1.16 (28)	3.6	R	4	

a) e. e. based on maximum literature rotations of: 1-phenyl-1-propanol, [α]D 27.7° (neat), reference 79; t-butylphenylcarbinol, [α]D 25.9° (benzene), reference 15; trifluoromethylphenylcarbinol, [α]D 31.8° (neat), reference 51; isopropylphenylcarbinol, [α]D 24.6° (neat), reference 80.

b) A. I. corresponds to product %e. e. corrected for % e. e. of reducing agent.

Table 2

Deuterium Labeling Experiments with Long Range Grignard Reductions



80, R = Me
58, R = H

13

14

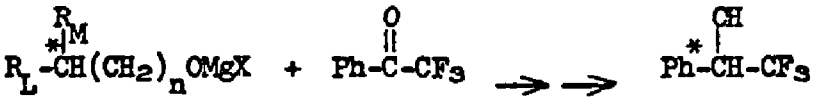
134, R = Me
135, R = H

Grignard Reagent	Carbinol, 14 R	H, %[a]	k_H/k_D[b]	Olefin Nonterminal Vinyl H, %[a]	H, %[a]	k_H/k_D[b]
(±)-threo-80	tBu	47	0.6	70	13	0.5
(±)-threo-80	CF_3	63	1.3	50	13	1.3
(±)-erythro-80	tBu	90	8	25	15	7
(±)-erythro-80	CF_3	68	1.7	47	15	1.7
(2R,3S)-threo-80	iPr	-	-	68	16	0.6
(2S,3R)-threo-80	tBu	-	-	74	16	0.5
(2S,3R)-threo-80	CF_3	-	-	55	17	1.2
(±)-threo-58	iPr	71	2.3	-	-	-
(±)-threo-58	tBu	71	2.3	35	-	2.1
(±)-threo-58	CF_3	60	1.3	42	-	1.

a) Uncorrected % hydrogen from nmr integration data.
b) k_H/k_D values corrected for less than 100 % deuterium incorporation in the reducing agents.

Table 3

Asymmetric Meerwein-Ponndorf-Verley Reductions of Trifluoromethyl Phenyl Ketone by Alkoxymagnesium Halides



Alcoholate						Solvent System	Product, 14-f			
R_L	R_M	n	Conf.	%e.e.	X		[α]D (t°)	%e.e.	Conf.	%A.I.
nHex	Me	0	R	93	Br	Benzene-Ether	-3.26 (22)	10.3	R	11
C_8C_{11}	"	"	S	70	"	" "	+9.34 (21)	29.4	S	42
Ph	"	"	R	99	Cl	" "	-17.1 (23)	53.8	R	54
"	"	"	S	86	Br	" "	+11.3 (27)	35.9	S	42
"	"	"	R	99	"	" -THF	-16.7 (27)	40.7	R	41
"	"	"	"	"	I	" -Ether	-21.7 (27)	52.0	"	52
Et	"	1	S	98	Cl	" "	-2.48 (22)	7.8	"	8.0
"	"	"	"	"	Br	" "	-1.60 (21)	5.0	"	5.1
"	"	"	"	"	"	" "	-1.70 (19)	5.3	"	5.4
"	"	"	"	"	"	Ether	-1.49 (22)	4.7	"	4.8
"	"	"	"	"	"	Benzene	-1.01 (22)	3.2	"	3.3
"	"	"	"	"	"	" -iPr$_2$O	-1.15 (22)	3.6	"	3.7
"	"	"	"	"	"	" -THF	+0.31 (21)	1.0	S	1.0
"	"	"	"	"	"	" -DME	+0.57 (23)	1.8	"	1.8
"	"	"	"	"	"	" -R*OH[a]	+0.31 (27)	1.0	"	1.0
"	"	"	"	"	I	" -Ether	-0.90 (23)	2.8	R	2.9

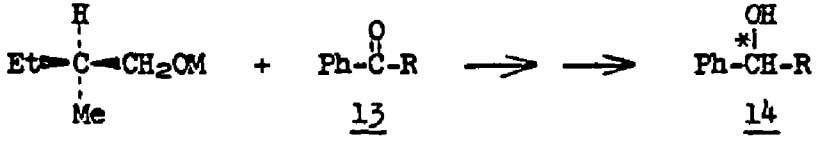
Table 3 (Cont.)

Alcoholate						Solvent System	Product, 14-f				
R_L	R_M	n	Conf.	%e.e.	X		[α]D	(t°)	%e.e.	Conf.	%A.I.
C_6H_{11}	Me	1	S	99	Br	Benzene-Ether	-6.87	(23)	21.6	R	22
"	"	"	R	46	"	" "	+3.34	(23)	10.5	S	23
"	Et	"	"	61	"	" "	+1.98	(24)	6.1	"	10
Ph	Me	"	S	99	"	" "	-0.68	(24)	2.1	R	2.1
"	"	"	R	46	"	" "	+0.89	(25)	2.8	S	6.1
"	"	"	"	"	"	" -THF	-0.17	(28)	0.5	R	1
"	"	"	"	"	I	" -Ether	+1.34	(28)	4.2	S	8.9
"	Et	"	S	90	Br	" "	-3.10	(26)	9.7	R	11
C_6H_{11}	Me	2	"	57	"	" "	-2.34	(24)	7.4	"	13
"	"	"	R	95	I	" "	+2.09	(28)	6.6	S	6.9
Ph	"	"	S	57	Cl	" "	+1.18	(23)	3.7	"	6.5
"	"	"	"	"	Br	" "	+3.23	(18)	10.1	"	18
"	"	"	R	95	"	" "	-6.26	(24)	19.7	R	21
"	"	"	"	"	"	" -THF	-2.56	(28)	8.1	"	8.5
"	"	"	"	"	I	" -Ether	-7.44	(27)	23.4	"	25
C_6H_{11}	"	3	"	89	Br	" "	-0.25	(28)	0.8	"	0.9
Ph	"	"	"	"	"	" "	+0.97	(27)	3.1	S	3.5

a) R^*OH = S-(-)-2-methyl-1-butanol.

Table 4

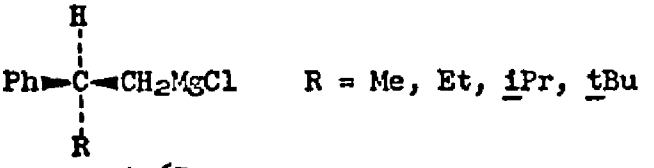
Miscellaneous Asymmetric Meerwein-Ponndorf-Verley Reductions



Alcoholate			Reduction	Reaction	Product			
M	%e.e.	R	Yield, %	Conditions	[α]D (t°)	%e.e.	Conf.	%A.I.
MgBr	34	tBu	3	3 wk., R.T.	-	-	-	-
				2 day, reflux	-0.23 (28)	0.89	S	2.3
MgBr	98	CF_3	20	16 hr., R.T.	-1.65 (22)	5.2	R	5.3
MgOR*[a]	"	"	ca. 90	" "	+0.70 (24)	2.2	S	2.2
Li	"	"	10	" "	0.00 (22)	0.0	-	0.0
Na	"	"	10	" "	0.00 (24)	0.0	-	0.0
"	"	"	ca. 10	" "	-0.15 (24)	0.5	R	0.5
"	"	"	ca. 0	" "	- -	-	-	-
$Al(OR^*)_2$[a]	"	"	10	" "	+0.12 (24)	0.4	S	0.4

a) R*O- = S-2-Methyl-1-butoxy.

including t-butyl behave as if they were smaller than phenyl. This is clearly contrary to the "normal" view of relative sizes which has been developed on the basis of cyclohexane "A" values in which t-butyl is much larger than phenyl. However, reductions of t-butyl phenyl ketone have provided several of the apparent violations of the transition state model, in which the product resulting from 66 predominates if phenyl is assumed to be larger than t-butyl. For example the reduction of t-butyl phenyl ketone (13-e) with a series of 2-phenyl-2-alkylethyl Grignard reagents S-67 provided an excess of enantiomer 35 as predicted by the model 65 with R = Et and iPr, but provided an excess of 34 as



R = Me, Et, iPr, tBu

S-67

predicted by model 66 with R = Me. This last result would seem to indicate that in this one case at least, t-butyl is larger than phenyl. Similar behavior has been noted in these laboratories for the reduction of t-butyl phenyl ketone with a Grignard reagent similar to 67 in which R = D.[62]

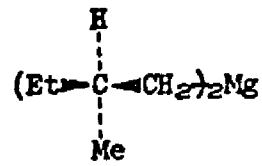
The amount of asymmetric synthesis observed for the series of phenyl alkyl ketones (13) in Grignard reductions has generally been shown to increase with increasing size of the alkyl group from methyl to isopropyl and then fall off from isopropyl to t-butyl.

An unusual apparent order of size has been noted for the reduction of trifluoromethyl phenyl ketone(13-f) with a variety of β-asymmetric Grignard reagents.[16,18] Almost without exception asymmetric reduction

of 13-f has provided an excess of the product predicted by a model in which trifluoromethyl is larger than either phenyl or t-butyl. The one exception involved the reduction of 13-f with the Grignard reagent 67, R = tBu. Although it is tempting to accept the rationalization that a CF_3 group is larger than either phenyl or t-butyl, there is little or no physical evidence to support this.[18] The van der Waals radius of fluorine is smaller than that of methyl, so that trifluoromethyl should be smaller than t-butyl, which in turn is usually smaller than phenyl in these reactions. Other evidence for the smaller size of trifluoromethyl includes rotational barrier measurements in substituted ethanes, cyclohexane "A" values and UV spectral measurements of the degree of deviation of the phenyl ring from coplanarity with the carbonyl group in the series of ketones 13. Another possible explanation would lie in the development of strong electronic interactions (either repulsions or attractions) between the CF_3 and substituents on the reducing agents which overcome normal steric effects. This might be reasonable for reducing agents such as 67 which contain aromatic groups with which these interactions might take place; but it seems highly unlikely in the case of a reducing agent such as 9 in which both of the substituents are alkyl groups.[18]

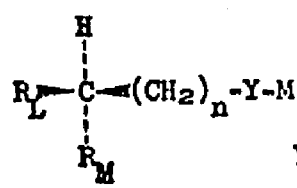
In the case of β-asymmetric Grignard reductions it has been determined that there is a relatively small decrease in the amount of asymmetric synthesis through a series in which the reducing agent was a magnesium chloride, bromide or iodide.[11] However, in the same series the yields of reduction products were found to decrease drastically.[11] Reduction by a dialkylmagnesium reagent 68 gave essentially the same amount of

asymmetric synthesis as the alkylmagnesium halides.[63] A change from ether to tetrahydrofuran as solvent was found to lower the amount of asymmetric synthesis only slightly in β-asymmetric Grignard reductions.[17,18]



68

The "normal" order for configurations* and relative amounts of asymmetric synthesis obtained in β-asymmetric Grignard reductions of a series of phenyl alkyl ketones is shown in Table 5. For ease of comparison the absolute configurations of products reported in this work, other than in Tables 1, 2, 3, 4, and 15, have been adjusted to those that would have resulted from the use of reducing agents with the stereoformula 69. It should be pointed out that there is no



Y = -CH_2- or -O-

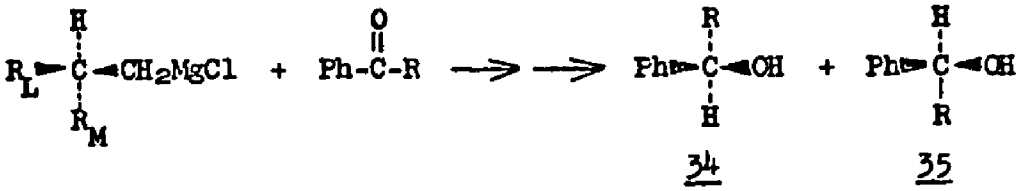
n = 0 to 3; M = Metal

69

* Comparisons of the configurations of phenylalkyl carbinols are given repeatedly in the discussion of this work. The term "opposite configuration" has real meaning when applied to structures such as 34 and 35 even though these structures may in some cases have the opposite Cahn-Ingold-Prelog (R and S) configurational designations[61] because of changes in the relative priority sequence between the phenyl and alkyl groups. In the remainder of the discussion the term "opposite configurations" will refer to the enantiomeric relationship of stereoformulas such as 34 and 35, regardless of the nature of R .

Table 5

β-Asymmetric Grignard Reductions of Phenyl Alkyl Ketones



Ketone R	Grignard Reagent: R_L = Et, R_M = Me A.I.,%	Pref. Conf.	R_L = Ph, R_M = Me A.I.,%	Pref. Conf.	R_L = Ph, R_M = Et A.I.,%	Pref. Conf.
Me	4	35	38	35	47	35
Et	6	"	38	"	52	"
iPr	24	"	59	"	82	"
tBu	16	"	22	34	16	"
CF_3	22	34	47	"	38	34

necessary relationship between the configurational results obtained for different values of n in 69.

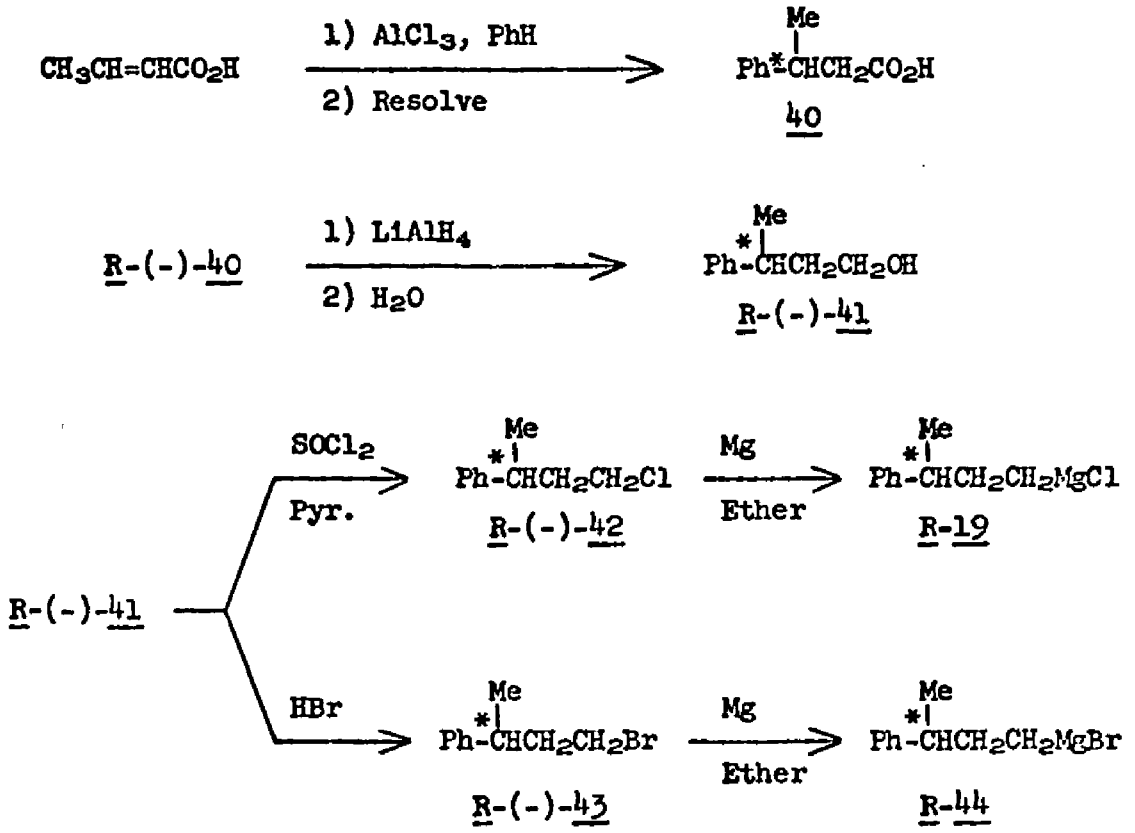
In the case of MPV reductions little has been done in the way of systematic studies other than several experiments in which the reduction of a series of ketones by a common alcoholate[42,64] or a series of alcoholates was used in the partial kinetic resolution of a racemic biphenyl ketone.[65] These studies have shown that the relative size orders deduced from Grignard reductions generally hold for MPV reductions as well.

Preparation of Reducing Agents

The optically active 3-phenyl-1-butyl Grignard reagents 19 and 44 were obtained by Scheme 1, involving the preparation of 3-phenylbutanoic acid (40) by Friedel-Crafts alkylation of benzene with crotonic acid, resolution of the acid as the α-methylbenzylamine salt, reduction of the acid to the alcohol with lithium aluminum hydride and halogenation of the alcohol with either thionyl chloride or 48% hydrobromic acid to furnish the chloride 42 and bromide 43 which were converted to the Grignard reagents 19 and 44 by standard methods.

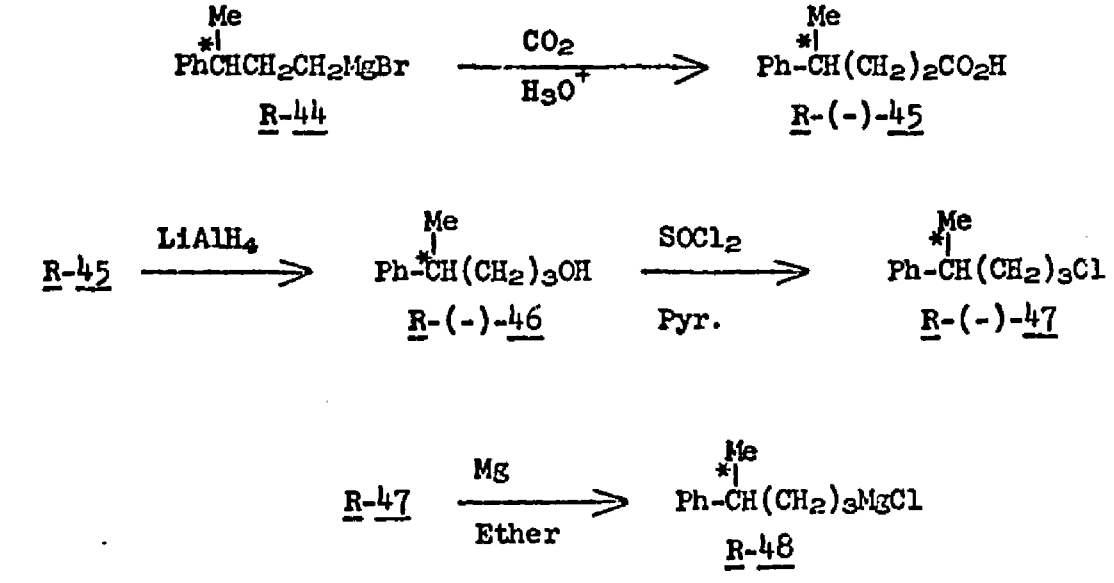
R-(-)-1-Chloro-4-phenylpentane R-(47) was prepared from R-43 as shown in Scheme 2 which involved carbonation of the Grignard reagent R-44 to furnish R-(-)-4-phenylpentanoic acid R-(45) which was reduced to the alcohol R-46 with lithium aluminum hydride. Alcohol R-46 was converted to the chloride R-47 using thionyl chloride and pyridine. The first two steps in Scheme 2 had been used previously[54] to prepare 45 and 46; however, the maximum rotations previously reported for these compounds should be adjusted since they were prepared from 3-phenyl-

Scheme 1



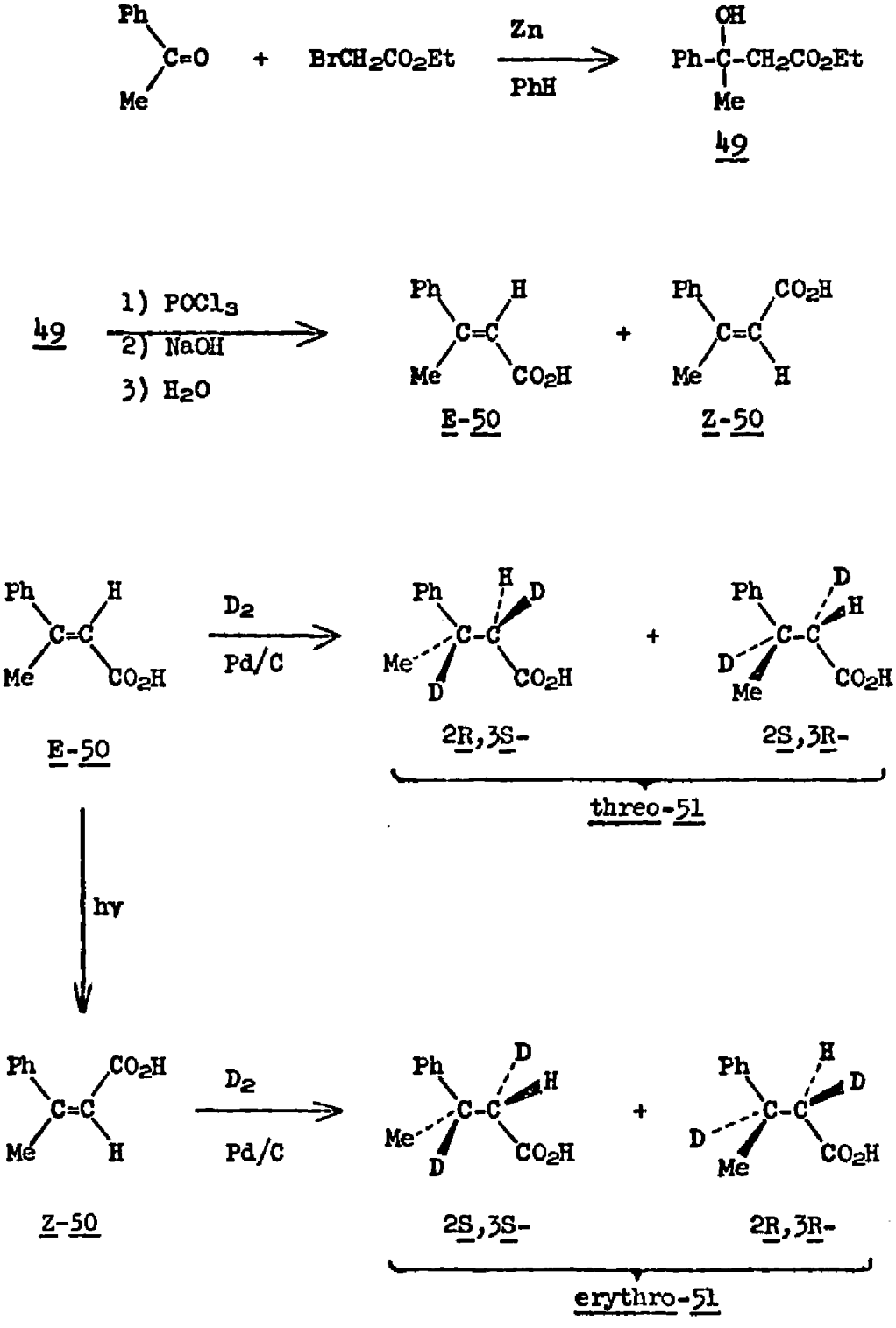
butanoic acid having only 90% of the rotation reported more recently[55] for the same compound. The R-4-phenylpentyl Grignard reagent (48) was prepared in the normal manner.

Scheme 2



The stereospecifically labeled 2,3-dideuterio-3-phenylbutyl Grignard reagents were prepared from the corresponding threo- and erythro-2,3-dideuterio acids, threo- and erythro-51, following Scheme 1. The resolution of the deuterated acids 51 was identical to that for the unlabeled material in every respect. The optical purities of the labeled materials were calculated using the rotation data for the unlabeled 3-phenylbutyl series[55] as reference. The precursor acids, threo- and erythro-51, were obtained from methyl phenyl ketone and ethyl bromoacetate by the series of reactions shown in Scheme 3. The hydroxy ester 49 was dehydrated and saponified to furnish a mixture of the (Z)- and (E)-β-methylcinnamic acids, (Z-50) and (E-50). The mixture of acids provided (E)-50 on crystallization from carbon disulfide, and irradiation of either (E)-50 or a mixture of the acids furnished (Z)-50. Catalytic deuterogenation was assumed to be 100% stereoselective in providing the products shown. Attempted nmr and IR analysis of each of the products, the acid 51, the alcohol 52 and the chloride 53, for any products resulting from the trans incorporation of deuterium was unsuccessful. Slight differences were noted in the nmr spectra of the erythro- and threo- series. However, even if the addition of deuterium were not 100% stereoselective, as assumed, it would only result in smaller deviations from the normal isotope effects and make these deviations more difficult to detect. The qualitative interpretation of the observed values would not have been affected. Another assumption made in the labeling experiments was that replacement of hydrogen at the asymmetric center by deuterium would have no detectable effect on the stereochemical result of the asymmetric synthesis.

Scheme 3


Ph
C=O
Me
+ BrCH2CO2Et
Zn
PhH
OH
Ph-C-CH2CO2Et
Me
49
49
1) POCl3
2) NaOH
3) H2O
Ph
H
C=C
Me
CO2H
E-50
+
Ph
CO2H
C=C
Me
H
Z-50
Ph
H
C=C
Me
CO2H
E-50
D2
Pd/C
Ph
H
D
C-C
Me
D
CO2H
2R,3S-
+
Ph
D
H
C-C
D
Me
CO2H
2S,3R-
threo-51
hν
Ph
CO2H
C=C
Me
H
Z-50
D2
Pd/C
Ph
D
H
C-C
Me
D
CO2H
2S,3S-
+
Ph
H
D
C-C
D
Me
CO2H
2R,3R-
erythro-51

The threo-2,3-dideuterio-3-phenylpropyl Grignard reagent (threo-58) was prepared from (E)-cinnamic acid (E-54) via the same type of scheme used for the 2,3-dideuterio-3-phenylbutyl series. In this case the assumption was made that the C-3 chiral center exerted a negligible effect on the reactivity of hydrogen and deuterium at C-2.

The optically active alcohols utilized in the preparation of MPV-type reducing agents were obtained by several means. The secondary alcohols, 2-octanol (59) and 1-phenylethanol (60), were resolved as their acid phthalates using optically active α-methylbenzylamine. The procedure, which seemed quite general, involved replacement of the brucine used in the classical resolutions[56,57] with the commercially available (+)- or (-)-α-methylbenzylamine. 2-Phenylpropanoic acid (61), 2-phenylbutanoic acid (62) and 3-phenylbutanoic acid (40) were resolved with strychnine,[58] cinchonidine[59] and -methylbenzylamine[60], respectively, and the acids were reduced to the corresponding alcohols with lithium aluminum hydride. The alcohols bearing cyclohexyl substituents were prepared by the hydrogenation of the corresponding phenyl substituted alcohols in methanol-glacial acetic acid using platinum oxide as catalyst. One exception was R-2-cyclohexyl-1-butanol (R-64) which was obtained by hydrogenation of R-2-phenylbutanoic acid in the manner described above, followed by reduction of the intermediate R-2-cyclohexylbutanoic acid with lithium aluminum hydride.

The alkoxymagnesium halides were prepared by adding the alcohols to low molecular weight ($\leq C_4$) Grignard reagents. In the case of reactions conducted in benzene-ether solution, a mixture of these solvents was distilled to a boiling point of about 55-56° to provide a mixture generally found to be a better solvent for the alcoholates than either of the pure components.

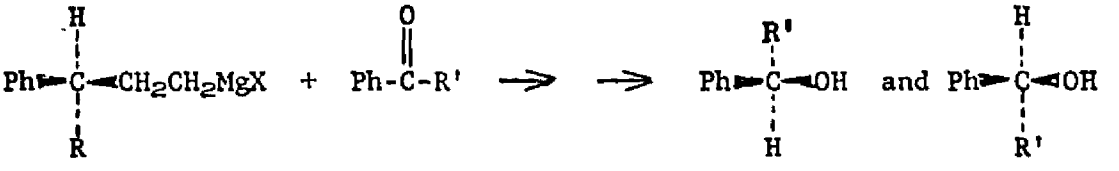
The lithium alcoholate was prepared from the alcohol and n-butyllithium. Other alcoholates were prepared either by direct reaction of the alcohol with the metal or from the corresponding metal methoxide and alcohol by distillation of a toluene solution to remove methanol.

1,4-Asymmetric Grignard Reductions

The configurationally normalized results from reductions with 3-phenylalkyl Grignard reagents are summarized in Table 6.

Table 6

Reductions by Chiral 3-Phenylalkyl Grignard Reagents



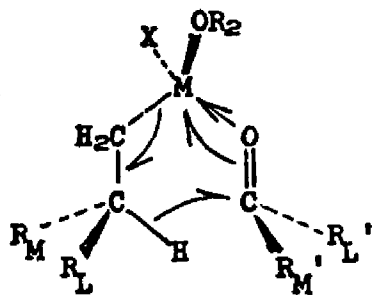
34 35

Grignard Reagent		Phenylalkylcarbinol		
R	X	R'	Preferred Configuration	A. I., %
Me	Cl	Et	35	18
"	"	iPr	"	25
Et	"	"	"	29
Me	"	tBu	"	9
"	"	CF_3	34	4
"	Br	tBu	"	2
"	"	CF_3	"	5

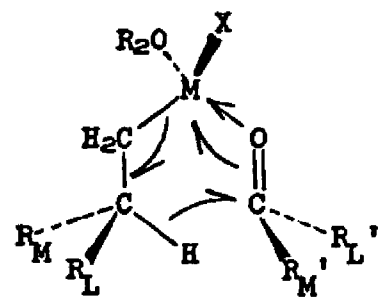
These results verify the earlier report[23] of 1,4-asymmetric reduction in every case tested. Comparison of the results in Tables 5 and 6 demonstrates the similar trends shown by both β-asymmetric and γ-asymmetric

Grignard reagents in the reduction of phenyl alkyl ketones. These trends are quite similar both with respect to the relative amounts of asymmetric synthesis through the series and to the "reversal"of configuration for trifluoromethyl phenyl ketone. These trends, observed for both alkyl and aryl substituted β-asymmetric reagents as well as the γ-asymmetric reagent, point up the large measure of control exerted by the ketone being reduced on the stereochemistry of asymmetric Grignard reductions.

The effect of halide on the outcome of 1,4-asymmetric Grignard reductions represents the most interesting result obtained in this series of reactions. The decrease in the amount of reduction products obtained with the use of bromide in place of chloride paralleled the behavior observed in 1,3-asymmetric reductions. However, the reversal of the preferred product configuration obtained from t-butyl phenyl ketone with the same change has no precedent. This reversal points up the extreme sensitivity toward seemingly minor variations in reaction conditions which was observed throughout these studies for long range asymmetric reductions. Possible rationalizations for the reversal with halide include the effect of the different sizes of the halides on an "asymmetric center" at magnesium such as shown in models 70 and 71 or the effect of electronegativity on coordination, solvation, or some other aspect of transition state for the reduction. It was also worthwhile to note that replacement of chloride with bromide gave little change or possibly a small increase in the excess of 34 obtained in the δ-asymmetric reduction of trifluoromethyl phenyl ketone. As mentioned previously, in the only case tested with β-asymmetric Grignard reductions[11] a change from



70



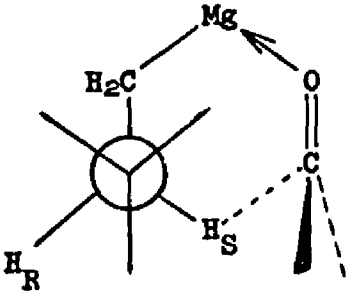
71

chloride to bromide caused a decrease in the stereoselectivity of the reduction.

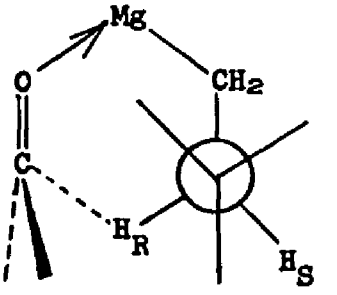
In view of the observed sensitivity of 1,4-asymmetric Grignard reductions towards seemingly minor changes in reaction conditions it would be of interest to test the effect of solvent variation of these reactions. In studies of the corresponding MPV reductions the variation of solvent from ether to tetrahydrofuran was found to cause reversal of the preferred product configuration.

The series of reductions of phenyl alkyl ketones with the 3-phenyl-1-butyl Grignard reagent (19) seemed to offer a "normal" series of 1,4-asymmetric reductions, upon which a tentative stereochemical model for these reactions might be based. The model preferred at this time is a simple extension of the widely used planar, cyclic transition state model for 1,3-asymmetric reductions. The conceptual device used for this model is a set of Newman projections such as 72 and 73, which are viewed down the bond connecting the asymmetric center to the C-2 methylene group involved in a cyclic, six-membered transition state. Assuming a staggered conformation, the relative hindrance for the three positions may be assigned as follows: The most hindered position is that between

the methylene and the hydrogen transferred, i.e., that turned into the ring in 72 and 73, the next most hindered position is assumed to be that between the methylene and the C-2 hydrogen not transferred, and the least hindered that between the methylene hydrogens. In this model it is



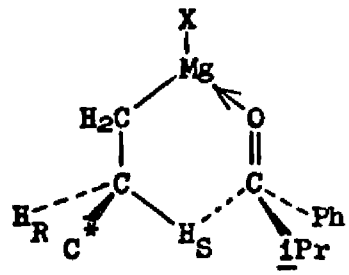
72



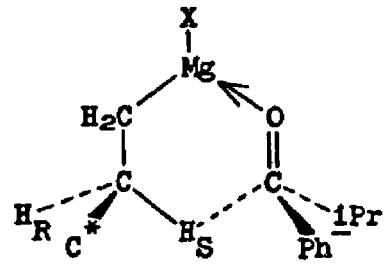
73

assumed that the most favored conformations are those in which the smallest ligand on the asymmetric center is turned into the ring. Then the relative locations of the medium and large ligands in 72 and 73 are determined by the absolute configuration at the asymmetric center. These locations in conjunction with the relative amounts of hindrance determine whether 72 or 73 is the preferred transition state model.

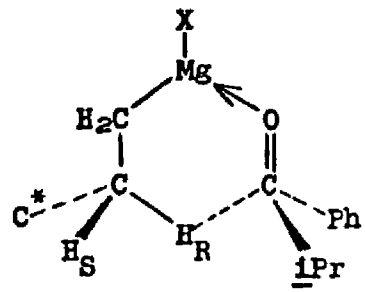
The utility of this model in rationalizing the stereochemical results of the reduction of isopropyl phenyl ketone with R-19 is demonstrated. This reduction may proceed via four diastereomeric transition states 74-77, which involve the transfer of either the pro-S (74 and 75) or pro-R (76 and 77) hydrogen to form either R- (74 and 76) or S-isopropylphenylcarbinol (75 and 77). On the basis of primary interactions between the "large" phenyl and 1-phenylethyl (C*) groups, two of these transition state models, 75 and 76, are assumed to have energies sufficiently greater than the other two, 74 and 77, so that they need not



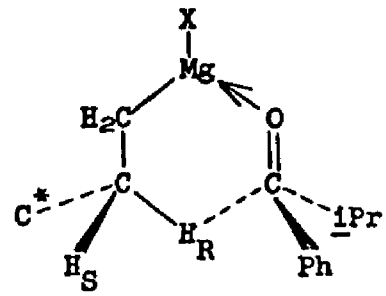
74



75

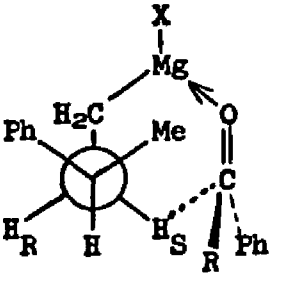


76

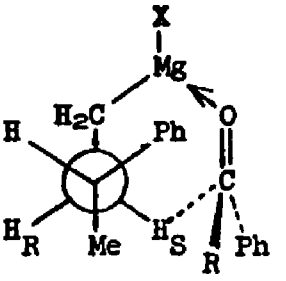


77

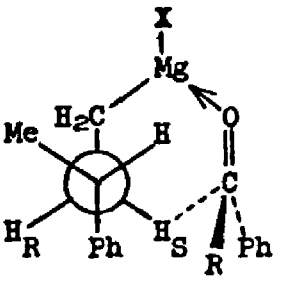
receive further consideration. This assumption is independent of the configuration of C*. Inspection of the six staggered conformations possible in 74 and 77 for the 1-phenylethyl group in R-19 allows the selection of 74-c and 77-a as the two in which the hydrogen occupies the preferred position and is turned into the ring. Then, since the phenyl group (R_L) in 74-c occupies the less hindered position between the methylene hydrogens while in 77-a it lies in the more hindered position between the methylene and hydrogen, the former is selected as the lowest energy transition state model for the reaction. If it is also assumed that the favored pathway determines both the hydrogen transferred and the configuration of the alcohol produced, then R-19 would be predicted to preferentially transfer the pro-S hydrogen to form an excess of the R-(+)-enantiomer of isopropylphenylcarbinol. These predictions are in



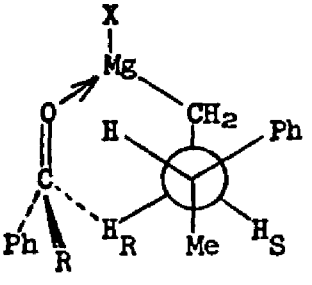
74-a



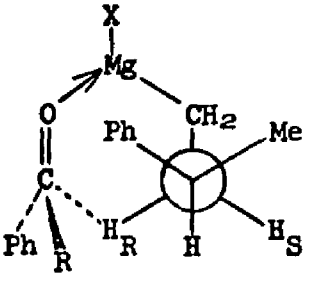
74-b



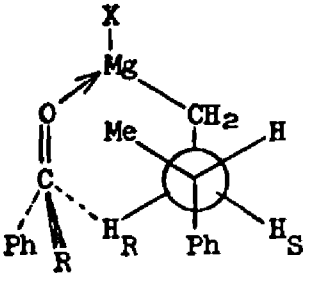
74-c



77-a



77-b



77-c

agreement with results observed experimentally for this ketone as well as those for t-butyl phenyl ketone.

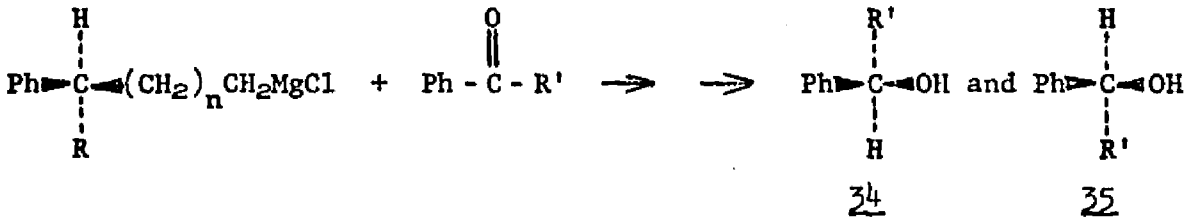
By use of this model it is also possible to visualize how relatively small variations in the structure of a reducing agent might alter the relative distribution of products resulting from the four possible pathways.

1,5-Asymmetric Grignard Reductions.

In Table 7 the normalized results of the reduction of t-butyl phenyl ketone and trifluoromethyl phenyl ketone with the Grignard reagent from R-(-)-4-phenyl-1-chloropentane are summarized and compared with those of the corresponding 1,3- and 1,4-asymmetric Grignard reductions.

Table 7

A Comparison of 1,3-, 1,4- and 1,5-Asymmetric Grignard Reductions



34 35

Grignard Reagent		Ketone and Product: R' = tBu			Ketone and Product: R' = CF_3		
R	n	Pref. Conf.	e.e. %	Yield Red.,%	Pref. Conf.	e.e. %	Yield Red.,%
Me	0	35	22	- 18	35	47	-18
Et	"	34	16	77 17	"	38	-17
Me	1	35	9	48	34	4	95
Me	2	35	10	90	35	4	95

In the initial consideration of testing the possibility of 1,5-asymmetric Grignard reductions it was felt that the time and chemicals involved might well be wasted since both the yield of reduction products and the stereoselectivity of the reductions were expected to be very small. These expectations were based on the assumption that both of these results would decrease from the values obtained in 1,4-asymmetric reductions due to the increased remoteness of the asymmetric center in the reducing agent.

It was therefore surprising to find that the reaction of t-butyl phenyl ketone with the δ-asymmetric Grignard reagent 48 provided the alcohol and olefin resulting from the reduction reaction to the almost

complete exclusion of the high boiling addition product. The high yield of reduction products was verified by analytical glpc and finally by the characterization of pure samples obtained by preparative glpc. The extent of reduction in this reaction was higher than that observed in the corresponding 1,4- or even the 1,3-asymmetric reductions. The yields of reduction products from 13-f were nearly quantitative although this observation is rather general for this particular ketone.

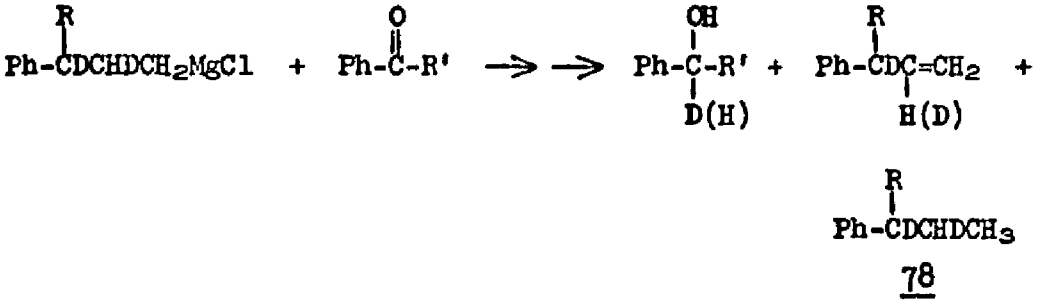
Only two ketones were reduced with δ-asymmetric Grignard reagent 48 due to the questionable nature of the expected results. Thus it was not possible to establish a standard of "normal" behavior as done with 1,4-asymmetric reductions and the configurations of the two carbinols obtained could only be compared with each other. Both of the carbinols were found to have the same configuration, a result which was slightly unusual but not without precedent in both 1,3- and 1,4-asymmetric Grignard reductions. However, in view of the other unusual behavior in these reactions, it would be worthwhile to reduce a complete series of phenyl alkyl ketones to determine whether the unusually high amount of reduction obtained is general, and to establish "normal" configurational behavior if possible.

Rather than the expected decrease in asymmetric synthesis on extending the methylene chain in Grignard reagents 15, 19, and 48, the % e.e. dropped substantially from the 1,3- to the 1,4-asymmetric reduction and then reached a plateau for the 1,4- and 1,5-asymmetric reductions. Although these results are quite unusual, it does not seem appropriate to attempt to rationalize the limited data available. This point will be discussed again under long range MPV reductions, where more comprehensive studies provided results bearing on the questions raised during these investigations.

Reductions with Deuterium Labeled Grignard Reagents

Unlike the remainder of the experiments involved in this work, the reductions with deuterium labeled Grignard reagents utilized methods of analysis which were somewhat unusual so that these methods are discussed for the sake of clarity.

In the reductions studied (eq. 8) it was realized that the reducing agents contained less than 100% deuterium at the positions shown. This result was due in part to the grade of deuterium used (98% D), but more importantly to the lowering of the isotopic purity of the deuterium by exchange with the carboxylic acid proton during the reduction of the unsaturated acid precursors. A second problem involved difficulties in completely removing small amounts of 78 from the olefins used for



analysis because several of the peaks used as internal standards in the deuterium analysis the olefin overlapped those of 78.

Correction for the hydrolysis product 78 in the olefin was accomplished by subtracting a normalized value (integral height/hydrogen) obtained from the integration of the aliphatic methyl doublet at ca. 0.9 ppm due to 78 from the normalized integrals for the combined aryl and downfield methyl (when R = methyl) peaks.

Although it was possible to analyze for the hydrogen content at the 2-position in the precursors of the reducing agents, the peaks were generally broad multiplets and analysis involved determining small variations from a much larger value. By making the assumption that the deuterium content of the 2- and 3-positions in the reducing agents was the same, it was possible to use the integrals of the benzylic hydrogen peak at ca. 6.6 ppm in the nmr spectra of the olefins to approximate the amount of deviation from 100% deuterium incorporation. Thus the spectra of the olefins isolated from the reductions provided normalized integrals for the aryl, R, terminal vinyl, benzylic, and nonterminal vinyl hydrogens after correction for 78. The first three values were used as internal standards to calculate the observed % hydrogen at the nonterminal vinyl hydrogen, $\% H_v$, and the observed amount of benzylic hydrogen, $\% H_{Bz}$. These values in turn were used to calculate the corrected (k_H/k_D) olefin values reported using the following equations:

I. Adjusted % H retained, $$\%H_{adj.} = \frac{\%H_v - \%H_{Bz}}{100 - \%H_{Bz}}$$

II. $$(k_H/k_D)_{olefin} = \frac{100 - \%H_{adj.}}{\%H_{adj.}}$$

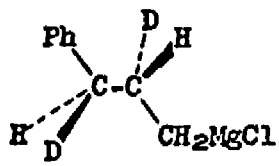
The alcohols were analyzed by comparing the normalized integrals for the carbinol hydrogen with those due to the aryl group (and peaks due to alkyl groups if any were present) as internal standards. The value obtained, the observed percentage hydrogen at the carbinol position, $\%H_c$, was used to calculate the corrected $(k_H/k_D)_{carbinol}$ values using the following equations:

$$\text{Adjusted \% hydrogen transferred, } \%H_{adj.} = \frac{\%H_{c} - \%H_{Bz}}{100 - \%H_{Bz}}$$

$$(k_H/k_D)_{carbinol} = \frac{\%H'_{adj.}}{100 - \%H'_{adj.}}$$

The rather close agreement between the k_H/k_D values obtained independently from the two products, the alcohol and the olefin, demonstrates that the use of the benzylic position in the olefin to determine the deviations from 100% deuterium incorporation in the reducing agents was a reasonable approximation. This agreement in combination with the observation that preferential transfer of hydrogen from the erythro- reagents was accompanied by preferential transfer of deuterium from the threo- reagents seems to place the qualitative interpretation of the results beyond question.

The isotope effects obtained from the threo-2,3-dideuterio-3-phenylpropyl Grignard reagents were assumed to be the same, within the limits of experimental error, as those that would have been obtained with a reagent such as 79. Thus these values are taken to represent the "normal" kinetic isotope effect for the reductions studied.



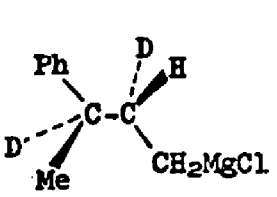
threo-58

$PhCH_2CHDCH_2MgCl$

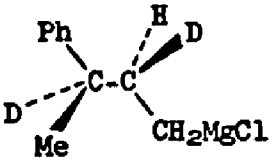
79

In the stereospecifically labeled 3-phenyl-1-butyl reagents, threo-80 and erythro-80, consideration of the structures of the enantiomers having

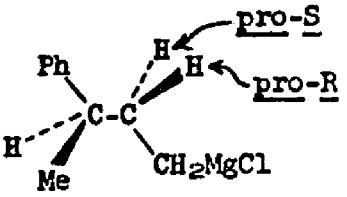
the 3R-configuration shows that 2S, 3R-threo-80 corresponds to R-19 in which the pro-S hydrogen has been labeled while 2R,3R-erythro-80 corresponds to labeling of the pro-R hydrogen.



2S,3R-threo-80



2R,3R-erythro-80



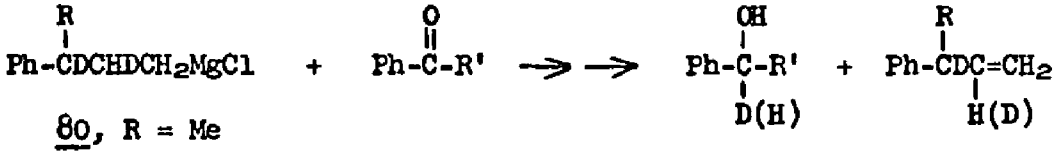
R-19

The results of the reductions with deuterium labeled Grignard reagents are summarized in Table 8.

Table 8

Kinetic Isotope Effects in 1,4-Asymmetric

Grignard Reduction Reactions



80, R = Me

58, R = H

Ketone R'	k_H/k_D "Normal", (±)-58	Threo-80	Erythro-80
iPr	2.3	0.6	-
tBu	2.1-2.3	0.5-0.6	7-8
CF_3	1.4-1.5	1.2-1.3	1.7

The "normal" isotope effects shown for t-butyl phenyl ketone and isopropyl phenyl ketone were the same within the limits of experimental error. That obtained for trifluoromethyl phenyl ketone was considerably lower, thus demonstrating a lower degree of selectivity for hydrogen transfer.

The increase in the amount of deuterium transferred by threo-80 and the increase in hydrogen transfer by erythro-80 relative to the normal isotope effects clearly demonstrates that reduction of all three ketones tested by R-19 involves a preferential transfer of the pro-S hydrogen.

The rather large preference for the transfer of the pro-S hydrogen was the same for the reduction of both t-butyl phenyl ketone and isopropyl phenyl ketone within the limits of experimental error. On the other hand reduction of trifluoromethyl phenyl ketone showed a much smaller preference as demonstrated by the similarity of the results from threo- and erythro-80.

These results verified an earlier prediction[23] that the reduction of isopropyl phenyl ketone (13-c) with R-3-phenylbutylmagnesium chloride (R-19) would show a preference for transfer of the pro-S hydrogen. As discussed earlier, the stereochemical model developed for 1,4-asymmetric Grignard reductions also rationalizes the same results. In the case of isopropyl phenyl ketone the observed preference for hydrogen transfer, in combination with the amount of asymmetric synthesis reported with R-19[23], allowed a mathematical demonstration that the preferred pathway for this reduction was a transition state involving the preferential transfer of the pro-S hydrogen to the si face of the ketone.

Inspection of the four transition state models 74-77 shows that in 74 and 75 the pro-S hydrogen is transferred, while in 76 and 77 the

pro-R is transferred. Also it may be seen that 74 and 76 form R-14-c while 75 and 77 form S-14-c.

From these observations and the experimentally determined preference for the formation of the R-enantiomer of 14-c (25% e.e.)[23] equations I and II are obtained. If it is assumed that the preference for the transfer of the pro-S hydrogen over the pro R hydrogen is 3 to 1, then equations III and IV may be obtained.

I: $74 + 76 = 62.5\%$

II: $75 + 77 = 37.5\%$

III: $74 + 75 = 75\%$

IV: $76 + 77 = 25\%$

From IV it follows that $76 \leq 25\%$, which in combination with I provides: $74 \leq 37.5\%$; but from II both 75 and 77 $\leq 37.5\%$. Therefore, except in the unlikely case that either 75 or 77 = 0, 74 is the preferred model for the transition state. For preferences of transfer for the pro-S to pro-R hydrogen of greater than 3 to 1, this conclusion becomes mathematically required. Thus using two sets of experimental data describing two different types of stereospecific reactions, it is possible, at least in this one case, to demonstrate which of four possible pathways has the lowest energy.

Although the data from the reduction of 13-e and 13-f do not provide such easily interpreted data, it seems likely on the basis of the conclusions for the reduction of 13-c that the favored transition state model for the reduction of t-butyl phenyl ketone is also 74, while that for trifluoromethyl phenyl ketone is 75. Thus it may be seen that studies of this type involving two different stereochemical behaviors in

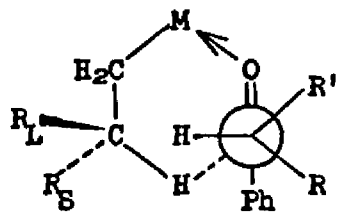
the same reaction can lead to detailed information not normally available about the nature of the transition states of reactions. In this case the amount of preference for the transfer of one of a pair of diastereotopic groups was used as the second type of behavior and to the author's knowledge represents the first use of this experimentally measurable value in the elucidation of mechanistic details and relative transition state energies.

The results obtained in the studies of both kinetic isotope effects and the preferential transfer of hydrogen during the reduction of several ketones may be used to speculate about the possible mechanisms of these reductions. For example, the fact that there are very similar kinetic isotope effects and preferences toward the transfer of diastereotopic hydrogens in reductions of isopropyl phenyl ketone and t-butyl phenyl ketone strongly indicates that there is little difference between the mechanisms and transition states for these reactions. On the other hand, the very different behavior of trifluoromethyl phenyl ketone in the same experiments strongly suggests that the mechanism of this reduction and probably all Grignard reductions of perfluoroalkyl carbonyl compounds, differs from those of "normal" ketones.

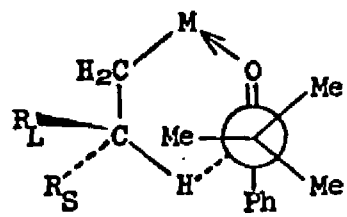
Using the results in Table 8 is is possible to speculate about the three types of behavior exhibited in the asymmetric reductions of alkyl phenyl ketones. The first type, considered "normal", is exhibited by methyl, ethyl and isopropyl phenyl ketones in which the configurational results do not vary within a given type of reduction and a regular increase in stereoselectivity and reduction yield is noted with increasing size of the alkyl group. The second involves the "abnormal" behavior of trifluoromethyl phenyl ketone, which consistently provides the

opposite configurational result from that of "normal" ketones, as well as unusually high yields of reduction products. The third type involves the schizophrenic behavior of t-butyl phenyl ketone which gives stereochemical results that vary widely with the reducing agent tested and sometimes is "normal" while at other times "abnormal".

The behavior of t-butyl phenyl ketone has been rationalized on the basis of its relative rate of reaction[67] due to high steric hindrance and also on the basis of the unusual orientation of the phenyl ring, which is twisted out of plane from the carbonyl group by the bulky t-butyl group. A third possible factor may be seen by inspection of 81 and 82, which represent reasonable conformations of the alkyl group in an alkyl



81



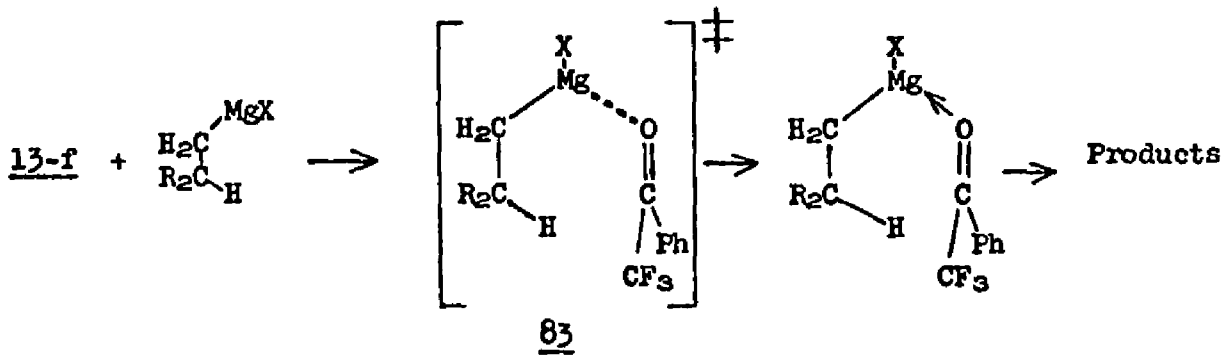
82

a) Methyl, R = R' = H
b) Ethyl, R = H, R' = Me
c) Isopropyl, R = R' = Me

phenyl ketone during a Grignard reduction. In 81- a to -c the methyl, ethyl and isopropyl groups may always present a small hydrogen to the most hindered position, that toward the reducing agent, so as to maintain a fairly constant effective size. However, in 82, with the t-butyl

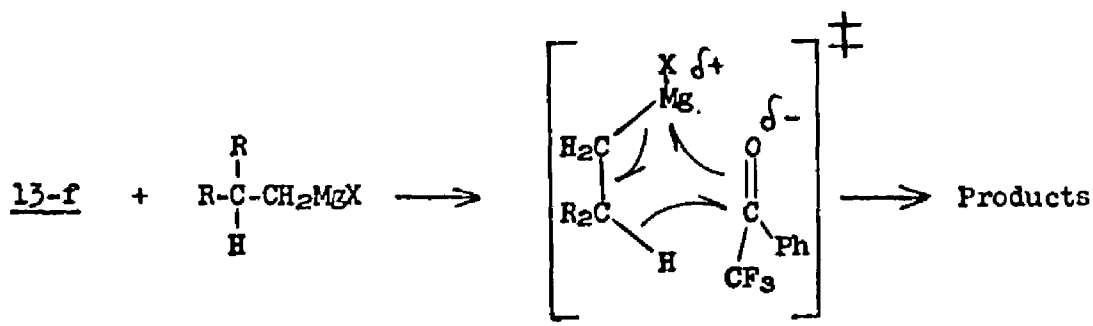
group, there is a sudden increase in the effective size of the alkyl group, especially in the "normal" preferred transition state model 66 where the t-butyl opposes the large group on the reducing agent. In a configuration such as 82 it might be expected that relatively minor variations in the reducing agent could increase the "size" of t-butyl so that it would be larger than phenyl and afford a product with an "abnormal" configuration. On the basis of the very similar behavior of isopropyl and t-butyl phenyl ketones shown in Table 8 it does not seem likely that the rate and/or mechanism of reductions of these ketones differ to any great extent. Thus, it would seem that rather subtle steric factors such as those discussed above offer a more satisfactory explanation of the unusual stereochemical results demonstrated by t-butyl phenyl ketone inTables 5, 6, and 7.

The low but measurable deuterium isotope effect observed for the reduction of trifluoromethylphenyl ketone, as well as the low stereoselectivity of hydrogen transfer observed, have considerable bearing on the question of the mechanism of Grignard reductions of perfluoroalkyl ketones. The observation of an isotope effect eliminates the possibility of a mechanism in which the rate-determining step is the formation of a complex between the ketone and the Grignard reagent, followed by a fast hydrogen transfer step.[7] The very low values observed for both the



83

kinetic isotope effect and the stereoselectivity of hydrogen transfer relative to normal ketones suggest, but do not require, that the transition state is much more reactant-like than normal. That is, there is relatively little breaking of the C-H bond in the transition state. The lack of observable complexation may then be rationalized by a mechanism shown below which combines both complex formation and hydrogen transfer in the rate-determining step. This mechanism may be altered

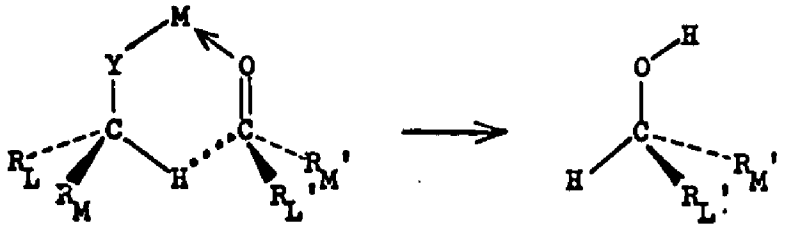


84

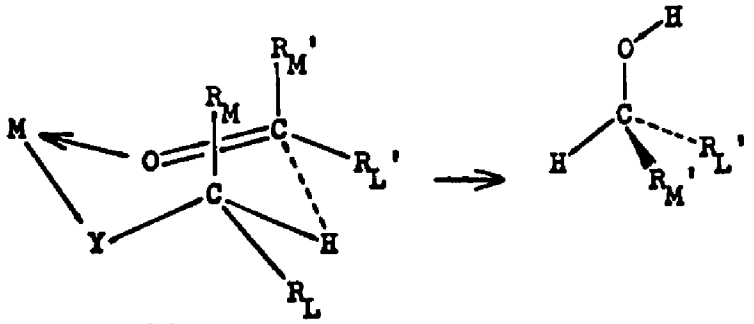
considerably toward either complex formation or hydrogen transfer without altering its essential features. It should be understood that this mechanism is suggested only for the reduction of perfluoroalkyl carbonyl compounds.

Another unusual feature exhibited by trifluoromethyl phenyl ketone which could be rationalized on the basis of this model is the apparent reversal of product configuration from that observed with similar ketones in asymmetric reductions. The cyclic transition state model for 1,3-asymmetric reductions is assumed to be planar or nearly so. However, it is interesting to note that appreciable deviation from planarity leads to transition states with cyclohexane-like character, such as 86, in which the most favored conformation would be expected to have both of the

large groups occupying equatorial or pseudo-equatorial cis- 1,3-positions. Such transition states would be expected to provide products containing an excess of the opposite enantiomer from that predicted on the basis of a planar model such as 66. Although this observation is interesting, it does not in itself provide any rationalization for the behavior of trifluoromethyl ketones. The rationalization may be provided, however,



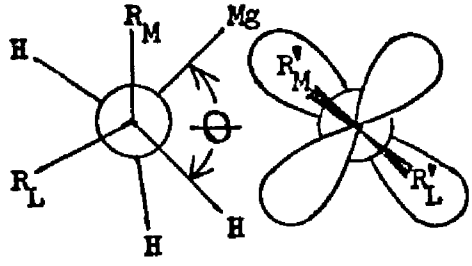
66



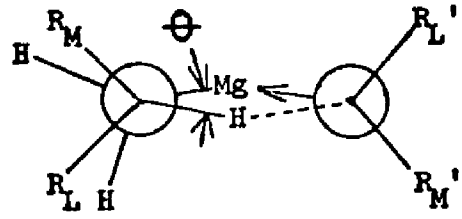
86

by inspection of a reactant-like transition state model such as 84. Assuming that the lone pairs of electrons on the carbonyl oxygen are perpendicular to orbitals forming the π-bond between carbon and oxygen and that a reactant-like transition state such as 84 would involve the simultaneous attack of magnesium on one of the lone pairs on oxygen (complexation) and hydrogen on the π-bond (hydrogen transfer), then the

incoming groups would approach the axis of the carbonyl bond at an angle of ca. 90°. About the same angle would be generated at the reducing agent and the overall situation could then be approximated by model 87.



87



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The real geometry of the transition states might lie somewhere between 87 and a planar planar model such as 88, i.e. $0° \leq \theta \leq 90°$. However, this would not alter the reasoning as long as there were sufficient deviation from planarity to provide transition states in which the behavior would follow that of a cyclohexane model such as 86.

The prediction of a favored cyclohexane-like transition state model such as 86 accommodates almost all of the results reported to date for Grignard reductions of trifluoroalkyl ketones. Two apparent exceptions are the reduction of 1,1,1-trifluoropropanone with S-9 and the reduction of trifluoromethyl phenyl ketone with S-67 (R = tBu) in which the opposite result was obtained. This model also accommodates the observation

that the preferred transition state for the reduction of trifluoromethyl phenyl ketone with R-19 is one in which the pro-S hydrogen is transferred to provide an excess of the R-carbinol.

Asymmetric Reductions by Optically Active, Deuterium Labeled Grignard Reagents.

In studies aimed at determining the contribution of each of a set of four transition states such as 74-77 for the reduction of alkyl phenyl ketones by γ-asymmetric Grignard reagents, reductions were conducted using Grignard reagents prepared from optically active threo-2,3-dideuterio-1-chloro-3-phenylbutane (53). Although the desired results* could not be obtained in time for inclusion in this thesis, several of the preliminary observations from these experiments will be reported but not discussed in detail. The isotope effects from these reductions were included with the results for racemic threo-80 (previous section).

Some pertinent results obtained with optically active threo-80 are compared with those of the corresponding unlabeled chiral Grignard reagent (R-19) in Table 9.

At first glance the results in Table 9 appeared to show a different type of behavior for each of the ketones tested. Isopropyl phenyl ketone showed a small decrease in asymmetric synthesis; t-butyl phenyl ketone became nonstereoselective, and in trifluoromethyl phenyl ketone the configuration was reversed. It should be mentioned that the lack of observable rotation obtained with t-butyl phenyl ketone places this

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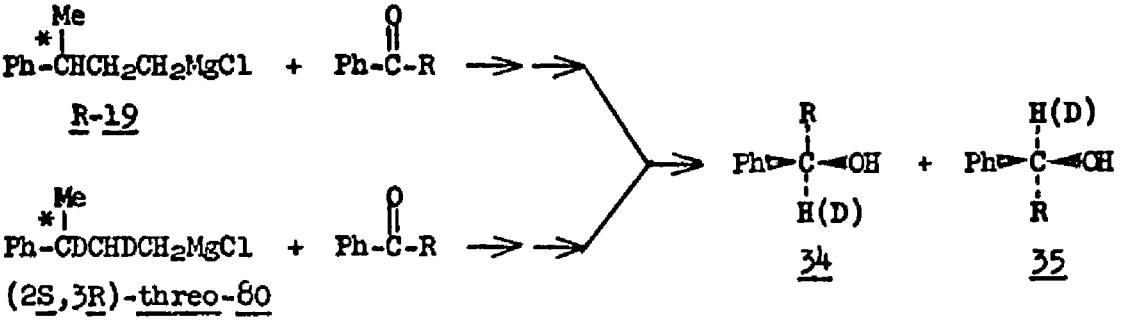
* The mixtures of labeled and unlabeled alkylphenylcarbinols, each containing a pair of enantiomers, are to be analyzed for the relative amount of each of the four components by integration of nmr spectra of the mixtures of esters prepared from optically active methoxytrifluoromethylphenyl acetic acid.[62]

Table 9

A Comparison of 1,4-Asymmetric Reduction by Labeled and Unlabeled Chiral Grignard Reagents



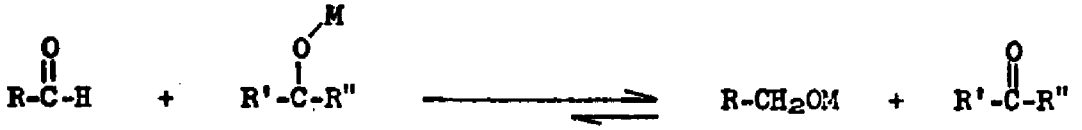
Ketone R	Grignard Reagent	Product: Preferred Configuration	Product: A. I.,%
iPr	R-19	35	19
iPr	(2S,3R)-80	35	25
tBu	R-19	35	9
tBu	(2S,3R)-80	-	0
CF_3	R-19	34	4
CF_3	(2S,3R)-80	35	7

result in question since it could result from racemization after reduction. The final results expected from the experiment, however, should distinguish between the possible explanations.

The best explanation of these results would appear to involve a change in the relative proportions of the diastereotopic hydrogens transferred in R-19 brought about by the normal deuterium isotope effect inherent in (2S,3R)-threo-80. If this is indeed the explanation, then the results from the reductions of the same ketones by (2R,3R)-erythro-80 would be of interest because in the cases of t-butyl phenyl ketone and isopropyl phenyl ketone the isotope effect and the asymmetrically induced preferential transfer of the pro-S hydrogen would reinforce each other. The resulting very high preference for transfer of the pro-S hydrogen would be expected to provide products with considerably higher amounts of asymmetric synthesis than either (2S-3R)-threo-80 or R-19. With trifluoromethyl phenyl ketone the amount of asymmetric synthesis would be expected to be slightly greater than that obtained with the threo reagent but with the opposite configuration produced in excess.

Meerwein-Ponndorf-Verley Reductions of Trifluoromethyl Phenyl Ketone

Our interest in MPV-type reductions developed in connection with studies of long range asymmetric synthesis by Grignard reductions. It was realized that reductions by primary alcoholates would complement these studies because the mechanisms of the two reactions were quite similar. However, in general, MPV reductions were known to be equilibrium reactions and to show a strong preference for the formation of primary alcoholate and ketone in equilibria involving primary and secondary alcoholates (Eq. 9).[31a]



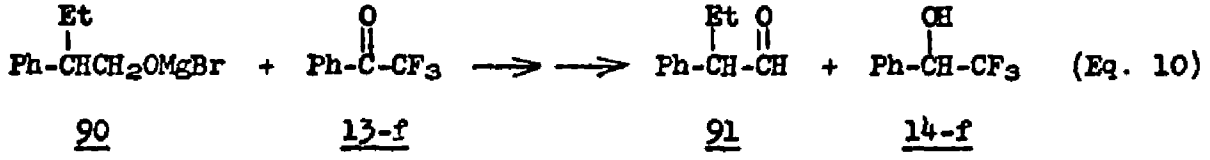
(Eq. 9)

Several examples of reductions of ketones by primary alcoholates had been reported,[47] but in most, if not all, of these cases the reaction had been forced to completion by distillation of the aldehyde as it was formed. In line with these results it was found that treatment of isopropyl phenyl ketone (13-c) with 2-phenylbutoxymagnesium bromide (90) at room temperature gave no detectable amount of isopropylphenylcarbinol (14-c).

During studies of Grignard reductions of alkyl phenyl ketones it was found that trifluoromethyl phenyl ketone (13-f) afforded excellent yields of trifluoromethylphenylcarbinol (14-f) when allowed to react with Grignard reagents which provided relatively poor yields of reduction with other alkyl phenyl ketones. Also, there had been numerous reports of unusually high yields of reduction products with perfluoroalkyl carbonyl compounds in general.[49]

Because of the above information trifluoromethyl phenyl ketone (13-f) was allowed to react with a solution of racemic 90 at room temperature. The reaction (Eq. 10) was found to be essentially complete after 16 hours and both 14-f and 2-phenylbutanal (91) could be isolated from the reaction

mixture. The reaction, then repeated with the chiral alcoholate prepared



(Eq. 10)

90 13-f 91 14-f

from S-(-)-2-phenyl-1-butanol (S-89) was found to provide products with appreciable optical rotations.

A preliminary study of the reaction of 13-f with 1-phenylethoxymagnesium bromide (92) demonstrated that reduction with secondary alcoholates also provide an excellent yield of 14-f and proceeded at an even faster rate than primary reagents such as 90.

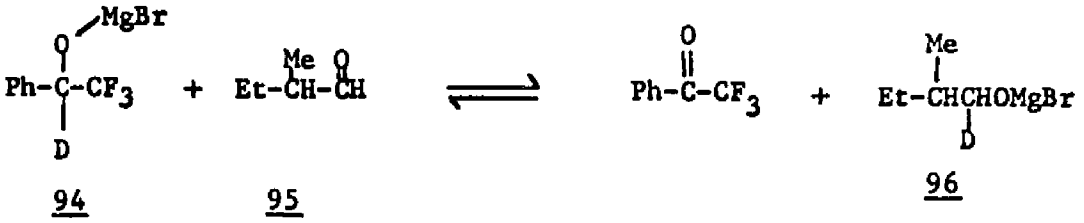
The observation that the reductions of 13-f were virtually quantitative when sufficient alcoholate was present prompted investigations into the reversibility of such reactions. In one set of experiments it was found

92 93

that variation of the reaction times for the reduction of 13-f with 93 from 1 to 26 hours had no appreciable effect on the rotation of the products obtained. These results indicated that either the amount of reversal was negligible or that neither the reactants nor the products were racemized to an appreciable extent.

A second test involved preparation of the deuterium labeled alcoholate 94, which was allowed to react with 2-methylbutanal (95) for 60 hours

(Eq. 11). The labeled alcohol corresponding to 94 isolated after hydrolysis was found to have incorporated only 4% hydrogen at the carbinol position. Use of an aldehyde such as 95 in this test for reversibility



94 95 96

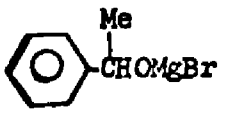
had two advantages. As shown in Eq. 9, equilibria between primary and secondary alcoholates generally greatly favor the former. Then if hydrogen transfer from 94 were to occur it would be much more likely to do so with an aldehyde than a ketone. A second factor was the favoring of the transfer of hydrogen from 96 in the reverse reaction because of a deuterium isotope effect. Thus there was somewhat less than 4% reversal of Eq. 11 over a period about four times that which was normally used (16 hours) in these studies. Then, at least under the conditions used in these studies, the reduction of 13-f could be considered irreversible for all practical purposes.

A possible source of error in these reductions was a "no reaction reaction" of the alcoholates with their corresponding carbonyl compounds. During these processes primary alcoholates may become racemized *via* enolization of their corresponding aldehydes[32], while secondary alcoholates such as 92 are directly racemized during the redox equilibration.[31b,32,68] This possibility was tested in the case of S-90 which forms 91 an aldehyde whose enolate would be expected to be unusually stable. A sample of S-(+)-2-phenyl-1-butanol recovered after partial reduction of

13-f with S-90 was found to retain 95% of the e.e. of the alcohol used in preparation of the alcoholate. This amount of racemization was not considered important in view of other uncertainties inherent in the method and the fact that the average racemization of the actual reducing agent must have been less than the 5% observed. A similar experiment was not conducted with chiral secondary alcoholates in view of the short reaction times involved and high amounts of asymmetric synthesis obtained. However, variable amounts of racemization of the reducing agents prior to reduction might explain the seeming lack of a trend obtained with reductions by alcoholates of 1-phenylethanol.

1,3-Asymmetric Meerwein-Ponndorf-Verley Reductions.

Although our interest in MPV reductions originated because of a desire to study long range asymmetric reductions, it was felt that investigation of a few representative 1,3-asymmetric reductions would be of value. Areas of interest include reductions by 1-phenylethoxy-magnesium halides such as 92, whose behavior could be compared with that of Grignard reagents such as 67 (R = methyl)[18] to determine whether the qualitative and quantitative results were similar for analogous reagents belonging to the series 69. It was also of interest to determine whether the "consistently abnormal" behavior of trifluoromethyl phenyl ketone observed in 1,3-asymmetric Grignard reductions extended to MPV reductions as well. Another point tested was the effect of possible electronic repulsions[17] when both the reducing agent and the ketone contained aromatic groups. This was accomplished by carrying out reductions of (13-f) with the corresponding phenyl- and cyclohexylethoxymagnesium bromides, 92 and 96 respectively.



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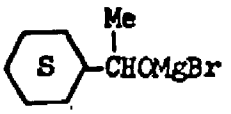

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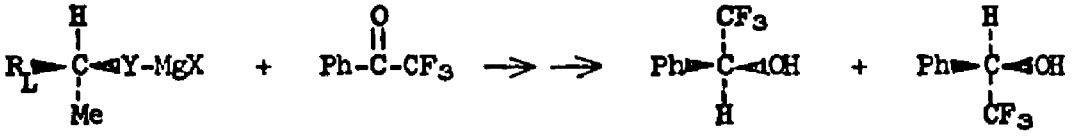
The normalized results of the 1,3-asymmetric MPV reductions studied are summarized in Table 10, and results from similar or analogous 1,3-asymmetric Grignard reductions are presented for comparison.

Table 10

1,3-Asymmetric Meerwein-Ponndorf-Verley Reductions of Trifluoromethyl Phenyl Ketone



S-14-f R-14-f

Reducing Agent			Product, 14-f	
R_L	Y	X	Preferred Configuration	A. I., %
Et	CH_2	Cl	S	22
nHex	-O-	Br	"	11
C_6H_{11}	"	"	"	42
Ph	CH_2	Cl	"	47
"	-O-	"	"	54
"	"	Br	"	42
"	"	" [a]	"	41
"	"	I	"	52

a) THF replaced ether as cosolvent.

Each of the reactions reported in Table 10 provided an excess of S-(+)-14-f, the opposite configuration from that predicted on the basis of a planar transition state model in which it is assumed that phenyl is larger than trifluoromethyl. Thus it seems very likely that asymmetric MPV reductions of perfluoroalkyl ketones as well as asymmetric Grignard will show "consistently abnormal" configurational results. These results could then also be rationalized on the basis of cyclohexane-like transition state models such as 86.

In cases where the MPV and Grignard reductions were quite similar except for the group -Y- (-O- or CH_2) attaching the magnesium to the rest ot the molecule, the degrees of stereoselectivity were similar. In the case where Y was the only variable the results were nearly identical. This seemed to indicate that consideration of the reducing agents and the transition states for both MPV and Grignard reductions as belonging to general classifications such as 99, and 65 and 66 not only was a convenient conceptual device but also represented a reasonable approximation of the true nature of the two reactions.

Reductions with cyclohexyl- (96) and phenyl- (92) substituted alcoholates gave identical results although these might not be quantitatively meaningful because of the possibility of small amounts of racemization in both reagents. However, the qualitative similarity of the results was apparent. This suggests that similar studies using cyclohexyl analogs of β-asymmetric Grignard reagents containing phenyl substituents, such as 15 might be quite interesting. With these Grignard reagents it would be possible to study the behavior ot a number of ketones, rather than only one as in the MPV reductions, and to test the proposal that electronic repulsions between phenyl groups are responsible for some unusually high

stereoselectivities observed in the reduction of alkyl phenyl ketones with phenyl substituted Grignard reagents such as 15.[17] Such studies would also be of interest because, although a planar transition state model would be expected to provide strong phenyl repulsions when both groups are on the same side of the ring[17] as in 16, a cyclohexane-like transition state model such as 86 would provide little interaction with the same arrangement of groups. Thus it seems possible that phenyl-phenyl interaction might be negligible only for reductions of perfluoroalkyl carbonyl compounds for which a cyclohexane-like transition state was discussed under Grignard reductions.

The other results shown in Table 10 are generally those expected on the basis of similar studies with Grignard reductions: the increase in asymmetric synthesis with increasing size of R_L, the small effect of changing the solvent from ether to THF, and the relatively small effect of the halide gegenion.

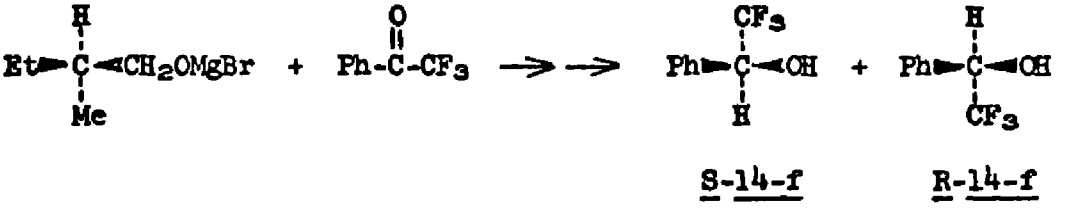
1,4-Asymmetric Meerwein-Ponndorf-Verley Reductions

Once initial studies had shown that 1,4-asymmetric MPV reductions of 13-f were possible, experiments were initiated using a variety of reducing agents that could be prepared from the readily available S-(-)-2-methyl-1-butanol (24). Although these studies were ultimately discontinued, the effect of solvent and the metal used to form the alcoholate on asymmetric reductions were studied.

The normalized results of these studies are summarized in Tables 11 and 12. The results in Table 11 show that variations in the relative composition of ether-benzene cosolvents have relatively little effect on the stereochemical outcome of these reactions. The effect of the size of the coordinating solvent appears to be small since diethyl and diisopropyl

Table 11

The Effect of Solvent on 1,4-Asymmetric Meerwein-Ponndorf-Verley Reductions of Trifluoromethyl Phenyl Ketone



S-14-f R-14-f

Cosolvent[a]	Product, 14-f: Preferred Configuration	A. I.,%
Ether	R	5.1-5.4
" [b]	"	4.8
None[c]	"	3.3
Diisopropyl Ether	"	3.7
THF[d]	S	1.0
DME[e]	"	1.8
S-2-Methyl-1-butanol	"	1.0

a) Unless stated otherwise, benzene used as the standard diluent.

b) No benzene was used.

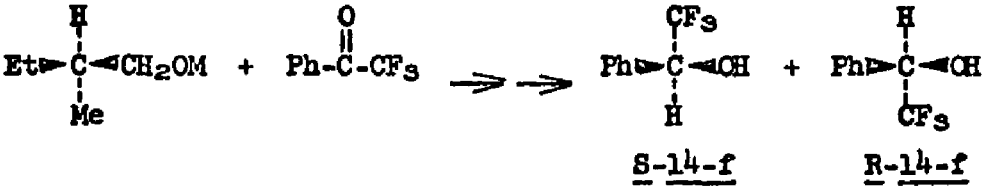
c) A mixture of ether and benzene was distilled to 81° to remove ether.

d) THF = Tetrahydrofuran.

e) DME = 1,2-Dimethoxyethane.

Table 12

The Effect of the Cation on 1,4-Asymmetric Meerwein-Ponndorf-Verley Reductions of Trifluoromethyl Phenyl Ketone



S-14-f R-14-f

Reducing Agent, M	Product, 14-f: Preferred Configuration	A. I., %	Yield, %[a]
MgCl	R	8.0	High
MgBr	"	5.1-5.4	"
MgI	"	2.9	"
MgOR*[b,c]	S	2.2	"
Li[d]	-	-	10
Na[e,f]	R	-	"
Na[c]	-	-	2
Al(OR*)$_2$[b,c,f]	S	-	10

a) "High" yields estimated to be 75-100% from IR spectrum of the crude products. Low yields verified by analytical glpc.

b) R*O- = S-2-Methyl-1-butoxy-.

c) Alcoholate prepared from the methoxy compound by distillation of methanol from a toluene solution.

d) Racemic product resulting from dissolving metal reduction.

e) Product had a small but real rotation but was formed largely by dissolving metal reduction.

ether provide quite similar results. However, the use of solvents such as THF, 1,2-dimethoxyethane and alcohols which are more basic than ether leads to an excess of the opposite product configuration and a much lower order of stereoselectivity than obtained with ether. Attempts to rationalize these solvent effects do not seem justified on the basis of the limited data available. However, the results observed were quite interesting and would seem to warrent further investigations of the nature of solvent effects in these reactions, especially in view of the lack of standardization of solvent systems used by various workers in this area.

The results in Table 12 show two apparent trends; the large decrease in stereoselectivity as the halide is varied from chloride to iodide, and the lack of appeciable reduction by alkoxides formed from metals other than magnesium. The first trend is in the same direction as that noted for β-asymmetric Grignard reductions[11,18] although the amount of change is much greater for the alkoxide reductions. The result obtained with the dialkoxymagnesium reagent cannot be interpreted at this time in as much as the reversal of configuration might well be due to coordinated methanol not removed by distillation.

The finding that only magnesium alcoholates provided appreciable yields of reduction under the conditions tested was unexpected. Initially it was thought that this might be a function of the solvent used, the method used to prepare the alkoxide, or some other variable not related to the metal. However, the results were verified by a series of reactions using the same method of preparation (alkoxide exchange on the metal methoxide) in the same solvent (toluene) using the series of Group II metals: sodium, magnesium and aluminum.

On the basis of their positions in the periodic table it would be expected that, for any single property of these three metals, that of magnesium would lie between those of sodium and aluminum. This suggested the possibility that a balance of two properties following opposite trends might be involved. Two such properties that could be invoked on the basis of a mechanism involving a transition state such as 84 discussed earlier for the reduction of perfluoroalkyl carbonyl compounds were: Lewis acidity (Al > Mg > Na); and electropositive character (Na > Mg > Al). In this mechanism the initial orientation of the reactants required to set the reduction in progress would involve dipolar attraction between the reagents and would be favored by more electropositive metals. However, since the rate determining step in this mechanism involves simultaneous complexation and hydrogen transfer, metals which are strong Lewis acids would be expected to lower the energy of the transition state. The magnesium alcoholates might possess the proper balance of these two properties to make them much better reducing agents for perfluoroalkyl carbonyl compounds than either sodium or aluminum. Such behavior has some precedent in MPV-type reductions. It has been observed that in the presence of relatively strong Lewis bases aluminum alcoholates are poor reducing agents since the aluminum presumably becomes tightly complexed with the base and cannot behave as a reducing agent.[29,31-b] Sodium alcoholates overcome this difficulty since they do not form strong complexes with Lewis bases in spite of the fact that they would not be expected to complex well with carbonyl groups either.

It should be pointed out that all of these reactions were run at ambient temperatures and that heating might greatly increase the rate of the reductions in some cases. This was found to be the case in the

reduction of t-butyl phenyl ketone with 93, where stirring at room temperature for three weeks provided only 3% reduction while heating at 55-56° for two days increased the yield to 20%. A second example of the effect of temperature was the observation that treatment of 13-f with 93 at -78° provided no detectable reduction after 60 hours while the same reaction was essentially complete at room temperature after 16 hours.

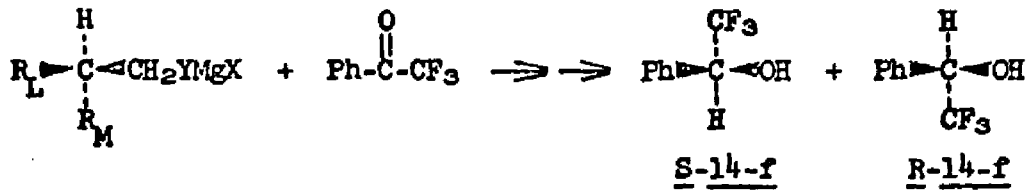
Another series of 1,4-asymmetric MPV reduction studies involved the reaction of 13-f with chiral alcoholates prepared from several different optically active primary alcohols. The normalized results of these studies are summarized in Table 13 and several results from similar 1,4-asymmetric Grignard reductions are shown for comparison.

The results in Table 13 indicate the preferential formation of R-14-f except in the two cases where tetrahydrofuran was substituted for ether as cosolvent. Aside from this no consistent trend could be found. The effect of halide on the asymmetric bias noted for the 2-phenyl-1-propoxy reagents 97 and 98 (I > Br) was the opposite that for the 2-methyl-1-butoxymagnesium halides (Cl > Br > I). The amount of asymmetric synthesis observed increased from R_L = ethyl to R_L = cyclohexyl and then dropped off for phenyl in the series where R_M = methyl. In the series R_M = ethyl there was little difference between R_L = phenyl and cyclohexyl. With a constant R_L the relative orders of asymmetric synthesis reversed; with R_L = cyclohexyl and R_M = methyl it was twice that for R_M = ethyl. On the other hand, with R_L = phenyl the amount of asymmetric synthesis doubled when R_M was changed from methyl to ethyl. Thus the predominant feature observed in these reductions was the lack of any apparent order in the results on the basis of the steric "sizes" of the groups involved.

The consistency of the configurational results obtained in these studies suggests that with additional background information it might be

Table 13

1,4-Asymmetric Meerwein-Ponndorf-Verley Reductions of Trifluoromethyl Phenyl Ketone



S-14-f R-14-f

Reducing Agent				Product, 14-f	
R_L	R_M	Y	X	Preferred Configuration	A. I., %
Et	Me	-O-	Cl	R	8.0
"	"	"	Br	"	5.1-5.4
"	"	"	" [a]	S	1.0
"	"	"	I	R	2.9
C_6H_{11}	"	"	Br	"	22-23
"	Et	"	"	"	10
Ph	Me	CH_2	Cl	"	4
"	"	"	Br	"	5
"	"	-O-	"	"	2-6
"	"	"	" [a]	S	1
"	"	"	I	R	9
"	Et	"	Br	"	11

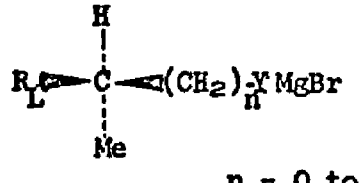
a) THF used as cosolvent rather than ether used in all others.

possible to use 1,4-asymmetric reductions of trifluoromethyl phenyl ketone as a simple and convenient empirical method of assigning the absolute configurations of the asymmetric alcohols from which the alcoholates are prepared. At this time there seems to be no such method available except for secondary alcohols. However, the sensitivity of 1,4-asymmetric reductions to seemingly minor variations in conditions such as solvent and metal would require careful standardization of experimental conditions to insure that the results obtained were meaningful. Although these results might be rationalized on the basis of a reactant-like transition state using reasoning similar to that involved in developing a model for "normal" 1,4-asymmetric Grignard reductions, the evidence available at this time does not seem sufficient to justify such an approach.

Table 13 also shows that analogous 1,4-asymmetric MPV and Grignard reductions are very similar both in the stereoselectivity shown and in the configurations of the products obtained.

1,5- and 1,6-Asymmetric Meerwein-Ponndorf-Verley Reductions

In studies of long range asymmetric MPV reductions it was possible to use the alcohol precursors for 1,n-asymmetric Grignard reductions to prepare the alcoholates for the corresponding 1,(n+1) asymmetric MPV reduction. Thus in the MPV series it was possible to study a series of 1,3-, 1,4-, 1,5- and 1,6-asymmetric reductions by alcoholates with the general structure 22 and obtain a rather comprehensive series for the



99

n = 0 to 3

R_L = phenyl or cyclohexyl

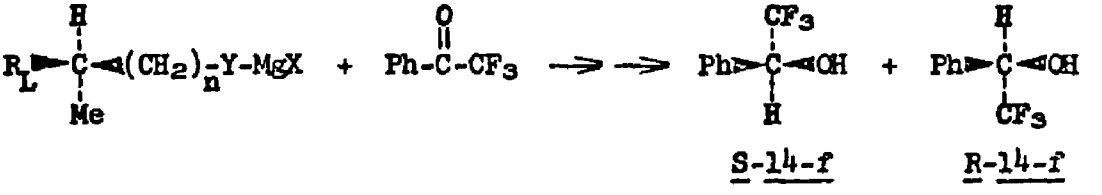
study of the effect of distance on asymmetric synthesis. Prior to conducting these experiments it was thought that the limit to the length of the methylene chain in 99 that would provide observable asymmetric reduction would be n = 1 or possibly 2. However, the rather large enantiomeric excesses obtained in the 1,4-asymmetric syntheses tested prompted extension of the series to include 1,5 and 1,6-asymmetric synthesis. As in previous studies the effect of both solvent and halide was investigated for the 1,5-asymmetric reduction series and in both cases the corresponding phenyl and cyclohexyl compounds were studied. The results from these reactions are summarized in Table 14 and the result of the corresponding 1,5-asymmetric Grignard reduction is shown for comparison.

The results in Table 14 demonstrate that both 1,5- and 1,6 asymmetric MPV reductions provide products with appreciable optical activity. In fact, some of the greatest asymmetric synthesis noted in studies of long range systems were obtained with alcoholates from 3-phenyl-1-butanol (1,5-asymmetric synthesis). However, the low order of asymmetric synthesis observed in the 1,6-cases seemed to indicate that further extention of the series might not be worth the effort involved.

The trends observed in both of these series, where they were tested, included greater stereoselectivity with R_L = phenyl than with cyclohexyl; an order of stereoselectivity of halides of Br > I for the reagents containing R_L = cyclohexyl, but of I > Br > Cl for R_L = phenyl. In addition, there was an appreciable decrease in the stereoselectivity observed on changing the cosolvent from ether to THF, but not a reversal or configuration as noted in the 1,4- cases.

Table 14

1,5- and 1,6-Asymmetric Meerwein-Ponndorf-Verley Reductions of Trifluoromethyl Phenyl Ketone



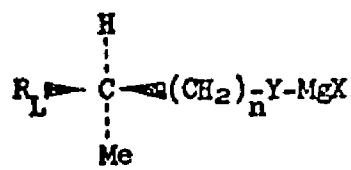
S-14-f R-14-f

Reducing Agent				Product, 14-f	
R_L	n	Y	X	Preferred Configuration	A. I., %
C_6H_{11}	2	-O-	Br	S	13
"	"	"	I	"	7
Ph	"	CH_2	Cl	R	4
"	"	-O-	"	"	7
"	"	"	Br	"	18-21
"	"	"	" [a]	"	9
"	"	"	I	"	25
C_6H_{11}	3	"	Br	"	1
Ph	"	"	"	S	3

a) THF used as cosolvent rather than ether used in all others.

Intramolecular Complexation in Long Range Asymmetric Reductions

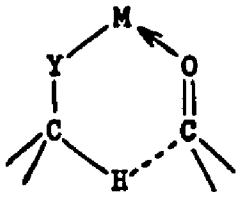
In the preceding discussion a number of unusual and "abnormal" results have been presented for long range asymmetric reductions of both the MPV- and Grignard-type. In most cases the results were mentioned, but little or no attempt was made to rationalize them. In this section many of these observations will be reconsidered from the standpoint of overall trends as the "distance" between the inducing and incipient asymmetric centers in the reactions was increased by extending the methylene chain through series of reducing agents of the general type 99. It is realized that n in 99 was not a real measure of distance, but in the



99

absence of other information this assumption is used.

In the studies discussed previously it often was difficult or impossible to compare results except within a group of 1,n-asymmetric reductions where n was held constant. However, by defining a "normal" series of reducing agents and assigning the same configurational result to all members of this series, it is possible to detect disparate behavior in other series. In this work a "normal" series was defined as one in which the secondary substituents in the reducing agent (i.e. those not involved in a skeletal transition state such as 100) could be expected to exert only steric influences on the stereochemistry of the reaction.



100

Examples of such series of reducing agents would be reagents of the type 99 with R_L = ethyl or cyclohexyl. These systems constitute a standard with which other results may be compared. In order to make possible comparisons of at least a semi-quantitative nature, it was desirable to use a normal system of the type 99 in which R_L had about the same steric size as the phenyl group present in most of the "non-normal" reagents whose behavior was to be tested. This objective was assumed to be met by the simple expedient of reducing each of the chiral phenyl substituted alcohols used in these studies to the corresponding cyclohexyl compound, and using both to prepare reducing agents.

Even when a normal series, 99 (R_L = cyclohexyl), had been defined, it was found that the configurations of the products obtained from the series varied in a random manner with chain length for the stereoformula shown in 99. In order to enable direct comparison between reagents in which the chain length varied the following convention was adopted: for a given chain length n the configuration of the "normal" alcoholate that provided an excess of the R-(-)-enantiomer of trifluoromethylphenylcarbinol was arbitrarily adapted as the standard configuration for all alcoholates of the same chain length. Then the configuration of the trifluoromethyl-

phenylcarbinol reported in the following results is that obtained from reduction by alcoholates with this standard configuration.

The results of the three series of long range asymmetric reductions of trifluoromethyl phenyl ketone are presented in this standardized form in Table 15. A graphical representation of the treatment used is shown in Figure 1 where the cyclohexyl substituted series 101 showed the asymtotic decrease in asymmetric synthesis with increasing chain length expected for a system involving only steric interactions. However, the phenyl substituted series 102 showed behavior that was quite different in that the individual results were qualitatively* abnormal for $n = 2$ and 3 and quantitatively abnormal for $n = 1$. The results from the Grignard reduction series with 103 showed the same type of "abnormal" behavior for the reagents with $n = 1$ and 2 as the analogous MPV reductions with 102; but the series was not extended to $n = 3$.

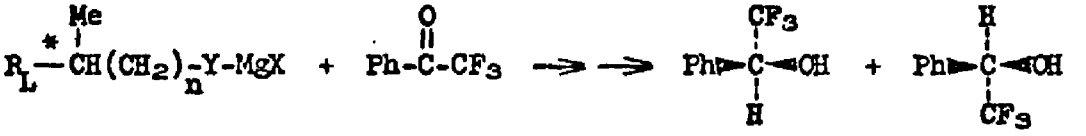
Other trends noted through the series of varying chain length are summarized in Tables 16 and 17 for completely saturated ("normal") reducing agents and those containing phenyl groups. Table 16 shows the effect of changing from ether to tetrahydrofuran as cosolvent on asymmetric synthesis as a function of chain length, while Table 17 shows the relative order of asymmetric synthesis observed for the variation of halide.

Table 16 seems to indicate that the behavior observed on changing the solvent system in long range asymmetric reductions is determined by

* In this work it was considered that each result obtained could show two distinct types of stereochemical behavior, qualitative and quantitative. Qualitative behavior was concerned only with which enantiomer was formed in excess, while quantitative behavior was concerned with the relative amounts of the excess.

Table 15

The Effect of Chain Length on Asymmetric Reductions of Trifluoromethyl Phenyl Ketone



101, $R_L = C_6H_{11}$, Y = -O-, X = Br

102, R_L = Ph, Y = -O-, X = Br

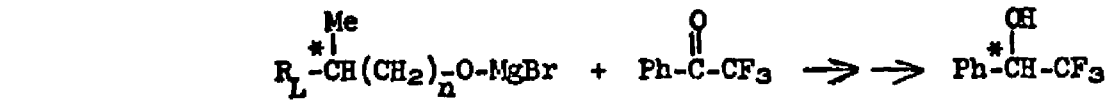
103, R_L = Ph, Y = CH_2, X = Cl

n	Enantiomer of 14-f Formed in Excess[a] (% e.e.)		
	Reducing Agent		
	101	102	103
0	R (42)	R (41)	R (47)
1	" (22)	" (4)	" (4)
2	" (13)	S (20)	S (4)
3	" (1)	" (3)	-

a) The R- configuration signifies a "normal" configurational result relative to the standardized series 101.

Figure 1

The Effect of Chain Length on Asymmetric Reductions of Trifluoromethyl Phenyl Ketone



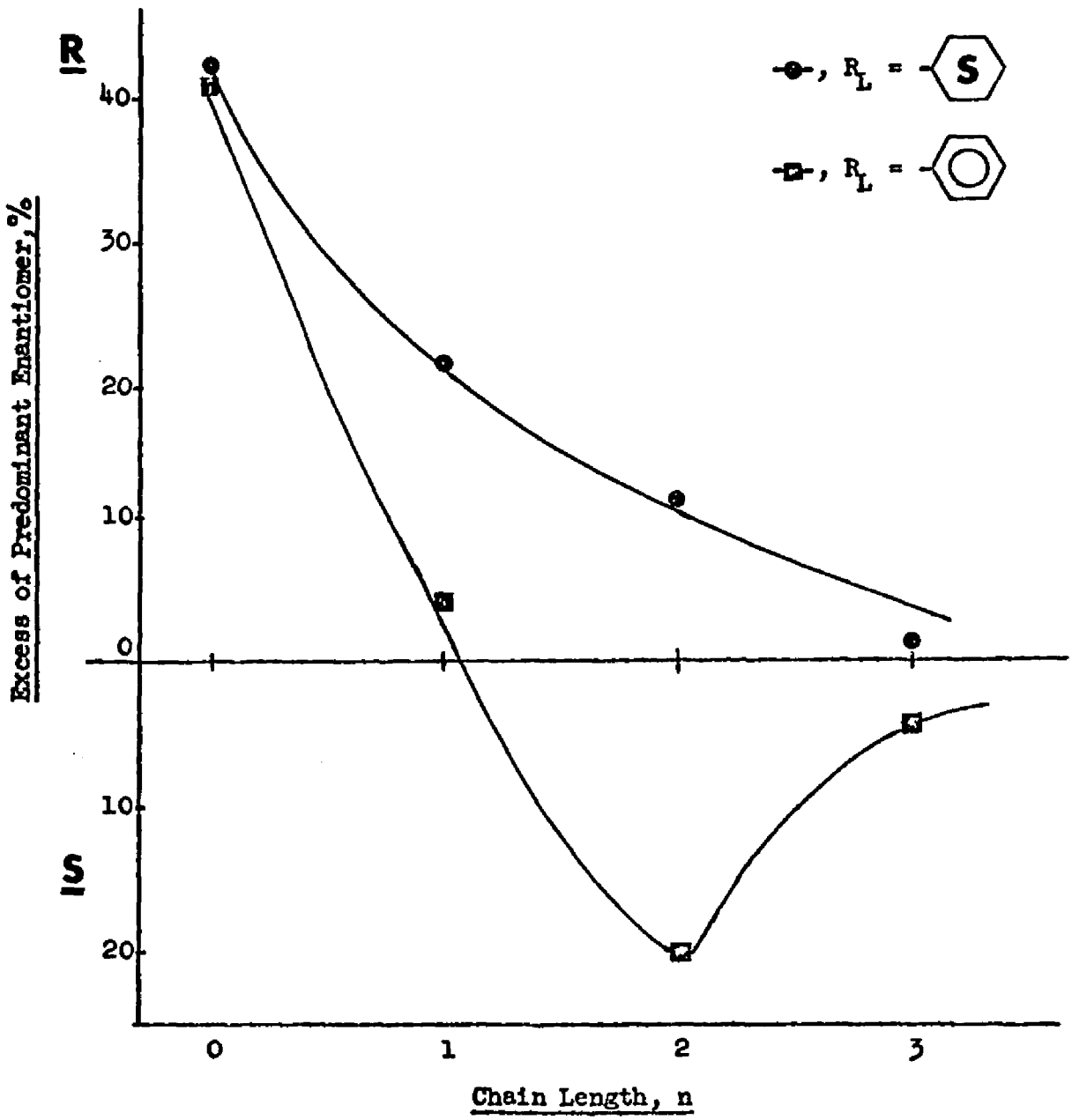


Table 16

The Effect of Changing from Ether to Tetrahydrofuran Cosolvent on Asymmetric Synthesis as a Function of Chain Length

Chain Length, n	"Normal"[a] Reducing Agent	Phenyl[a] Reducing Agent
0	Small[b] Decrease	Small[b] Decrease
1	Reversal	Reversal
2	-	Decrease

a) A "normal" reducing agent is defined as one containing only saturated alkyl substiuents. A "phenyl" reducing agent contains a phenyl group.

b) Decrease refers to the amount of asymmetric synthesis.

c) Reversal refers to the configuration of the product obtained.

Table 17

The Effect of Halide on the Amount of Asymmetric Synthesis as a Function of Chain Length

Chain Length, n	"Normal"[a] Reducing Agent	Phenyl[a] Reducing Agent
0	Cl > Br > I	-[b]
1	Cl > Br > I	I > Br
2	Br > I	I > Br > Cl

a) See footnote a) in Table 16.

b) Small differences with no trend were observed.

the chain length of the reducing agent, not the type of substituents it contains. This observation should be tested for a greater number of cases for both normal and phenyl substituted reducing agents of the type 99 and for ketones other than trifluoromethyl phenyl ketone before definite conclusions may be made.

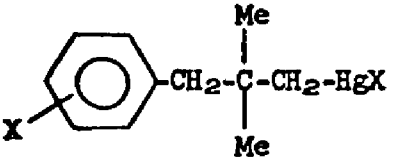
The results in Tables 15 and 17 and in Figure 1 all seem to demonstrate similar variations in behavior. With both of the measures used the "normal" reducing agents show regular trends while the corresponding long range asymmetric reductions ($n \geq 1$) by reagents containing phenyl groups show behavior that is either qualitatively or quantitatively quite different. Although it would be desirable to obtain additional examples of both types of behavior to establish greater generality there seems to be little question about the trends for the reduction of trifluoromethyl phenyl ketone in the series tested to date.

A feasible rationalization of the abnormal behavior of long range asymmetric reductions by reagents containing phenyl groups is intramolecular complexation by the reducing agents. In this manner a reagent such as 102 could exist in equilibrium with 102-a (Eq. 9). In the case of 1,3-asymmetric reductions, $n = 0$, the reagent would exist almost exclusively in the uncomplexed form, but for $n = 1$ or 2 the stable five- and six-membered rings in the complexed reagents would be expected to be highly favored. For $n = 3$ or greater the preference for the complexed reagent would be expected to decrease rapidly due to the unfavorable geometries of seven-membered or larger rings.

(Eq. 9)

102 102-a

Although the strength of the π-coordination in complexes such as 102-a involving donation by an aromatic ring to a metal acceptor would be expected to be very small, this strength could be magnified by a chelate effect in complexes with suitable geometry. In a recent study Keifer and coworkers[69] reported the great preference for the intra-



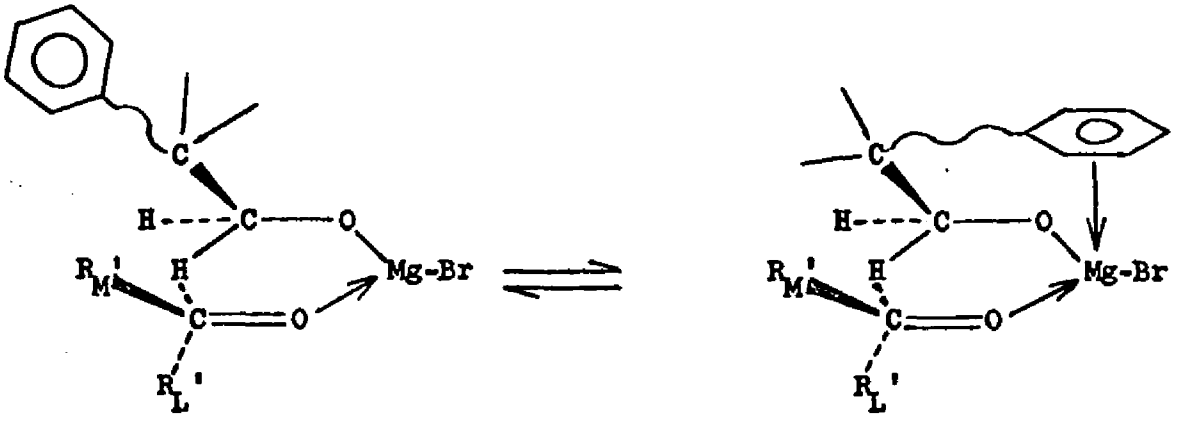
104

molecularly complexed form of organomercury reagents 104, which are quite similar to 102 and 102-a where n = 1. It is interesting to note that the use of benzene as a solvent for reagents of the type 104 had

little effect on the amount of intramolecular complexation even though intermolecular complexation with the solvent would have furnished coordinate bonding of approximately equal strength. Increasing solvent basicity was found to decrease the amount of intramolecular complexation in the organomercury studied.[69]

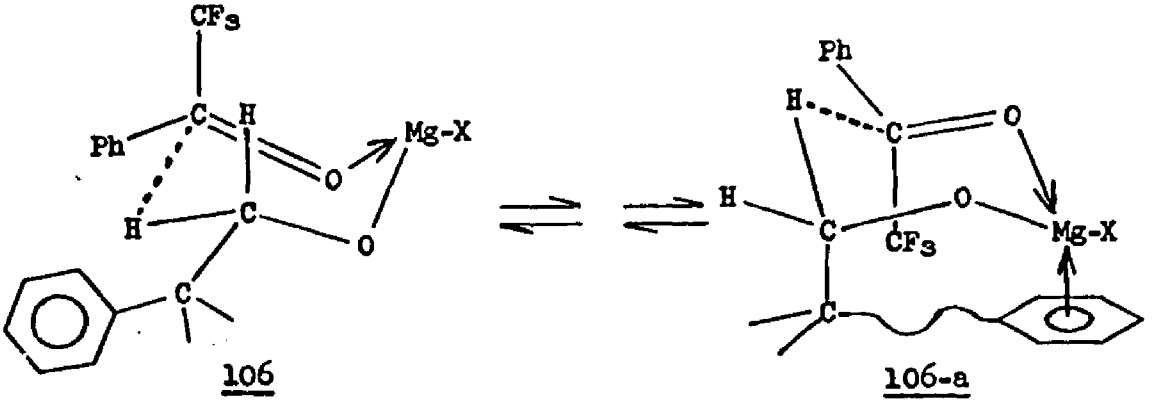
Intramolecular complexation of the reducing agents also offers an attractive rationalization for the reversal of product configuration noted for long range asymmetric reductions of trifluoromethyl phenyl ketone by the series 101 and 102.

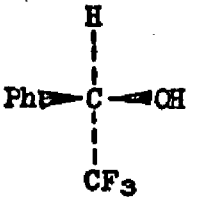
It would not be expected that complexation by the large group in a planar transition state model such as 105 would alter the stereochemical course of the reaction, i.e. 105 and 105-a would be expected to provide the same result. However, in the cyclohexane-like transition state model discussed for the reduction of perfluoroalkyl ketones,



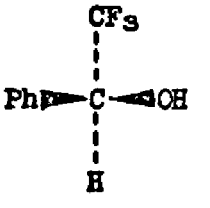
105 105-a

the expected requirement for a 1,3-diaxial type of orientation for the complex in the six-membered ring 106-a would place the large phenyl bearing group in a pseudo-axial position. This requirement would provide product with the opposite configuration of that predicted from the large group in the pseudo-equatorial position normally assumed for the uncomplexed model 106. Thus both transition state models provide the same prediction or the preferred product configuration with complexed reducing agents, but for different reasons.





R-14-f



S-14-f

Transition state model such as 106 and 106-a rationalize the reversal of product configuration observed from 101 to 102 for

n = 2 or 3. The greatly decreased amount of asymmetric synthesis obtained with reducing agents containing phenyl groups with n = 1 may then be rationalized on the basis of competitive reduction via both complexed and uncomplexed intermediates in which the contributions of each largely cancel each other. This result might represent a case where the greater rate of reduction by uncomplexed reagent 102 due to the formation of a more favorable transition state such as 106 overcomes the greater concentration of complexed reagent 102-a leading to a less favored transition state such as 106-a.

Although drawings are inadequate, inspection of molecular models representing 106 and 106-a demonstrates that it might be difficult for a molecule to meet the geometric requirements for both reduction and complexation at the same time for small values of n. Then in the case where n = 1 the reduction might proceed largely through the small equilibrium concentration of an uncomplexed transition state such as 106, but with sufficient contribution from 106-a to provide the observed result. One result which appears to be at variance with this reasoning is the observation that the halide effect for 97 and 98 is I > Br, with both providing an excess of the product expected from an uncomplexed reducing agent. The reverse order might have been expected.

Several other observations might also be rationalized by models involving intramolecular complexation. The reversal or the order of the relative amounts of asymmetric synthesis by methyl- and ethyl-substituted MPV reducing agents in the 1,4-series on changing R_L from cyclohexyl to phenyl is such a case. A possible rationalization for this change could be the great sensitivity of a rather crowded,

complexed transition state such as 106-a toward the size of alkyl groups. This might increase the amount of reduction via uncomplexed transition states for ethyl substituents relative to methyl.

The results of the 1,5-asymmetric reduction of t-butyl phenyl ketone by 47 are of particular interest because they represent the only case in which a ketone other than 13-f was reduced by a reagent which clearly demonstrated "abnormal" behavior toward 13-f. The observation of an exceptionally high yield of reduction products could be attributed to a large increase in the steric bulk of a Grignard reagent in which the phenyl group and chain attaching it to the ring were held over one side of the ring by complexation. The rather rigid orientation of such a complexed group could well make the reagent "larger" than the β-asymmetric reagent 15, which provides a lower yield of reduction products. It was interesting that the configurational result from t-butyl phenyl ketone was the same as that for the reduction 13-f by the same reagent. This was the result predicted from the complexed, planar transition state model 105-a for the t-butyl ketone and a complexed, cyclohexane-like transition state model 106-a for the trifluoromethyl ketone. It should be pointed out, however, that these results by no means require or prove these models and explanations.

EXPERIMENTAL

General

Methods

Melting Points. Melting points (mp) were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Infrared Absorption Spectra. All infrared (IR) spectra were obtained using a Perkin-Elmer Model 337 grating spectrophotometer. The spectra of liquids were obtained as films between salt plates. The spectra of solids were obtained as thin films of crystals obtained by evaporating solutions on a salt plate.

Nuclear Magnetic Resonance Spectra. All nuclear magnetic resonance (nmr) spectra were determined using a Varian Model A-60 spectrometer. Chemical shifts are given in ppm relative to TMS as internal standard.

Optical Rotation Data. Optical rotations were determined on a Carl Zeiss Photoelectric Precision Polarimeter, 0.005° equipped with a mercury vapor light source and filtered to give readings at 578, 546, 435, 405 and 365 nm, or in a few cases on a Franz Schmidt and Haensch polarimeter with a sodium vapor lamp as the light source. Rotations are reported at the sodium D line unless otherwise stated, and were obtained from the values of 578 and 546 nm with the Zeiss instrument either using the Drude equation or graphically. In all cases tested the values obtained from the two instruments on the same sample were in good agreement.

Gas Liquid Partition Chromatography. Gas liquid partition chromatography (glpc) analyses were conducted using either a Perkin-Elmer Model 154 Vapor Fractometer or an Aerograph Autoprep Model A-700. Preparative glpc was conducted using an Aerograph Autoprep Model A-700.

Dry Solvents. Diethyl ether was utilized in two forms: Fisher Anhydrous Ether, where trace amounts of water could be tolerated, such as in lithium aluminum hydride reductions; or in cases where absolute dryness was essential, Fisher Anhydrous Ether was dried over sodium wire and protected from the atmosphere.

Dimethoxyethane (DME), tetrahydrofuran (THF) and diisopropyl ether were refluxed over, and distilled from, calcium hydride. The distilled products were stored over molecular sieves (Union Carbide Corporation, Linde Division Type 3-A, 1/16" pellets were used throughout this work) in bottles with septum caps, and transferred via syringe.

Benzene and toluene were dried by azeotropic distillation of about one-fourth of the solvent and were then distilled and stored over sodium wire or molecular sieves and protected from the atmosphere.

Pyridine was dried by refluxing over, and distilling from, potassium hydroxide pellets. The distilled product was stored over molecular sieves.

Reaction Procedures

Due to the great number of repetitions of certain reactions during the course of this work, general procedures are given for several of the most commonly used. Unless otherwise stated, these procedures are understood to have been used in the appropriate detailed experimental descriptions.

Hydrogenations. All hydrogenations were conducted on a Parr Low Pressure apparatus using hydrogen or deuterium (Baker Technical Grade). Unless otherwise stated the solvent was 9:1 methanol-glacial acetic acid and the catalyst was platinum oxide (Engelhard Industries). Prereduced catalysts were prepared by shaking under deuterium in the hydrogenation apparatus with the solvent to be used, evacuating the system and repeating the procedure several times. Product mixtures were worked up by filtering the catalyst, evaporating the solvent and purifying the residues. IR spectra of the final products showed no absorptions due to the group(s) being reduced unless otherwise stated.

Lithium Aluminum Hydride Reductions. A variety of functional groups were reduced by adding an ethereal solution of a substrate to a well-stirred suspension of lithium aluminum hydride (LAH) in ether in a round-bottomed, three necked flask fitted with a mechanical stirrer, pressure equalizing addition funnel and efficient reflux condenser capped with a drying tube. The resultant suspensions were refluxed for 2 to 6 hours, then cooled in an ice bath and hydrolyzed by either an "acid" or a "basic" procedure. In the acid hydrolysis the excess LAH was destroyed by careful addition of ice water, then sufficient 10-15% hydrochloric acid was added to dissolve all of the solid residue and provide two easily separable layers. The basic hydrolysis involved adding, in turn, 1 ml of water, 1 ml of 15% sodium hydroxide solution and 3 ml of water for every gram of LAH used in the reaction. By this procedure the inorganic salts are precipitated as crystalline solids from which the clear supernatant ether layer can be easily decanted. It was found that addition of a small amount of anhydrous magnesium sulfate aided nucleation of the crystals in cases where an intractable

white paste was obtained. The ether solutions of the crude products were dried ($MgSO_4$) and concentrated under reduced pressure.

Preparation of Alkyl Chlorides. Alkyl chlorides were prepared by adding thionyl chloride (Fisher Purified) to a well stirred solution of the corresponding alcohol and dry pyridine in a round-bottomed, three-necked flask fitted with a mechanical stirrer, pressure-equalizing addition funnel, reflux condenser, immersion thermometer and drying tube. The temperature was maintained between 0° and -10° throughout the addition. The thick paste obtained was stirred 3-6 hours with continued cooling, allowed to warm to room temperature and, finally, heated on a steam bath for 2 to 8 hours to decompose the chlorosulfite ester. Stirring was discontinued while the mixture was still hot to facilitate separation into two layers. The flask was cooled in an ice bath to solidify the bottom layer. The upper layer of crude alkyl chloride was decanted. The bottom layer was extracted several times by successively warming to melt the solid, adding ether, stirring well for 10 to 15 minutes, cooling to solidify the bottom layer and decanting the ether extract. The combined chloride layer and ether extracts were washed with 10% HCl (two or three times) and water (once) to remove any pyridine, dried ($MgSO_4$) and concentrated.

Preparation of Grignard Reagents. A round-bottomed, three-necked flask was fitted with a magnetic stirrer, pressure-equalizing addition funnel, reflux condenser and nitrogen inlet. Magnesium was added and the apparatus was flamed out under a stream of nitrogen to remove moisture. A small amount of a concentrated, solution of the halide (about 1/1) in the reaction solvent was added to initiate

the reaction. Reluctant reactions were initiated by adding a few drops of ethylene dibromide or by heating. Once initiated, the reaction was moderated by adding solvent. When the initial vigorous reaction subsided the remainder of the halide solution was added at a rate which maintained a reflux. Solutions were stirred or allowed to stand at room temperature for an additional period of time to complete the reaction. In a few cases where initiation procedures failed, all of the ingredients were added and the mixture was refluxed for 8 to 24 hours until most of the magnesium dissolved.

The Grignard reagents used in reactions where purity and concentration were important were filtered through a sintered glass filter stick under nitrogen pressure, stored under nitrogen in graduated cylinders fitted with septum caps, and standardized. Standardization was accomplished by adding aliquots to excess standard acid and titrating to a phenolphthalein end point with standard base. Standardized reagents were handled and measured in nitrogen-flushed syringes. Sodium-dried ether was used unless otherwise stated. Commercial halides were used without further purification except for tertiary butyl chloride, which was treated with potassium carbonate and distilled prior to use. Three grades of magnesium were used during this work. Triply sublimed magnesium turnings* were used for Grignard reduction reactions. Singly sublimed magnesium turnings were employed for reagents utilized in the preparation of magnesium alcoholates and Fisher Magnesium Turnings for Grignard Reactions were used for most preparative reactions.

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* The triply sublimed magnesium was a gift from the Dow Chemical Co., Midland, Michigan.

Grignard Reductions of Ketones. A round-bottomed, three-necked flask fitted with magnetic stirrer, pressure equalizing addition funnel, reflux condenser, septum cap and nitrogen inlet was flamed out under a stream of nitrogen. The appropriate amount of a filtered and standardized solution of Grignard reagent was added by syringe. An ethereal solution of the ketone to be reduced was added through the addition funnel at a rate which maintained a gentle reflux and the reaction mixture was then stirred for 4 to 8 hours. The mixture was hydrolyzed with ammonium chloride solution. The organic layer was separated, combined with 2 or 3 ether extracts of the aqueous layer, dried ($MgSO_4$) and concentrated. The product mixtures were separated into major fractions by distillation through a 10-cm Vigrous column. The products used for final analysis were obtained by preparative glpc using 10' x 1/4" 10% Carbowax-20-M on 60-80 mesh Chromosorb W (CW-20-M) or 10' x 1/4" 10% Apiezon L on 60-80 mesh Chromosorb W (Apiezon L) columns and Helium flow rates of 60 cc/minute. Purified samples were analyzed by glpc and in the case of rotation samples contained less than 1% of any optically inactive impurity such as ketone and much less than 1% of any impurity that might have been optically active. The samples for nmr analysis contained less than 2% of any impurity detectable by analytical glpc.

Meerwein-Ponndorf-Verley Reductions. A round bottomed, three-necked flask fitted with a magnetic stirrer, pressure-equalizing addition funnel, reflux-distillation head, septum cap and nitrogen inlet was flamed out under a stream of nitrogen. An aliquot of a filtered and titrated solution of a Grignard reagent, n-propylmagnesium bromide in ether unless otherwise stated, was injected with a nitrogen

flushed syringe. The alcohol was added, usually in a solvent, and the solvent composition adjusted to that desired. In reactions run in "ether-benzene" the mixtures were uniformly distilled to bp 55-56°. The ketone to be reduced was added in one portion to provide clear, homogeneous solutions ca. 1 molar in alcoholate unless otherwise stated. The mixture was stirred at ambient temperatures for the stated reaction time, then hydrolyzed with ammonium chloride solution. The organic layer was separated, combined with two or three ether extracts of the aqueous layer, dried ($MgSO_4$) and concentrated. An IR spectrum was taken of the crude products. Trifluoromethyl phenyl ketone (13-f) and trifluoromethylphenylcarbinol (14-f) gave very characteristic sharp absorptions at 960 cm^{-1} and 1270 cm^{-1}, respectively which allowed a semiquantitative analysis of the amount of reduction which had taken place. The products were partially separated by distillation and the trifluoromethylphenylcarbinol was purified successively by preparative glpc on CW-20-M (180°) and Apiezon-L (175°) columns. Rotation samples of trifluoromethylphenylcarbinol were analyzed by glpc and IR and shown to contain less than 1% of any optically inactive impurity and much less than 1% of any other impurity. The IR spectra were identical to that of a carefully purified authentic sample and were especially revealing in the region 2800-3000 cm^{-1}, aliphatic C-H stretch, where most impurities absorbed strongly while (14-f) gave only a weak absorption.

Grignard Reductions

Precursors for Grignard Reductions

Ketones. Commercial samples of ethyl phenyl ketone and isopropyl phenyl ketone were distilled prior to use.

t-Butyl Phenyl Ketone (13-e). A solution of t-butylmagnesium chloride prepared from t-butyl chloride (150 g, 1.6 mole), magnesium turnings (37.0 g, 1.52 mole) and dry ether (700 ml) was filtered through a glass wool plug under nitrogen and added to a well-stirred suspension of cuprous chloride (2.5 g), benzonitrile (125 g, 1.25 mole) and dry ether (100 ml). The mixture was stirred overnight and then hydrolyzed by refluxing with concentrated hydrochloric acid until two clear layers were obtained. The organic layer was separated, combined with 2 ether extracts of the aqueous layer, washed with 10% sodium bicarbonate solution, dried with anhydrous calcium chloride and concentrated. Distillation provided two fractions: no. 1, bp 51-75° (0.7 mm), (48.0 g), shown by IR to be ketone contaminated with a small amount of unreacted nitrile, and no. 2, a clear,colorless liquid, bp 75-78° (0.7 mm), (120 g, 60% yield) whose IR and nmr spectra were identical with those of an authentic sample of t-butyl phenyl ketone.

Trifluoromethyl Phenyl Ketone, (13-f). This ketone was prepared from trifluoroacetic acid and phenylmagnesium bromide using Fuchs and Park's modification[70] of the procedure of Dishart and Levene.[71] Trifluoromethyl phenyl ketone was obtained as a clear, colorless liquid, bp 49-51° (12 mm), in yields ranging from 65 to 73%.

(+)-3-Phenylbutanoic Acid (40). The acid was prepared from crotonic acid, (301 g, 3.5 mole), dry benzene (2.3 l) and aluminum chloride (800 g) by the method of Marvel et al.[72] The product was obtained as a clear, colorless liquid, bp 114-118° (0.45 mm),(458 g, 80% yield), whose IR and nmr spectra were identical with those of an authentic sample.

R-(-)-3-Phenylbutanoic Acid, R-(40). R-(-)-acid was obtained by resolution of the racemic acid with R-(+)-α-methylbenzylamine (Norse Chemical) in aqueous ethanol, following the procedure of Weidler and Bergson.[60] The recrystallized salt, mp 146-147°, provided 65 to 70% of the theoretical amount of R-(-)-acid, α_D^{29} -55.3° (neat, 1 = 1), 96 to 98% enantiomeric excess (e.e.) based on a maximum rotation of α_D^{25} -56.5°.[55] The evaporated mother liquors from the resolution provided partially active S-(+)-acid, 50 to 60% e.e.

R-(-)-3-Phenyl-1-butanol, R-(41). This alcohol was prepared by the reduction of R-(-)-3-phenylbutanoic acid, α_D^{29} -54.4°, (200 g, 1.22 mole) with lithium aluminum hydride (45 g, 1.2 mole) in ether (1-1) using an acid hydrolysis. The alcohol, α_D^{24} -18.46°, (neat, 1 = 0.5), 95% e.e. based on a maximum rotation of α_D^{25} -39.0°[55], was obtained as a clear liquid, bp 85-86° (1 mm), (173.8, 95% yield). Partially active S-(+)-3-phenyl-1-butanol was obtained in the same manner from several reductions of partially active S-(+)-3-phenylbutanoic acid.

S-(+)-1-Chloro-3-phenylbutane, S-(42). The chloride was prepared from S-(+)-3-phenyl-1-butanol, α_D^{27} +21.9° (neat, 1 = 1), 56% e.e., (49.5 g, 0.33 mole) using thionyl chloride (57 g, 0.47 mole) and dry pyridine (50 ml). The chloride was obtained as a clear liquid, bp 52-54° (0.45 mm), (45.2 g, 81.5% yield), α_D^{37} +50.1° (neat, 1 = 1), 59% e.e. based on a maximum rotation of α_D^{23} -85.23° for chloride prepared from R-3-phenyl-1-butanoic acid of 99+% e.e.[73]

R-(-)-1-Bromo-3-phenylbutane, R-(43). The bromide was prepared from R-(-)-3-phenyl-1-butanol, α_D^{24} -36.9°, (neat, 1 = 1), 95% e.e. (30.0 g, 0.20 mole) by refluxing with 48% hydrobromic acid (Baker Chemical) (70.0 g, 0.4 mole) for

2.5 hours. The organic layer was separated, washed with water (twice) and combined with an ether extract of the combined acid and aqueous wash layers. The combined organic layers were dried ($MgSO_4$) and concentrated. Distillation provided the bromide as a clear liquid, bp 75-77° (1 mm), (29.3 g, 69% yield), α_D^{26} -94.4° (neat, 1 = 1), 90% e.e. based on a maximum rotation of α_D^{25} -104.3°.[55]

R-(-)-4-Phenylpentanoic Acid, R-(45). The Grignard reagent prepared from R-(-)-1-bromo-3-phenylbutane, α_D^{26} -94.4° (neat, 1 = 1), 90% e.e., (107 g, 0.50 mole), magnesium (13.5 g, 0.55 g-atom) and ether (400 ml) was placed in a 1-l, three-necked, round-bottomed flask fitted with mechanical stirrer, reflux condenser, nitrogen inlet, and an Erlenmeyer flask connected through Gooch tubing. The apparatus was cooled in a dry ice-isopropanol bath, and powdered dry ice (ca. 200 g) was added through the Gooch tubing to the well-stirred Grignard reagent. The external cooling was removed and the excess dry ice was allowed to evaporate under nitrogen while stirring was continued. When the flask had warmed to room temperature, the mixture was hydrolyzed with sufficient 15% HCl to provide two clear layers. The organic layer was combined with two ether extracts of the aqueous layer and extracted four times with 10% sodium bicarbonate solution. The combined basic extracts were extracted twice with ether and acidified. The oil which separated was taken up in ether, dried ($MgSO_4$) and concentrated. The acid was obtained as a clear, colorless liquid, bp 119-122° (0.4 mm), $[\alpha]_D^{32}$ -22.1° (neat), 90% e.e. based on $[\alpha]_D^{25}$ -24.6°[54], (52.8 g, 59% yield). The yield was inadvertently lowered considerably by the loss of material during both the carbonation and hydrolysis steps.

R-(-)-4-Phenyl-1-pentanol, R-(46). The alcohol was prepared by the reduction of R-(-)-4-phenylpentanoic acid, 90% e.e., (51.5 g, 0.29 mole) with LAH (9.5 g, 0.25 mole) in ether (250 ml) using an acid hydrolysis. The alcohol was obtained as a clear, colorless liquid, bp 90-91° (0.5 mm), (39.7 g, 83.5% yield), $[\alpha]_D^{29}$ -18.6° (neat), 89% e.e. based on $[\alpha]_D^{25}$ -20.9°.[54]

R-(-)-1-Chloro-4-phenylpentane, R-(47). This compound was prepared from R-(-)-4-phenyl-1-pentanol, $[\alpha]_D^{29}$ -18.6° (neat), (23.0 g, 0.14 mole) using thionyl chloride (24.8 g, 0.21 mole) and dry pyridine (25 ml). The chloride was obtained as a clear, colorless liquid bp 55-56° (0.2 mm), α_D^{27} -15.9° (neat, 1 = 1), (18.6 g, 73% yield).

(+)-Ethyl-3-Hydroxy-3-phenylbutanoic Acid, (49). This acid was prepared by the Reformatsky reaction from methyl phenyl ketone (60.0 g, 0.50 mole), ethyl bromoacetate (90.0 g, 0.54 mole), zinc metal (10 mesh) (35 g, 0.54 g-atom) and dry benzene (400 ml). The crude product was used in the next step without purification.

(E)-β-Methylcinnamic Acid, (E)-(50). The crude ethyl 3-hydroxy-3-phenylbutanoic acid obtained from 0.5 mole of methyl phenyl ketone was dehydrated by refluxing with benzene (400 ml) and phosphorous oxychloride (2 ml) in a Dean-Stark apparatus until no more water was collected. The crude mixture of unsaturated esters obtained was saponified by refluxing with sodium hydroxide (40 g, 1.0 mole) and water (300 ml). The saponification mixture was extracted with ether and acidified to provide a crude mixture of unsaturated acids. The E-β-methylcinnamic acid was obtained by recrystallization from carbon disulfide as white crystals, mp 97-98.5° (lit.[74] 98.5°) (49.1 g, 61% yield).

(Z)-β-Methylcinnamic Acid, (Z)-(50). The (Z)-acid was obtained as white crystals mp 132-134° by irradiating[74] a benzene solution of either the E-acid or the low melting mixture of E- and Z-acids, mp ca. 70-80°, and recrystallizing the products from carbon disulfide. Yields of pure Z-acid were about 50% of the acid irradiated and the procedure could be repeated on the mother liquors as often as desired.

(±)-Threo-2,3-Dideuterio-3-Phenylbutanoic Acid, (±)-Threo-(51). E-β-Methylcinnamic acid was recrystallized from boiling ethyl acetate to remove traces of carbon disulfide which poisoned the hydrogenation catalyst. The recrystallized acid, mp 97-98.5°, (32.4 g, 0.20 mole) was hydrogenated with deuterium (Baker Technical) using ethyl acetate (200 ml) as solvent and predeuterated 5% palladium on carbon as catalyst (1.0 g) (Engelhart Industries). Deuterium uptake stopped after about 1 hour. The acid was obtained as a clear, colorless liquid, bp 112-114° (0.5 mm), (31.9 g, 96% yield), whose IR (no. 8104) and nmr (no. 5773) spectra were identical to those of an authentic sample of 3-phenylbutanoic acid except for differences expected for the incorporation of deuterium.

(±)-Threo-2,3-Dideuterio-3-phenyl-1-butanol, (±)-Threo-(52). The alcohol was prepared by the reduction of threo-2,3-dideuterio-3-phenylbutanoic acid (41.5 g, 0.25 mole) with LAH (8.0 g, 0.21 mole) and ether (300 ml) using an acid hydrolysis. The alcohol was obtained as a clear, colorless liquid, bp 82-90° (0.45 mm), (34.0 g, 89% yield) whose IR (no. 8107) and nmr (no. 5798) spectra were consistent with the desired product.

(±)-Threo-2,3-Dideuterio-1-chloro-3-phenylbutane, Threo-(53). This chloride was prepared from threo-2,3-dideuterio-3-phenyl-1-butanol (30.4 g, 0.20 mole) using

thionyl chloride (30 g, 0.25 mole) and dry pyridine (30 ml). The chloride was obtained as a clear, colorless liquid, bp 52-54° (0.45 mm), (25.8 g, 75.4% yield), whose IR (no. 8111) and nmr spectra (no. 5800) spectra were consistent with the desired product.

(±)-Erythro-2,3-Dideuterio-3-phenylbutanoic Acid, (±)-Erythro-(51). (Z)-β-Methylcinnamic acid, Z-(50), was recrystallized from boiling ethyl acetate to remove any traces of carbon disulfide. The recrystallized acid, mp 132-134°, (38.0 g, 0.234 mole), was hydrogenated in two portions with deuterium (Baker Technical) using ethyl acetate (400 ml) as solvent and predeuterated 5% palladium an carbon (Engelhart Industries) (0.5 g) as catalyst. Deuterium uptake was complete in about 8 hours. The acid was obtained as a clear, colorless liquid, bp 105-108° (0.2 mm), (35.0 g, 90% yield), whose IR (no. 8675) and nmr (no. 6698) spectra were consistent with the expected product and differed only slightly from those of the threo isomer.

Erythro-2,3-Dideuterio-3-phenyl-1-butanol, (±)-Erythro-(52). The alcohol was prepared by the reduction of erythro-2,3-dideuterio-3-phenylbutanoic acid (30.0 g, 0.18 mole) with LAH (6.0 g, 0.16 mole) and anhydrous ether (200 ml) using a basic hydrolysis. The alcohol was obtained as a clear, colorless liquid, bp 80-84° (0.4 mm), (24.7 g, 86.7% yield), whose IR (no. 8678) and nmr (no. 6699) spectra were consistent with the expected product.

Erythro-2,3-Dideuterio-1-chloro-3-phenylbutane, (±)-Erythro-(53). The chloride was prepared from erythro-2,3-dideuterio-3-phenyl-1-butanol (23.4 g, 0.15 mole) using thionyl chloride (25 g, 0.21 mole) and dry pyridine (25 ml).

The chloride was isolated as a clear, colorless liquid, bp 53-55° (0.5 mm), (19.0 g, 74% yield) whose IR (no. 8691) and nmr (no. 6700) spectra were consistent with the expected product.

(2S,3R)-(-)-Threo-2,3-Dideuterio-3-phenylbutanoic Acid, (2S,3R)-Threo-(51). The acid was prepared by resolution of the racemic acid (116 g, 0.70 mole) with R-(+)-α-methylbenzylamine (Norse Chemical Co.) (85.0 g, 0.70 mole) in aqueous ethanol in a manner identical to that used for the resolution of 3-phenylbutanoic acid. Recrystallized salt, mp 146-147.5°, provided the R-(-)-acid as a clear liquid, bp 110-112° (0.4 mm), α_D^{28} -54.3° (neat, 1 = 1), (38.8 g, 67% of theory), ca. 96% e.e. The evaporated mother liquors of the crystallizations provided partially active S-(+)-acid, α_D^{27} +31.0° (neat, 1 = 1), 55% e.e., (67.2 g, total recovery 90%).

(2S,3R)-(-)-Threo-2,3-Dideuterio-3-phenyl-1-butanol, (2S,3R)-Threo-(52). The alcohol was prepared by reduction of (-)-threo-2,3-dideuterio-3-phenylbutanoic acid, α_D^{28} -54.3° (neat, 1 = 1), (37.4 g, 0.225 mole) with LAH (7.6 g, 0.20 mole) in anhydrous ether (200 ml) using an acid hydrolysis. The alcohol was obtained as a clear liquid, bp 90-92° (1.0 mm), α_D^{27} -35.2° (neat, 1 = 1), ca. 90% e.e., (31.9 g, 89% yield).

(2S,3R)-(-)-Threo-2,3-Dideuterio-1-Chloro-3-phenylbutane, (2S,3R)-(-)-(53). The chloride was prepared from (2S,3R)-(-)-threo-2,3-dideuterio-3-phenyl-1-butanol, α_D^{27} -35.2° (neat, 1 = 1) (30.5 g, 0.20 mole), thionyl chloride (33 g, 0.28 mole) and dry pyridine (30 ml). The chloride was isolated as a colorless liquid, bp 63-66° (0.6 mm), α_D^{26} -77.7° (neat, 1 = 1), ca. 91% e.e., (25.1 g, 73% yield).

(±)-Threo-2,3-Dideuterio-3-phenylpropanoic Acid, (±)-Threo-(55). (E)-Cinnamic acid (Fisher Certified Reagent), mp 133-134°, (50.0 g, 0.338 mole) was hydrogenated in two portions with deuterium (Baker Technical Grade) using ethyl acetate (400 ml) as solvent and predeuterated 5% palladium on carbon (0.5 g) as catalyst. Deuterium uptake was complete in about 2.5 hours. The acid was initially obtained as a light yellow solid which was crystallized from 60-80° petroleum ether to provide white crystals, mp 48-49° (lit.[75], mp 48°, for 3-phenylpropanoic acid) (45.5 g, 89% yield).

(±)-Threo-2,3-Dideuterio-3-phenyl-1-propanol, (±)-Threo-(56). The alcohol was prepared by the reduction of threo-2,3-dideuterio-3-phenylpropanoic acid, mp 48-49°, (45.0 g, 0.30 mole) with LAH (10.0 g, 0.26 mole) in ether (275 ml) using a basic hydrolysis. The alcohol was isolated as a clear liquid, bp 110-112° (10 mm), (36.7 g, 88.5% yield).

(±)-Threo-2,3-Dideuterio-1-chloro-3-phenylpropane, (±)-Threo-(57). The chloride was prepared by the reaction of threo-2,3-dideuterio-3-phenyl-1-propanol (33.0 g, 0.24 mole) with thionyl chloride (33.0 g, 0.28 mole) and dry pyridine (30 ml). The chloride was obtained as a clear liquid, bp 88-89° (10 mm), (28.5 g, 76% yield).

Grignard Reductions

The Grignard Reagent, S-(19), from S-(+)-1-Chloro-3-phenylbutane. The reagent was prepared using S-(+)-chloride prepared from several batches of partially resolved S-(+)-3-phenylbutanoic acid (67.5 g, 0.40 mole), magnesium (10.0 g, 0.41 g-atom) and ether (200 ml). Filtration gave a clear solution of the reagent (300 ml, 0.95 N, 72% yield). An

aliquot of the filtered reagent was hydrolyzed and the resulting products were purified by distillation and preparative glpc to give a sample of S-(+)-2-phenylbutane, α_D^{28} +11.9° (neat, 1 = 1) indicating that the solution contained a 49% excess of the S-enantiomer of the Grignard reagent based on a maximum rotation of α_D^{23} +24.3 (neat, 1 = 1) for 2-phenylbutane.[55]

In a similar manner another batch of S-reagent was obtained after filtration as a slightly cloudy mixture (265 ml, 1.6 N). This reaction would not start using the normal methods so that a solution of S-reagent prepared earlier, ca. 50 to 60% e.e., was added and the mixture refluxed overnight to dissolve most of the magnesium and provide a suspension containing large amounts of white precipitate. Hydrolysis of an aliquot and purification gave a sample of S-(+)-2-phenylbutane, α_D^{25} +12.8° (neat, 1 = 1), corresponding to Grignard reagent of 53% e.e.

Reduction of t-Butyl Phenyl Ketone with S-19. The ketone (24.0 g, 0.15 mole) was allowed to react with an ether solution of the Grignard reagent S-19 containing a 49% e.e. of the S-enantiomer (160 ml, 0.95 N, 0.15 mole). After stirring for 4 hours the mixture was hydrolyzed. Distillation of the products furnished four fractions: no. 1, 10.0 g, bp 60-75° (16 mm); no. 2, 1.1 g, bp 75° (16 mm) to 66° (0.6 mm); no. 3, 7.1 g, bp 65-80° (0.45 mm) and no. 4, 21.1 g, bp 145-170°, (0.45 mm). Analytical glpc showed the following approximate compositions of major components in the fractions: no. 1, 3-phenyl-1-butene (81%) and 2-phenylbutane (15%); no. 2, t-butylphenylcarbinol (63%) and t-butyl phenyl ketone (37%); no. 3, t-butylphenylcarbinol (95%) and t-butyl phenyl ketone (5%). A sample of pure S-(-)-t-butylphenylcarbinol, mp 45-46°, $[\alpha]_D^{24}$ -1.2°, α_D^{24}

-0.080° (PhH, c=13.3; l=0.5) was obtained from fraction no. 3 by preparative glpc, CW-20-M (190°).

Reduction of Trifluoromethyl Phenyl Ketone with S-19. Trifluoromethyl phenyl ketone (11.8 g, 0.068 mole) was allowed to react with an ether solution of Grignard reagent 19 containing a 49% e.e. of the S-enantiomer (80 ml, 0.95 N, 0.076 mole) and stirred for 4 hours. Distillation of the products provided five fractions: no. 1, 9.7 g, bp 56-75° (17 mm); no. 2, 0.9 g, bp 75-85° (17 mm); no. 3, 9.0 g, bp 85-95° (17 mm); no. 4, 2.8 g, bp 51-75° (0.45 mm); and no. 5 1.0 g, bp 135-160° (0.45 mm). Analytical glpc of the fractions showed the following compositions of major components: no. 1, 3-phenyl-1-butene (69%), 2-phenylbutane (20%) and trifluoromethylphenylcarbinol (8%); no. 2, trifluoromethylphenylcarbinol (90%); no. 3, trifluoromethylphenylcarbinol (95%); no. 4, 1-chloro-3-phenylbutane (95%). A sample of pure S-(+)-trifluoromethylphenylcarbinol, α_D^{28} +0.12 (neat, l = 0.2), was obtained by preparative glpc of fraction no. 3 (CW-20-M, 180°, and Apiezon L, 150°, in turn).

Reduction of t-Butyl Phenyl Ketone with S-19; Rerun. t-Butyl phenyl ketone (9.7 g, 0.060 mole) was allowed to react with an ether solution of the Grignard reagent 19 containing a 53% e.e. of the S-enantiomer (38 ml, 1.6 N, 0.062 mole) and stirred for 6 hours. Distillation of the products furnished four fractions: no. 1, 3.8 g, bp 50-100° (10 mm); no. 2, 4.9 g, bp 60-66° (0.5 mm); no. 3, 0.6 g, bp 68-110° (0.5 mm); and no. 4, 7.5 g, bp 147-160° (0.5 mm). Analytical glpc showed the following major components in the fractions: no. 1, 3-phenyl-1-butene (80%), 2-phenylbutane (15%); no. 2, t-butylphenylcarbinol (65%) and t-butyl phenyl ketone (20%); no. 3, t-butylphenylcarbinol (90%) and 1-chloro-3-phenylbutane (10%).

A sample of S-(+)-3-phenyl-1-butene, α_D^{28} +0.885° (neat, l = 0.2)[55], was obtained by preparative glpc of Fraction no. 1 (CW-20-M, 150°). The nmr spectrum and analytical glpc of the sample showed that it contained only 2-phenylbutane and 3-phenyl-1-butene in detectable amounts while integration of the nmr spectrum showed that 11-12% 2-phenylbutane was present.

A sample of pure t-butylphenylcarbinol, $[\alpha]_D^{27}$ -1.1°, α_D^{27} -0.150° (c = 13.2, benzene, l = 1), was obtained by preparative glpc of Fraction no. 2 (CW-20-M, 190°).

Reduction of Ethyl Phenyl Ketone with S-19. Ethyl phenyl ketone (40.0 g, 0.298 mole) was allowed to react with an ether solution of Grignard reagent 19 containing a 53% excess of the S-enantiomer (190 ml, 1.6 N, 0.30 mole) and stirred for 6 hours. Distillation of the products furnished three fractions: no. 1, 4.3 g, bp 50-67° (10 mm); no. 2, 6.9 g, bp 73° (10 mm) to 85° (0.5 mm); and no. 3, 69.6 g, 145-155° (0.5 mm). Analytical glpc showed the following compositions of the fractions: no. 1, 3-phenyl-1-butene (60%), 2-phenylbutane (35%); no. 2, ethyl phenyl ketone (60%), ethylphenylcarbinol (30%), other (15%, long retention time). A sample of pure ethylphenylcarbinol, α_D^{27} -0.265 (neat, l = 0.1) was obtained by preparative glpc (CW-20-M, 160°).

The Grignard Reagent, R-(44), from R-(-)-1-Bromo-3-phenylbutane. The reagent was prepared using R-(-)-bromide, α_D^{26} -94.4° (neat, l = 1) 90% e.e., (26.0 g, 0.122 mole), triply sublimed magnesium (3.20 g, 0.13 g-atom) and ether (100 ml). Filtration gave a clear solution of the reagent (110 ml, 0.86 N, 78% yield).

Reduction of t-Butyl Phenyl Ketone with R-44. The ketone (6.00 g, 0.037 mole) was allowed to react with the

Grignard reagent R-44 (44 ml, 0.86 N, 0.038 mole) to provide a clear, homogeneous solution which was stirred for 6 hours. Distillation of the products gave two fractions: no. 1, 1.8 g, bp 50-65° (15 mm); no. 2, 3.0 g, bp 40-70° (0.2 mm) and pot residue, 6.9 g. A pure sample of t-butylphenylcarbinol, $[\alpha]_D^{27}$ -0.42°, α_D^{27} -0.045° (c = 10.65, benzene, l = 1) was obtained by preparative glpc of Fraction no. 2 (CW-20-M, 180°, followed by Apiezon L, 150°).

Reduction of Trifluoromethyl Phenyl Ketone with R-44. The ketone (3.50 g, 0.020 mole) was allowed to react with the Grignard reagent R-44 (25 ml, 0.86 N, 0.021 mole) in dry ether (25 ml) and stirred for 6 hours. Distillation of the products provided two fractions: no. 1, 2.8 g, bp 50-80° (24 mm); no. 2, 2.7 g, bp 80-95° (24 mm), and 0.8 g of pot residue. A pure sample of trifluoromethylphenylcarbinol, α_D^{28} -0.38° (neat, l = 0.2), was obtained by preparative glpc of Fraction no. 2.

The Grignard Reagent, R-(48), from R-(-)-1-Chloro-4-phenylpentane. The reagent was prepared using R-(-)-chloride, α_D^{27} -7.97° (neat, l = 0.5), (18.2 g, 0.10 mole), triply sublimed magnesium (2.65 g, 0.11 g-atom)and 70 ml dry ether. The clear, homogeneous solution obtained (ca. 80 ml, 1.1 N) was withdrawn directly from the flask with a syringe without filtration.

Reduction of t-Butyl Phenyl Ketone with R-48. t-Butyl phenyl ketone (8.9 g, 0.055 mole) in dry ether (10 ml) was allowed to react with the Grignard reagent, R-48, (50 ml, 1.1 N, 0.055 mole) and stirred for 6 hours. Distillation provided three fractions: no. 1, 3.6 g, bp 50-90° (16 mm); no. 2, 2.6 g, bp 30-55° (0.5 mm); no. 3, 7.2 g, bp 60-80° (0.5 mm); and pot residue, less than one ml.

A sample of pure R-(-)-4-phenyl-1-pentene, α_D^{27} -7.98° (neat, 1 = 0.5) was obtained by preparative glpc (CW-20-M, 150°) of Fraction no. 1. A sample of pure t-butylphenylcarbinol, $[\alpha]_D^{30}$ -2.3°, α_D^{30} -0.127° (c = 10.92, benzene, 1 = 0.5), was obtained by preparative glpc of Fraction no. 3 (CW-20-M, 180°).

Reduction of Trifluoromethyl Phenyl Ketone with R-48. The ketone (4.70 g, 0.027 mole) in dry ether (10 ml) was allowed to react with a solution of R-48 (25 ml, 1.1 N, 0.027 mole) and stirred for 6 hours. Distillation of the products provided two fractions: no. 1, 4.9 g, bp 40-82° (16 mm); no. 2, 2.3 g, bp 82-91° (16 mm), and ca. 0.5 ml of pot residue. A sample of pure trifluoromethylphenylcarbinol, α_D^{28} -0.30° (neat, 1 = 0.2) was obtained by preparative glpc.

Deuterium Labeling Experiments, General. The Grignard reduction reactions were conducted in the usual manner. The weights of distilled products were recorded but in general the yields were not determined. In most cases both of the reduction products, the secondary alcohol and the olefin, were purified by preparative glpc and analyzed for deuterium content by repeated integration on the nmr spectra of the purified samples using peaks due to nondeuterated functions as internal standards. The average values obtained over a specified number of integrations are reported as percentage hydrogen at a particular position. In the case of the olefin, the values have been corrected for small amounts of an impurity, ca. 10% of the corresponding saturated compound, not completely removed by the purification procedure. For the alcohols the carbinol position was analyzed while for the olefins both the nonterminal vinyl and benzyl positions were analyzed.

The Grignard Reagent, (+)-Threo-80, from (+)-Threo-2,3-Dideuterio-1-Chloro-3-phenylbutane. The reagent was prepared from the chloride (22.1 g, 0.13 mole), triply sublimed magnesium (3.30 g, 0.135 g-atom) and ether (100 ml). It was necessary to reflux all of the ingredients for 24 hours to dissolve most of the magnesium and the mixture formed contained large amounts of precipitate. After filtration, a cloudy filtrate was obtained, (122 ml, 0.87 N, 78% yield).

Reduction of t-Butyl Phenyl Ketone with (+)-Threo-80. t-Butyl phenyl ketone (9.50 g, 0.59 mole) in ether (20 ml) was added to the (+)-threo-Grignard reagent (70 ml, 0.87 N, 0.061 mole) and the reaction mixture was stirred for 9 hours. Distillation of the products provided three fractions: no. 1, 2.5 g, bp 50-63° (12 mm); no. 2, 3.0 g, bp 75° (12 mm) to 59° (0.4 mm); no. 3, 2.4 g, bp 60-75° (0.4 mm); and ca. 10 g pot residue. 3-Phenyl-1-butene and t-butylphenylcarbinol were obtained from Fractions no. 1 and no. 3, respectively, by preparative glpc. Integration of the nmr spectra showed that the alcohol contained 47% hydrogen at the carbinol position (20 integrations) while the olefin was found to contain 13% benzyl hydrogen and 70% nonterminal vinyl hydrogen, (20 integrations).

Reduction of Trifluoromethyl Phenyl Ketone with (+)-Threo-80. Trifluoromethyl phenyl ketone (5.80 g, 0.033 mole) in ether (20 ml) was added to the (+)-threo-Grignard reagent (40 ml, 0.87 N, 0.035 mole) and stirred for 9 hours. Distillation of the products provided two fractions: no. 1, 4.1 g, bp 38-75° (11 mm), and no. 2, 4.4 g, bp 75-77° (11 mm). 3-Phenyl-1-butene and trifluoromethylphenylcarbinol were obtained from Fractions no. 1 and no. 2, respectively, by preparative glpc. Integration of the nmr spectra showed that the alcohol contained 63% carbinol hydrogen (30 inte-

grations), while the olefin contained 13% benzyl hydrogen and 50% nonterminal vinyl hydrogen (20 integrations).

The Grignard Reagent,(+)-Erythro-80,from (+)-Erythro-2,3-Dideuterio-1-chloro-3-phenylbutane. The reagent was prepared from the chloride (17.4 g, 0.102 mole), triply sublimed magnesium (2.70 g, 0.11 g-atom) and ether (100 ml). After filtration a slightly cloudy filtrate was obtained, (112 ml, 0.75 N, 76% yield).

Reduction of t-Butyl Phenyl Ketone with (+)-Erythro-(80). t-Butyl phenyl ketone (9.40 g, 0.058 mole) in ether (20 ml) was reacted with the (+) erythro-Grignard reagent (76 ml, 0.75 N, 0.057 mole) and stirred for 9 hours. Distillation of the products provided four fractions: no. 1, 3.1 g, bp 30-60° (10 mm); no. 2, 1.9 g, bp 60° (10 mm) to 59° (0.3 mm); no. 3, 3.7 g, bp 59-75° (0.3 mm) and 7.2 g of pot residue. 3-Phenyl-1-butene and t-butylphenylcarbinol were obtained from Fractions no. 1 and no. 3, respectively, by preparative glpc. Integration of the nmr spectra showed that the alcohol contained 90% carbinol hydrogen (20 integrations), while the olefin contained 15% benzyl hydrogen and 25% nonterminal vinyl hydrogen (20 integrations).

Reduction of Trifluoromethyl Phenyl Ketone with (+)-Erythro-(80). Trifluoromethyl phenyl ketone (4.36 g, 0.025 mole) in ether (10 ml) was added to the (+)-erythro-Grignard reagent (32 ml, 0.75 N, 0.024 mole) and stirred for 9 hours. Distillation of the products provided two fractions: no. 1, 2.6 g, bp 45-71° (10 mm) and no. 2, 3.4 g, bp 71-75° (10 mm). 3-Phenyl-1-butene and trifluoromethylphenylcarbinol were obtained from Fractions no. 1 and no. 2, respectively, by preparative glpc. Integration of the nmr spectra showed that the alcohol contained 68% carbinol hydrogen (20 integrations) while the olefin contained 15% benzyl hydrogen and

4% nonterminal vinyl hydrogen (20 integrations).

The Grignard Reagent, (2S,3R)-Threo-80, from (2S,3R)-(-)-Threo-2,3-Dideuterio-1-chloro-3-phenylbutane. The reagent was prepared from the (-)-chloride, α_D^{26} -77.7° (neat, 1 = 1), (24.0 g, 0.140 mole), triply sublimed magnesium (3.90 g, 0.16 g-atom) and ether (100 ml). Filtration provided a clear solution of the reagent (115 ml, 1.0 N, 75% yield).

Reduction of t-Butyl Phenyl Ketone with (2S,3R)-Threo-80. t-Butyl phenyl ketone (12.3 g, 0.076 mole) in ether (25 ml) was added to the (2S,3R)-threo-Grignard reagent (75 ml, 1.0 N, 0.075 mole) and stirred for 6 hours. Distillation of the products provided two fractions: no. 1, 3.8 g, bp 40-70° (16 mm); no. 2, 5.4 g, bp 58-100° (0.5 mm) and 13.3 g of pot residue. R-(-)-3-Phenyl-1-butene, α_D^{28} -4.00° (neat, 1 = 0.5), and t-butylphenylcarbinol, $[\alpha]_D^{28}$ 0.0°, α_D^{28} 0.00° (c = 10.90, benzene, 1 = 0.5), were obtained by preparative glpc of fractions no. 1 and no. 2, respectively. The t-butylphenylcarbinol was purified by preparative glpc on both CW-20-M (twice) and Apiezon L (once) to insure that it contained no impurities. Integration of the nmr spectrum of the olefin showed that it contained 16% benzyl hydrogen and 74% nonterminal vinyl hydrogen (10 integrations). The olefin was shown by nmr integration to contain 11% 2-phenylbutane.

Reduction of Trifluoromethyl Phenyl Ketone with (2S,3R)-Threo-80. The ketone (8.00 g, 0.046 mole) in ether (10 ml) was added to the (2S,3R)-threo-Grignard reagent (35 ml, 1.0 N, 0.035 mole) and stirred for 6 hours. Distillation of the products provided two fractions: no. 1, 6.8 g, bp 40-80° (16 mm) and no. 2, 4.9 g, bp 80-89° (16 mm). R-(-)-3-Phenyl-1-butene, α_D^{27} -3.29 (neat, 1 = 0.5) and trifluoromethylphenylcarbinol, α_D^{28} +0.53° (neat, 1 = 0.2) were

obtained by preparative glpc of fractions no. 1 and no. 2, respectively. Integration of the nmr spectrum of the olefin showed that it contained 16% benzyl hydrogen and 55% nonterminal vinyl hydrogen (10 integrations). The olefin was shown by nmr integration to contain 5% 2-phenylbutane.

The Grignard Reagent ,(2R,3S)-Threo-80,from (2R,3S)-(+)-Threo-2,3-Dideuterio-1-chloro-3-phenylbutane. The reagent was prepared from the (+)-threo-chloride, α_D^{30} +42.2 (neat, 1 = 1), 50% e.e., (41.0 g, 0.24 mole), triply sublimed magnesium (6.00 g, 0.25 g-atom) and ether (175 ml). Filtration provided a clear solution of the reagent (198 ml, 0.96 N, 79% yield).

Reduction of Isopropyl Phenyl Ketone with (2R,3S)-Threo-80. Isopropyl phenyl ketone (24.0 g, 0.16 mole) in ether (50 ml) was allowed to react with the S-threo-Grignard reagent (170 ml, 0.96 N, 0.16 mole) and stirred for 6 hours. Distillation of the products provided two fractions: no. 1, 2.0 g, bp 50° (16 mm) to 50° (4 mm) (collected in dry ice trap); no. 2, 6.9 g, bp 52-100° (0.5 mm) and 41.4 g of pot residue. S-(+)-3-Phenyl-1-butene, α_D^{28} +0.82° (neat, 1 = 0.2) and isopropylphenylcarbinol, α_D^{26} -0.23° (neat, 1 = 0.1), were obtained by preparative glpc. The isopropylphenylcarbinol was obtained in very low yield and was difficult to purify so that the sample was repeatedly subjected to preparative glpc on CW-20-M until a nearly constant rotation was obtained on two consecutive passes. Integration of the nmr spectrum of the olefin showed that it contained 17% benzyl hydrogen and 68% nonterminal vinyl hydrogen (20 integrations). The olefin was also shown to contain 5% 2-phenylbutane.

The Grignard Reagent,(+)-Threo-58,from (+)-Threo-2,3-Dideuterio-1-chloro-3-phenylpropane. The reagent was prepared from the threo chloride (26.6 g, 0.17 mole), triply

sublimed magnesium (4.5 g, 0.18 g-atom) and ether (125 ml). Filtration provided a clear solution of the reagent (150 ml, 1.0 N, 81% yield).

Reduction of t-Butyl Phenyl Ketone with (+)-Threo-58. t-Butyl phenyl ketone (6.50 g, 0.040 mole) in ether (25 ml) was added to the threo-Grignard (40 ml, 1.0 N, 0.040 mole) and stirred for 6 hours. Distillation of the products provided two fractions: no. 1, 2.5 g, bp 38-42° (10 mm); no. 2, 4.8 g, bp 59-63° (0.4 mm) and ca. 10 g pot residue. 3-Phenyl-1-propene and t-butylphenylcarbinol were obtained by preparative glpc of fractions no. 1 and no. 2, respectively. Integration of the nmr spectra showed that the alcohol contained 71% carbinol hydrogen (20 integrations) and the olefin contained 35% nonterminal vinyl hydrogen (10 integrations).

Reduction of Trifluoromethyl Phenyl Ketone with (+)-Threo-58. Trifluoromethyl phenyl ketone (4.40 g, 0.025 mole) in ether (20 ml) was added to the threo-Grignard reagent (25 ml, 1.0 N, 0.025 mole) and stirred for 6 hours. Distillation of the products provided two fractions: no. 1, 1.8 g, bp 38-66° (11 mm) and no. 2, 3.3 g, bp 67-74° (11 mm). 3-Phenyl-1-propene and trifluoromethylphenylcarbinol were obtained by preparative glpc of Fractions no. 1 and no. 2, respectively. Integration of the nmr spectra showed that the alcohol contained 60% carbinol hydrogen (30 integrations) and the olefin contained 42% nonterminal vinyl hydrogen (10 integrations).

Reduction of Isopropyl Phenyl Ketone with (+)-Threo-58. Isopropyl phenyl ketone (11.8 g, 0.080 mole) in ether (30 ml) was reacted with the threo-Grignard reagent (80 ml, 1.0 N, 0.080 mole) and stirred for 6 hours. Distillation of the products provided three fractions: no. 1, 0.5 g, bp

35-45° (11 mm); no. 2, 0.4 g, bp 70° (11 mm) to 50° (0.4 mm); no. 3, 2.7 g, bp 51-80° (0.4 mm) and pot residue. Isopropylphenylcarbinol was obtained by preparative vpc of Fraction no. 3. Integration of the nmr spectra showed that the alcohol contained 71% carbinol hydrogen (20 integrations).

Meerwein-Ponndorf-Verley Reductions

2-Octyl Hydrogen Phthalate (107) and 1-Phenylethyl Hydrogen Phthalate (108). The hydrogen phthalates were prepared from the corresponding alcohols and phthalic anhydride using the procedure of Houssa and Kenyon.[76] The crude hydrogen phthalates were obtained as solids in nearly quantitative yields and were recrystallized from 60-80° petroleum ether and benzene, respectively, to provide 2-octyl hydrogen phthalate, mp 56-58°, and 1-phenylethyl hydrogen phthalate, mp 107-109°.

R-(-)- and S-(+)-2-Octanol, R- and S-(59). 2-Octyl hydrogen phthalate was resolved by a procedure identical to that described by Vogel[56], except that brucine was replaced by an equimolar amount of R-(+)-α-methylbenzylamine (Norse Chemical Co.). In this manner 2-octyl hydrogen phthalate (100 g, 0.36 mole) provided, after three crystallizations of the enantiomeric hydrogen phthalates from 90% acetic acid, hydrolysis and distillation, (+)- and (-)-2-octanol, $[\alpha]_D^{22}$ ±9.2° (neat), 93% e.e. based on $[\alpha]_D^{20}$ 9.9°[77] (12-13 g, ca. 0.09-0.10 mole).

R-(+)- and S-(-)-1-Phenylethanol, R- and S-(60). 1-Phenylethyl hydrogen phthalate (20 g, 0.45 mole) was resolved by a procedure similar to that of Downer and Kenyon[57] with replacement of brucine by an equimolar amount of R-(+)-α-methylbenzylamine (Norse Chemical Company) (55.0 g, 0.45 mole) and replacement of methyl acetate with 50% aqueous

ethanol for crystallizations of the salt after initial precipitation from acetone. Three crystallizations from 50% aqueous ethanol, (4 ml/g of salt) provided fine white needles, mp 162-163°. This salt was treated in the manner described by Downer and Kenyon to provide R-(+)-1-phenylethanol, $[\alpha]_D^{29}$ +43.4° (neat) (99+% e.e. based on $[\alpha]_D^{17}$ 43.7° (neat))[57], (15.2 g, 0.125 mole).

The mother liquors from all crystallizations were combined, concentrated and hydrolyzed to provide the hydrogen phthalate as a very dark brown, viscous oil which was purified by dissolving in base, extracting with ether and acidifying. The light tan, semi-solid hydrogen phthalate was treated as above to provide S-(-)-1-phenylethanol, $[\alpha]_D^{29}$ -40.5° (neat) (93% e.e.), (11.0 g, 0.090 mole).

S-(+)-1-Cyclohexylethanol, S-(109). The S-alcohol was prepared from S-(-)-1-phenylethanol, α_D^{27} -19.1° (neat, 1 = 0.5), 86% e.e. (12.2 g, 0.10 mole) by hydrogenation in 9:1 methanol-glacial acetic acid using platinum oxide (Engelhard Industries) (0.8 g) as catalyst. On an initial attempt very little reduction occurred, but after isolating and redistilling the 1-phenylethanol, the reduction proceeded smoothly over 24 hours with the uptake of the theoretical amount of hydrogen. The product was isolated as a clear liquid, bp 70-72° (8.6 g, 67% yield) α_D^{22} +1.85° (neat, 1 = 0.5), 70% e.e. based on $[\alpha]_D^{20}$ 5.68° (neat).[14] The IR spectrum of the product showed no absorption due to either aromatic or carbonyl groups.

Diethyl Methylphenylmalonate (49). The ester prepared from diethyl phenylmalonate (Matheson, Coleman and Bell) (132 g, 0.55 mole), methyl iodide (85.3 g, 0.60 mole) and sodium ethoxide.[78] The product was isolated as a clear, colorless liquid, bp 113-114° (0.3 mm), (129.3 g, 93% yield).

(±)-2-Phenylpropanoic Acid, (±)-(61). Diethyl methylphenylmalonate (115 g, 0.46 mole) was saponified by refluxing for 2 hours with aqueous potassium hydroxide. The clear solution obtained was distilled to remove the ethanol formed, acidified and refluxed to decarboxylate the methylphenylmalonic acid. The 2-phenylpropanoic acid was isolated as a clear, colorless liquid, bp 106-110° (0.3 mm) (55.7 g, 80.5% yield), which gave nmr and IR spectra consistent with the expected product.

S-(+)-2-Phenylpropanoic Acid, S-(61). The racemic acid (100 g, 0.67 mole) was resolved as the strychnine salt by crystallization from aqueous ethanol following the procedure of Bakshi and Turner.[58] Repeated crystallizations, obtaining second and third crops from mother liquors and combining crops of similar rotation provided salt, $[\alpha]_D^{23}$ ca. -30.0° ($CHCl_3$), (113.5 g). Hydrolysis of the resolved salt provided S-(+)-2-phenylpropanoic acid, α_D^{27} +94.0° (neat, 1 = 1), (29.1 g, 0.194 mole).

The mother liquors from all crystallizations were combined, concentrated and hydrolyzed. Distillation of the products provided a mixture of ethyl 2-phenylpropanoate and 2-phenylpropanoic acid, bp 81-120° (1 mm), (61.8 g), which was used without further separation to prepare R-(+)-2-phenyl-1-propanol.

S-(-)-2-Phenyl-1-propanol S-(110). The alcohol was prepared by the reduction of S-(+)-2-phenylpropanoic acid, α_D^{27} +94.0° (neat, 1 = 1) (28.0 g, 0.186 mole), with LAH (6.0 g, 0.16 mole) in ether (200 ml). The product was obtained as a clear colorless liquid, bp 65-67° (0.2 mm), $[\alpha]_D^{27}$ -17.3° (neat), 99+% e.e. based on $[\alpha]_D^{24}$ -17.4°[58], (18.8 g, yield 74%).

R-(+)-2-Phenyl-1-propanol, R-(110). The alcohol was obtained by reduction of a distilled mixture of ethyl 2-phenylpropanoate and R-(+)-2-phenylpropanoic acid obtained from the mother liquors of the resolution of 2-phenylpropanoic acid with styrchnine. The mixture (61.8 g, ca. 0.4 mole) was reduced with LAH (13.0 g, 0.34 mole) in ether (200 ml) using a basic hydrolysis. The product was isolated as a clear liquid, bp 80-82° (0.45 mm), $[\alpha]_D^{27}$ +8.00° (neat), 46% e.e., (46.3 g, yield 89%).

S-(-)- and R-(+)-2-Cyclohexyl-1-propanol, S- and R-(111). The alcohols were prepared by hydrogenation of S-(-)- and R-(+)-2-phenyl-1-propanol, respectively. S-(-)-phenyl-1-propanol, $[\alpha]_D^{27}$ -17.34°, 99+% e.e., (9.5 g, 0.070 mole) furnished S-(-)-2-cyclohexyl-1-propanol, bp 65-67° (0.4 mm), α_D^{24} -1.24° (neat, 1 = 1), (6.0 g, 60% yield). R-(+)-2-Phenyl-1-propanol, $[\alpha]_D^{27}$ +8.00°, 46% e.e., (24.4 g, 0.18 mole), provided R-(+)-2-cyclohexyl-1-propanol, bp 66-68° (0.4 mm), α_D^{21} +0.345° (neat, 1 = 0.5), (16.3 g, 63% yield).

S-(+)-2-Phenylbutanoic Acid, S-(62). 2-Phenylbutanoic acid was resolved as the cinchonidine salt using 70% aqueous ethanol following the procedure of Levine and coworkers.[59] Racemic acid (Eastman Organics), (100 g, 0.61 mole) provided, after four recrystallizations, hydrolysis and distillation, S-(+)-2-phenylbutanoic acid as a clear liquid, bp 120-122° (1.0 mm), α_D^{27} +83.9° (neat, 1 = 1), 88% e.e. based on a maximum rotation of $[\alpha]_D^{23}$ +95.8° (neat)[60], (60.5 g, 0.37 mole).

The mother liquors from several cinchonidine resolutions were combined, evaporated and hydrolyzed to furnish R-(-)-2-phenylbutanoic acid, bp 117-118° (0.4 mm), α_D^{25} -58.4° (neat, 1 = 1), 61% e.e.

S-(+)-2-Phenyl-1-butanol, S-(89). The S-alcohol was prepared by the reduction of S-(+)-2-phenylbutanoic acid, α_D^{27} +83.9° (neat, 1 = 1), 88% e.e., (25.0 g, 0.152 mole) with LAH (7.0 g, 0.18 mole) in ether (150 ml) using an acid hydrolysis. The product was isolated as a clear liquid, bp 63-69° (0.4 mm), α_D^{25} +14.9° (neat, 1 = 1), 90% e.e., based on a maximum rotation of $[\alpha]_D^{25}$ +16.5° (neat)[17], (18.4 g, 81% yield).

R-(+)-2-Cyclohexylbutanoic Acid, R-(63). The R-acid was prepared by hydrogenation of R-(-)-2-phenylbutanoic acid, α_D^{25} -58.4° (neat, 1 = 1), 61% e.e., (18.0 g, 0.11 mole) using 100 ml of solvent and 0.5 g of catalyst. The product was obtained as a white solid, mp 48-52°, $[\alpha]_D^{26}$ +0.31° (c = 9.71, 95% ethanol, 1 = 1), (14.3 g, 76% yield).

R-(+)-2-Cyclohexyl-1-butanol, R-(64). The R-alcohol was prepared by reduction of R-(+)-2-cyclohexylbutanoic acid, $[\alpha]_D^{26}$ +0.31° (c = 9.71, ethanol), (13.6 g, 0.08 mole) with LAH (2.8 g, 0.07 mole) in ether (100 ml), using an acid hydrolysis. The R-(+)-2-cyclohexyl-1-butanol was isolated as a clear liquid, bp 72-73° (0.3 mm), α_D^{25} +1.74° (neat, 1 = 0.5), (11.6 g, 93% yield).

R-(+)- and S-(-)-3-Cyclohexyl-1-butanol, R- and S-(112). The alcohols were prepared by hydrogenation of the corresponding 3-phenyl-1-butanols. R-(-)-3-phenyl-1-butanol, α_D^{24} -18.46°, 95% e.e., (neat, 1 = 0.5), (15.0 g, 0.10 mole) provided R-(+)-3-cyclohexyl-1-butanol, bp 75-77° (0.4 mm), α_D^{30} +4.66° (neat, 1 = 0.5), (13.0 g, 83% yield). S-(+)-3-Phenyl-1-butanol, α_D^{27} +10.96° (neat, 1 = 0.5), 59% e.e., (15.0 g, 0.10 mole) provided the S-(-)-enantiomer, bp 115-117° (10 mm), α_D^{26} -2.93° (neat, 1 = 0.5), (13.4 g, 86% yield).

R-(+)-4-Cyclohexyl-1-pentanol, R-(113). The R-alcohol was prepared by hydrogenation of R-(-)-4-phenyl-1-pentanol, α_D^{29} -9.0° (neat, 1 = 0.5), 89% e.e., (10.0 g, 0.061 mole). The product was isolated as a clear liquid, bp 87-89° (0.5 mm), α_D^{28} +4.86° (neat, 1 = 0.5), (9.8 g, 87% yield).

2,2,2-Trifluoro-1-phenylethanol-O,1-d_2, (114). The deuterium labeled alcohol was prepared by hydrogenation of trifluoromethyl phenyl ketone (10.4 g, 0.060 mole) with deuterium using ethyl acetate (150 ml) as solvent and pre-deuterated 5% palladium on carbon as catalyst. Deuterium uptake stopped short of the theoretical amount but no attempt was made to complete the reaction because the two products were easily separable by distillation. The carbinol was isolated as a clear liquid, bp 73-75° (10 mm), (6.0 g, 58% yield), shown by repeated integration of its nmr spectrum to contain 21% hydrogen at the carbinol position (30 integrations).

Reductions of Trifluoromethyl Phenyl Ketone, (13-f)

R-2-Octoxymagnesium Bromide, R-(115), in Ether-Benzene. The alcoholate was prepared in the normal manner from n-propylmagnesium bromide (28 ml, 1.7 N, 0.048 mole), R-(-)-2-octanol, $[\alpha]_D^{22}$ -9.2° (neat), 93% e.e., (6.50 g, 0.050 mole), and dry benzene. Trifluoromethyl phenyl ketone (7.90 g, 0.045 mole) in dry benzene was added and the mixture stirred for 30 minutes. Distillation provided two fractions: no. 1, 3.8 g, bp 40-70° (10 mm), and no. 2, 7.7 g, bp 70-75° (10 mm). Preparative glpc of Fraction no. 2 (CW-20-M only) provided trifluoromethylphenylcarbinol, α_D^{22} -2.10° (neat, 1 = 0.5).

S-1-Cyclohexylethoxymagnesium Bromide, S-(96), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (16 ml, 1.7 N, 0.027 mole), S-(+)-1-cyclohexylethanol, α_D^{22} +1.85° (neat, l = 0.5), 70% e.e. (3.6 g, 0.028 mole) and dry benzene. Trifluoromethyl phenyl ketone (4.50 g, 0.026 mole) in dry benzene was added to provide a cloudy mixture which was then stirred for 16 hours. Distillation provided two fractions: no. 1, 2.1 g, bp 70-78° (10 mm) and no. 2, 4.0 g, bp 78-82° (10 mm). Preparative glpc of Fraction no. 1 (CW-20-M only) provided trifluoromethylphenylcarbinol, α_D^{21} +6.02° (neat, l = 0.5).

R-1-Phenylethoxymagnesium Chloride, R-(116), in Ether-Benzene. The alcoholate was prepared from a solution of t-butylmagnesium chloride in ether (43 ml, 0.68 N, 0.029 mole), R-(+)-1-phenylethanol, α_D^{29} +43.8° (neat, l = 1), 99% e.e. (3.80 g, 0.031 mole) and dry benzene. Trifluoromethyl phenyl ketone (5.20 g, 0.030 mole) in dry benzene was added to provide a suspension of solid; and the mixture was stirred for 1 hour. Distillation of the products provided clear liquid, bp 75-80° (6.5 g), which on preparative glpc (CW-20-M only) furnished trifluoromethylphenylcarbinol, α_D^{23} -4.41° (neat, l = 0.2).

(+)-1-Phenylethoxymagnesium Bromide, (+)-(92), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (28 ml, 1.7 N, 0.048 mole), (+)-1-phenylethanol (6.10 g, 0.050 mole) and dry benzene. Trifluoromethyl phenyl ketone (7.90 g, 0.045 mole) in dry benzene was added to provide a slightly cloudy mixture. An aliquot taken after 15 minutes furnished a crude product mixture whose IR spectrum showed that the reduction was ca. 50% completed. The entire mixture was hydrolyzed after stirring for 60 minutes. The IR spectrum of the crude product mixture obtained showed that

the reduction was essentially completed.

S-1-Phenylethoxymagnesium Bromide, S-(92), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (28 ml, 1.7 N, 0.048 mole), S-(-)-1-phenylethanol, α_D^{27} -19.1° (neat, l = 0.5), 86% e.e., (6.10 g, 0.050 mole) and dry benzene. Trifluoromethyl phenyl ketone (7.90 g, 0.045 mole) in dry benzene was added to give initially a clear solution which deposited a precipitate in ca. 5 minutes. The resulting mixture was stirred for 30 minutes. Distillation of the products provided a clear liquid, bp 72-85° (10 mm), which on preparative glpc (CW-20-M only) furnished trifluoromethylphenylcarbinol, α_D^{27} +2.93° (neat, l = 0.2).

R-1-Phenylethoxymagnesium Bromide, R-(92), in THF-Benzene. The alcoholate was prepared from a solution of n-propylmagnesium bromide in THF (16 ml, 2.0 N, 0.032 mole), R-(+)-1-phenylethanol, α_D^{29} +43.8° (neat, l = 1), (4.00 g, 0.033 mole) and dry benzene. Trifluoromethyl phenyl ketone (5.40 g, 0.031 mole) in dry benzene was added and the mixture was stirred for 2 hours. Distillation provided a clear liquid, bp 80-95° (16 mm), which on preparative glpc (CW-20-M only) furnished trifluoromethylphenylcarbinol, α_D^{27} -3.34° (neat, l . 0.2).

R-1-Phenylethoxymagnesium Iodide, R-(117), in Ether-Benzene. The alcoholate was prepared from a solution of methylmagnesium iodide in ether (14 ml, 2.3 N, 0.032 mole), R-(+)-1-phenylethanol, α_D^{29} +43.8° (neat, l = 1), (4.00 g, 0.033 mole) and dry benzene. Trifluoromethyl phenyl ketone (5.40 g, 0.031 mole) in dry benzene was added and the mixture was stirred for 2 hours. Distillation provided a clear liquid, bp 80-95° (16 mm), and pot residue (ca. 0.5 g). Preparative glpc (CW-20-M only) of the distilled material provided trifluoromethylphenylcarbinol, α_D^{27} -4.73, (neat, l = 0.2).

S-2-Methyl-1-butoxymagnesium Chloride, S-(118), in Ether-Benzene. The alcoholate was prepared from a solution of t-butylmagnesium chloride in ether (33 ml, 0.85 N, 0.028 mole), S-(-)-2-methyl-1-butanol, $[\alpha]_D^{26}$ -5.76°, (neat), 98% e.e. based on $[\alpha]_D^{20}$ -5.9° (neat)[82], (2.60 g, 0.030 mole) and dry benzene. Trifluoromethyl phenyl ketone (4.50 g, 0.026 mole) in dry benzene was added and the mixture was stirred for 16 hours. Distillation provided a clear liquid, bp 50-75° (10 mm), which on preparative glpc furnished trifluoromethylphenylcarbinol, α_D^{22} -1.60° (neat, l = 0.5).

S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in Ether-Benzene; 1 Hour. The alcoholate was prepared from n-propylmagnesium bromide (30 ml, 1.6 N, 0.048 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, l = 0.5), 98% e.e., (4.40 g, 0.050 mole), and dry benzene. Trifluoromethyl phenyl ketone (8.5 g, 0.048 mole) in dry benzene was added and the mixture was stirred for 60 minutes. The IR spectrum of the crude product mixture indicated ca. 50% reduction had occurred. Distillation provided three fractions: no. 1, 0.5 g, bp 122-130° (atm.); no. 2, 2.8 g, bp 30-70° (10 mm); and no. 3, 3.6 g, bp 73-95° (10 mm), α_D^{20} -0.95° (neat, l = 0.5). Preparative glpc of Fraction no. 3 provided trifluoromethylphenylcarbinol, α_D^{21} -1.03° (neat, l = 0.5).

S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in Ether-Benzene; 26 Hours. The alcoholate was prepared from n-propylmagnesium bromide (28 ml, 1.7 N, 0.048 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, l = 0.5), 98% e.e., (4.40 g, 0.050 mole) and dry benzene. Trifluoromethyl phenyl ketone (7.80 g, 0.045 mole) in dry benzene was added and the mixture was stirred for 26 hours. Distillation of the products provided 5.4 g of material, bp 73-75° (10 mm), α_D^{21} -1.02° (neat, l = 0.5), which on preparative glpc

furnished trifluoromethylphenylcarbinol, α_D^{19} -1.10° (neat, 1 = 0.5).

S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in Ether. The alcoholate was prepared from n-propylmagnesium bromide (18 ml, 1.7 N, 0.030 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e., (2.70 g, 0.031 mole) and dry ether in place of benzene to give a slightly cloudy mixture. Trifluoromethyl phenyl ketone (5.00 g, 0.029 mole) in dry ether was added to give a clear solution which slowly formed a precipitate. The mixture was stirred for 16 hours. Distillation provided 4.3 g of clear liquid, bp 50-85° (10 mm) and pot residue (ca. 1 g). Preparative glpc of the distilled products furnished trifluoromethylphenylcarbinol, α_D^{22} -0.96° (neat, 1 = 0.5).

S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in Ether; Low Temperature. The alcoholate was prepared from n-propylmagnesium bromide (20 ml, 0.18 N, 0.036 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35 (neat, 1 = 0.5), 98% e.e., (4.30 g, 0.038 mole) and dry ether. The apparatus was placed in a dry ice-acetone bath and stirred for ca. 30 min. while a solution of trifluoromethyl phenyl ketone (6.10 g, 0.035 mole) and dry ether was cooled in the same bath in a flask fitted with a septum. Both solutions were clear and homogeneous when equilibrated. The ketone solution was injected into the alcoholate using a cold nitrogen-flushed syringe to provide a clear solution which was stirred for 60 hours at ca. -78°. The mixture was hydrolyzed by slowly passing a large excess of gaseous hydrogen chloride into the flask with cooling. The mixture was warmed to room temperature, water was added and it was worked up in the normal manner. The IR spectrum of the crude product mixture showed a negligible amount of trifluoromethylphenylcarbinol. Distil-

lation provided two fractions: no. 1, 6.2 g, bp 30-50° (12 mm) and no. 2, 1.7 g, bp 50-85° (12 mm). Analytical glpc of fraction no. 2 showed mostly (>95%) unreacted ketone and only a trace of trifluoromethylphenylcarbinol which was insufficient for isolation.

S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in Ether; Attempted Preparation of Aldehyde. The alcoholate was prepared from n-propylmagnesium bromide (60 ml, 1.8 N, 0.10 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e., (9.20 g, 0.105 mole) and dry ether. Trifluoromethyl phenyl ketone (21.0 g, 0.120 mole) in dry ether was added to furnish a clear solution which slowly formed a precipitate during the 10 hours the mixture was stirred. Distillation of the products at atmospheric pressure provided a mixture of 2-methyl-1-butanol and 2-methylbutanal containing mostly the former, although the latter could be detected in the IR spectrum.

S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in "Benzene". The alcoholate was prepared from n-propylmagnesium bromide (16 ml, 1.7 N, 0.027 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5, 98% e.e., (2.5 g, 0.028 mole) and dry benzene. The mixture was distilled to bp 80-81° and distillation continued at this temperature until ca. 10 ml of distillate had been collected. The mixture was cooled and trifluoromethyl phenyl ketone (4.50 g, 0.026 mole) in benzene was added to provide a slightly cloudy mixture which was stirred for 16 hours. Distillation of the products provided 3.6 g of clear liquid, bp 50-78° (10 mm), which on preparative glpc furnished trifluoromethylphenylcarbinol, α_D^{22} -0.65° (neat, 1 = 0.5).

S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in Diisopropyl Ether-Benzene. The alcoholate was prepared from a solution of n-propylmagnesium bromide in diisopropyl ether (20 ml, 1.1 N, 0.22 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e., (2.10 g, 0.024 mole) and dry benzene. Trifluoromethyl phenyl ketone (3.6 g, 0.021 mole) in dry benzene was added to provide a total volume of ca. 45 ml and the mixture stirred for 16 hours. Distillation of the products provided 2.6 g of clear liquid, bp 50-77° (10 mm), which on preparative glpc furnished trifluoromethylphenylcarbinol, α_D^{22} -0.74° (neat, 1 = 0.5).

S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in THF-Benzene. The alcoholate was prepared from a solution of n-propylmagnesium bromide in THF (22 ml, 1.8 N, 0.040 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e., (3.70 g, 0.042 mole) and dry benzene. The mixture was distilled to bp 70° to provide a suspension of white precipitate in a clear solution at room temperature. Trifluoromethyl phenyl ketone (6.60 g, 0.038 mole) in dry benzene was added to furnish a translucent mixture which became clearer during the 16 hours it was stirred. Distillation of the products provided 6.3 g of clear liquid, bp 70-77° (11 mm), which on preparative glpc furnished trifluoromethylphenylcarbinol, α_D^{21} +0.20° (neat, 1 = 0.5).

S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in Dimethoxyethane-Benzene. A solution of n-propylmagnesium bromide in DME (55 ml, 0.44 N, 0.024 mole) was concentrated to a volume of ca. 15 ml by distillation. The alcoholate was prepared from this solution using S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e., (2.20 g, 0.025 mole), and dry benzene. Trifluoromethyl phenyl ketone (4.00 g, 0.023 mole) in dry benzene was added to provide a slightly

cloudy solution which slowly became clear and then turned cloudy again. The mixture was stirred for 16 hours at room temperature. Distillation of the products provided 3.8 g of liquid, bp 70-80° (10 mm), which on preparative glpc furnished trifluoromethylphenylcarbinol, α_D^{23} +0.37° (neat, 1 = 0.5).

S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in S-(-)-2-Methyl-1-butanol-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (28 ml, 1.7 N, 0.048 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e., (22.0 g, 0.25 mole) and benzene. The mixture was distilled to bp 80° to remove ether and cooled to provide a viscous, translucent liquid. Trifluoromethyl phenyl ketone (7.80 g, 0.045 mole) in dry benzene was added to provide a fluid, translucent mixture which became clear and then turned translucent in ca. one-half hour. The reaction mixture was stirred for 16 hours. Distillation provided three fractions: no. 1, 13.5 g, bp 125-130° (1 atm); no. 2, 1.2 g, bp 30-75° (10 mm) and no. 3, 8.8 g of liquid, bp 75-80° (10 mm). Preparative glpc of Fraction no. 3 provided trifluoromethylphenylcarbinol, α_D^{27} +0.08° (neat, 1 = 0.2).

S-2-Methyl-1-butoxymagnesium Iodide, S-(119), in Ether-Benzene. The alcoholate was prepared from a solution of methylmagnesium iodide in ether (25 ml, 1.6 N, 0.040 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35°, (neat, 1 = 0.5), 98% e.e., (3.70 g, 0.041 mole) and dry benzene. Trifluoromethyl phenyl ketone (6.80 g, 0.039 mole) in dry benzene was added to give a clear solution which slowly formed a precipitate during the 16 hours the mixture was stirred. Distillation provided 3.9 g of clear liquid, bp 65-75° (10 mm), and ca. 1 ml of pot residue. Preparative glpc of the distilled products provided trifluoromethylphenylcarbinol, α_D^{23} -0.58° (neat, 1 = 0.5).

Di-(S-2-Methyl-1-butoxy)magnesium, S-(120), in "Toluene". The alcoholate was prepared by adding S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e, (3.70 g, 0.042 mole) in dry toluene to a solution of dimethoxymagnesium prepared by reacting singly sublimed magnesium (0.50 g, 0.020 g-atom) with a large excess of anhydrous methanol, adding toluene and distilling most of the methanol. The alcoholate mixture was distilled to 110° (1 atm) and 10 ml of material collected at this temperature to remove loosely bound methanol and furnish a suspension of a solid in a clear liquid phase. Trifluoromethyl phenyl ketone (7.00 g, 0.040 mole) in dry toluene was added to give a suspension of solid which slowly dissolved to provide a clear, homogeneous solution during the 16 hours the mixture was stirred. Distillation of the products provided 6.6 g of clear liquid, bp 85-90° (12 mm), which on preparative glpc furnished trifluoromethylphenylcarbinol, α_D^{24} +0.45° (neat, 1 = 0.5).

S-2-Methyl-1-butoxylithium, S-(121), in Ether-Benzene. The alcoholate was prepared from an unfiltered solution of n-butyllithium in ether which contained appreciable amounts of solids (36 ml, 1.1 N, 0.040 mole), S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e., (3.70 g, 0.042 mole) and dry benzene to give a suspension of precipitate. Trifluoromethyl phenyl ketone (6.80 g, 0.039 mole) in dry benzene was added and the suspension obtained was stirred for 20 hours. An IR spectrum of the crude product mixture showed that very little reduction had taken place. Distillation of the products provided 1.3 g of clear liquid, bp 50-75° (10 mm), which on preparative glpc (CW-20-M only) furnished trifluoromethylphenylcarbinol, α_D^{23} 0.00° (neat, 1 = 0.5), (total of 0.55 ml of alcohol was obtained from the entire sample).

S-2-Methyl-1-butoxysodium, S-(122), in Ether-Benzene. The alcoholate was prepared from S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e.,(4.55 g, 0.052 mole), freshly cut sodium (0.90 g, 0.039 g-atom), ether and benzene to give a clear solution containing a small amount of undissolved sodium even after stirring at room temperature for 8 hours and refluxing for several hours. Trifluoromethyl phenyl ketone (6.60 g, 0.038 mole) in dry benzene was added to provide a cloudy mixture which was stirred for 16 hours. The IR spectrum of the crude product mixture showed that very little reduction had taken place. Distillation of the products provided 0.7 g of liquid, bp 70-75° (10 mm) which on preparative glpc (CW-20-M only) furnished trifluoromethylphenylcarbinol, α_D^{24} 0.00° (neat, 1 = 0.2).

S-2-Methyl-1-butoxysodium, S-(122), in Benzene. The alcoholate was prepared from S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e.,(4.40 g, 0.050 mole), freshly cut sodium (1.10 g, 0.048 g-atom) and dry benzene. The mixture obtained contained a very small amount of undissolved sodium even after stirring at room temperature for 6 hours and refluxing for 12 hours. Trifluoromethyl phenyl ketone (8.00 g, 0.046 mole) in dry benzene was added and the mixture was stirred for 20 hours during which time the sodium dissolved. The IR spectrum of the crude product mixture showed that very little reduction had taken place. Distillation of the products provided 1.1 g of liquid, bp 50-78° (10 mm), which on preparative glpc (CW-20-M only) furnished trifluoromethylphenylcarbinol, α_D^{24} -0.04° (neat, 1 = 0.2).

S-2-Methyl-1-butoxysodium, S-(122), in Toluene. The alcoholate was prepared from S-(-)-2-methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e., (3.70 g, 0.042 mole), sodium methoxide (Fisher Scientific, Purified) (2.24 g, 0.041

mole) and dry toluene. The mixture was distilled to bp 110° (1 atm) to remove any loosely bound methanol and furnish a suspension of precipitate. Trifluoromethyl phenyl ketone (7.00 g, 0.040 mole) in toluene was added and the resulting suspension stirred for 20 hours. The IR spectrum of crude products showed that little if any reduction had occurred. Distillation of the products provided 0.3 g of liquid, bp 50-85° (12 mm), which contained insufficient trifluoromethylphenylcarbinol for isolation or characterization.

Tri(S-2-Methyl-1-butoxy)aluminum, S-(123), in Toluene. A solution of crude trimethoxyaluminum was prepared from aluminum foil (0.40 g, 0.015 g-atom) and excess methanol. Dry toluene was added and the resulting suspension of dark gray solid was distilled to remove most of the methanol. S-(-)-2-Methyl-1-butanol, α_D^{26} -2.35° (neat, 1 = 0.5), 98% e.e., (3.70 g, 0.042 mole) in dry toluene was added and the gray suspension distilled to bp 110° (1 atm) to remove any loosely bound methanol. Trifluoromethyl phenyl ketone (7.00 g, 0.040 mole) in dry toluene was added and the suspension was stirred for 26 hours during which time the solid slowly turned white. The IR spectrum of the crude product mixture showed that only a small amount of reduction had occurred. Distillation of the products provided ca. 0.6 g of liquid, bp 55-90° (12 mm), which on preparative glpc (CW-20-M only) furnished trifluoromethylphenylcarbinol, α_D^{24} +0.015° (neat, 1 = 0.1).

S-2-Cyclohexyl-1-propoxymagnesium Bromide, S-(124), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (16 ml, 1.8 N, 0.029 mole), S-(-)-2-cyclohexyl-1-propanol, α_D^{24} -1.24° (neat, 1 = 1), (4.30 g, 0.030 mole) and dry benzene. Trifluoromethyl phenyl ketone (4.85 g, 0.028 mole) in dry benzene was then added and the

mixture was stirred for 16 hours. Distillation of the products provided 6.9 g of liquid, bp 70-80° (10 mm) and pot residue (0.7 g). Preparative glpc of the distilled products provided trifluoromethylphenylcarbinol, α_D^{23} -1.77° (neat, 1 = 0.2).

R-2-Cyclohexyl-1-propoxymagnesium Bromide, R-(124), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (16 ml, 1.7 N, 0.027 mole), R-(+)-2-cyclohexyl-1-propanol, α_D^{21} +0.345° (neat, 1 = 0.5), (4.00 g, 0.028 mole) and dry benzene. Trifluoromethyl phenyl ketone (4.50 g, 0.026 mole) in dry benzene was added and the mixture was stirred for 16 hours. Distillation provided 5.9 g of liquid, bp 50-80° (10 mm), which on preparative glpc furnished trifluoromethylphenylcarbinol, α_D^{23} +2.16° (neat, 1 = 0.5).

R-2-Cyclohexyl-1-butoxymagnesium Bromide, R-(125), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (17 ml, 1.7 N, 0.029 mole), R-(+)-2-cyclohexyl-1-butanol, α_D^{25} +1.74° (neat, 1 = 0.5), (4.70 g, 0.030 mole) and dry benzene. Trifluoromethyl phenyl ketone (4.90 g, 0.028 mole) in dry benzene was added and the mixture was stirred for 16 hours. Distillation provided three fractions: no. 1, 2.2 g, bp 77-82° (10 mm); no. 2, 3.7 g, bp 82-100° (10 mm); no. 3, 2.3 g, bp 100-110° (10 mm) and ca. 1 ml of pot residue. Preparative glpc of Fraction no. 1 provided trifluoromethylphenylcarbinol, α_D^{24} +0.51° (neat, 1 = 0.2).

S-2-Phenyl-1-propoxymagnesium Bromide, S-(97), in Ether-Benzene. The alcoholate was prepared from n-propyl magnesium bromide (25 ml, 1.7 N, 0.042 mole), S-(-)-2-phenyl-1-propanol $[\alpha]_D^{27}$ -17.3° (neat, 1 = 1), 99+% e.e., (6.00 g, 0.044 mole) and dry benzene. Trifluoromethyl

phenyl ketone (7.00 g, 0.040 mole) in dry benzene was added and the reaction mixture was stirred for 16 hours. Distillation provided three fractions: no. 1, 1.8 g, bp 70-77° (10 mm); no. 2, 4.4 g, bp 77-84° (10 mm) and no. 3, 3.5 g, bp 85-95° (10 mm). Preparative glpc of Fraction no. 1 provided trifluoromethylphenylcarbinol, α_D^{24} -0.175° (neat, 1 = 0.2).

R-2-Phenyl-1-propoxymagnesium Bromide, R-(97), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (30 ml, 1.6 N, 0.048 mole), R-(+)-2-phenyl-1-propanol, $[\alpha]_D^{27}$ +8.0° (neat, 1 = 1), 46% e.e. (7.50 g, 0.055 mole) and dry benzene. Trifluoromethyl phenyl ketone (8.50 g, 0.048 mole) in dry benzene was added and the mixture was stirred for 60 minutes. Distillation provided three fractions: no. 1, 3.3 g, bp 41-52° (11 mm), no. 2, 3.2 g, bp 52-88° (11 mm), α_D^{26} -9.11° (neat, 1 = 0.5), and no. 3, 5.0 g, bp 88-100° (11 mm). Preparative glpc of Fraction no. 2 furnished trifluoromethylphenylcarbinol, α_D^{25} +0.23° (neat, 1 = 0.2) and a crude sample of 2-phenylpropanal, α_D 0.0° (neat, 1 = 0.1).

R-2-Phenyl-1-propoxymagnesium Bromide, R-(97), in THF-Benzene. The alcoholate was prepared from a solution of n-propylmagnesium bromide in THF (16 ml, 2.0 N, 0.032 mole), R-(+)-2-phenyl-1-propanol, $[\alpha]_D^{27}$ +8.0°, 46% e.e., (4.62 g, 0.034 mole) and dry benzene. Trifluoromethyl phenyl ketone (5.40 g, 0.031 mole) in dry benzene was added and the mixture was stirred for 16 hours. Distillation provided 4.8 g of liquid, bp 80-95° (16 mm), and ca. 4 g of pot residue. Preparative glpc of the distilled products furnished trifluoromethylphenylcarbinol, α_D^{28} -0.045° (neat, 1 = 0.2).

R-2-Phenyl-1-propoxymagnesium Iodide, R-(98), in Ether-Benzene. The alcoholate was prepared from a solution of methylmagnesium iodide in ether (14 ml, 2.3 N, 0.032 mole), R-(+)-2-phenyl-1-propanol, $[\alpha]_D^{27}$ +8.0° (neat, 1 = 1), 46% e.e., (4.62 g, 0.034 mole) and dry benzene. Trifluoromethyl phenyl ketone (5.40 g, 0.031 mole) in dry benzene was added to furnish a clear solution which formed a precipitate while being stirred for 16 hours. Distillation provided 4.8 g of material, bp 80-100° (16 mm), and ca. 4 g of pot residue. Preparative glpc of the distilled products provided trifluoromethylphenylcarbinol, α_D^{28} +0.345° (neat, 1 = 0.2).

(±)-2-Phenyl-1-butoxymagnesium Bromide, (±)-(90), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (47 ml, 1.6 N, 0.075 mole), (±)-2-phenyl-1-butanol, (12.0 g, 0.08 mole) and dry benzene. Trifluoromethyl phenyl ketone (7.0 g, 0.04 mole) in benzene was added to provide ca. 80 ml of a clear, homogeneous solution. Aliquots were withdrawn from the solution by syringe after 1, 4 and 16 hours and hydrolyzed with ammonium chloride solution. IR spectra of the crude products obtained from the aliquots showed that the reaction proceeded at a conveniently slow rate and was essentially complete after 16 hours. The remainder of the reaction mixture was hydrolyzed after 24 hours. Distillation provided only a few drops of material, bp $<$ 70° (10 mm); 4.1 g of liquid, bp 72-80° (10 mm), shown by its IR spectrum to be nearly pure trifluoromethylphenylcarbinol; and ca. 8 ml of clear, liquid pot residue. Preparative glpc (CW-20-M only) of the distilled products provided a sample of trifluoromethylphenylcarbinol, $[\alpha]_D^{24}$ 0.00° (neat, 1 = 0.5) which contained much less than 1% of any impurity detectable by analytical glpc.

S-2-Phenyl-1-butoxymagnesium Bromide, S-(90), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (31 ml, 1.6 N, 0.050 mole), S-(+)-2-phenyl-1-butanol, α_D^{25} +14.9°, 90% e.e., (8.25 g, 0.055 mole) and dry benzene. Trifluoromethyl phenyl ketone (8.50 g, 0.048 mole) in dry benzene was added to provide a clear solution which formed a precipitate while the reaction mixture was stirred for 60 minutes. Distillation provided four fractions: no. 1, 2.3 g, bp 32-70° (10 mm); no. 2, 3.2 g, bp 70-90° (10 mm), α_D^{27} +11.0° (neat, 1 = 0.5); no. 3, 1.3 g, bp 90-105° (10 mm) and no. 4, 3.9 g, bp 86-90° (1 mm). Preparative glpc of Fraction no. 2 provided trifluoromethylphenylcarbinol, α_D^{26} -0.80° (neat, 1 =0.2) and a sample of 2-phenylbutanal, α_D^{27} 0.00° (neat, 1 = 0.1). Preparative glpc (CW-20-M, 180°) of Fraction no. 4 provided S-(+)-2-phenyl-1-butanol, α_D^{27} +2.85° (neat, 1 = 0.2).

S-3-Phenyl-1-butoxymagnesium Chloride, S-(126), in Ether-Benzene. The alcoholate was prepared from a solution of t-butylmagnesium chloride in ether (60 ml, 0.68 N, 0.041 mole), S-(+)-3-phenyl-1-butanol, α_D^{27} +11.0° (neat, 1 = 0.5), 57% e.e., (6.30 g, 0.042 mole) and dry benzene. Trifluoromethyl phenyl ketone (7.00 g, 0.040 mole) in dry benzene was added and the mixture was stirred for 16 hours. Distillation provided two fractions: no. 1, 3.5 g, bp 70-80° (10 mm); no. 2, 2.7 g, bp 80-100° (10 mm) and pot residue (ca. 3 g). Preparative glpc of Fraction no. 1 provided trifluoromethylphenylcarbinol, α_D^{23} +0.76° (neat, 1 = 0.5).

S-3-Phenyl-1-butoxymagnesium Bromide, S-(127), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (50 ml, 1.6 N, 0.078 mole), S-(+)-3-phenyl-1-butanol, α_D^{27} +11.0°, (neat, 1 = 0.5), 57% e.e., (12.0 g, 0.080 mole) and dry benzene. While the solvent

composition was being adjusted, the mixture was inadvertently distilled to bp 65° to give a cloudy solution which became clear on adding dry ether and remained clear on redistilling to bp 56°. Trifluoromethyl phenyl ketone (13.2 g, 0.075 mole) in dry benzene was added and the mixture was stirred for 60 minutes. Distillation of the products provided four fractions: no. 1, 3.1 g, bp 32-65° (10 mm); no. 2, 5.5 g, bp 68-74° (10 mm); no. 3, 1.6 g, bp 75-110° (10 mm); no. 4, 5.1 g, bp 112-115° (10 mm) and ca. 5 ml pot residue. Preparative glpc (CW-20-M only) of Fraction no. 2 provided trifluoromethylphenylcarbinol, α_D^{25} +2.07° (neat, 1 = 0.5).

R-3-Phenyl-1-butoxymagnesium Bromide, R-(127), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (20 ml, 1.8 N, 0.036 mole), R-(-)-3-phenyl-1-butanol, α_D^{24} -18.46° (neat, 1 = 0.5), 95% e.e., (5.70 g, 0.038 mole) and dry benzene. Trifluoromethyl phenyl ketone (6.10 g, 0.035 mole) in benzene was added and the mixture stirred for 16 hours. Distillation provided two fractions: no. 1, 3.9 g, bp 75-85° (14 mm); no. 2, 1.8 g, bp 50-85° (1 mm) and pot residue (3.4 g). Preparative glpc of Fraction no. 1 provided trifluoromethylphenylcarbinol, α_D^{24} -4.04° (neat, l = 0.5).

R-3-Phenyl-1-butoxymagnesium Bromide, R-(127), in THF-Benzene. The alcoholate was prepared from a solution of n-propylmagnesium bromide in THF (16 ml, 2.0 N, 0.032 mole), R-(-)-3-phenyl-1-butanol, α_D^{24} -18.46° (neat, 1 = 0.5), 95% e.e., (5.10 g, 0.034 mole) and dry benzene. Trifluoromethyl phenyl ketone (5.40 g, 0.031 mole) in dry benzene was added and the mixture was stirred for 16 hours. Distillation of the products provided 4.8 g of liquid, bp 70-85° (16 mm) and 5.4 g of pot residue. Preparative glpc of the distilled material provided trifluoromethylphenylcarbinol, α_D^{28} -0.66° (neat, 1 = 0.2).

R-3-Phenyl-1-butoxymagnesium Iodide, R-(128), in Ether-Benzene. The alcoholate was prepared from a solution of methylmagnesium iodide in ether (14 ml, 2.3 N, 0.032 mole), R-(-)-3-phenyl-1-butanol, α_D^{24} -18.46° (neat, 1 = 0.5), 95% e.e., (5.10 g, 0.034 mole) and dry benzene. Trifluoromethyl phenyl ketone (5.40 g, 0.031 mole) in dry benzene was added to provide a clear solution which formed a precipitate during the 16 hours the mixture was stirred. Distillation provided 4.7 g of liquid, bp 70-100° (16 mm), and 5.1 g of pot residue. Preparative glpc of the distilled products provided trifluoromethylphenylcarbinol, α_D^{27} -1.92° (neat, 1 = 0.2).

S-3-Cyclohexyl-1-butoxymagnesium Bromide, S-(129), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (28 ml, 1.7 N, 0.048 mole), S-(-)-3-cyclohexyl-1-butanol, α_D^{26} -2.93° (neat, 1 = 0.5), (7.80 g, 0.050 mole) and dry benzene to provide a heterogeneous mixture. Trifluoromethyl phenyl ketone (7.90 g, 0.045 mole) in benzene was added to furnish a suspension of solid which gradually dissolved to provide a clear, homogeneous solution during the 60 minute reaction time. Distillation of the products provided four fractions: no. 1, 0.7 g, bp 38-72° (10 mm); no. 2, 2.6 g, bp 74-84° (10 mm); no. 3, 4.4 g, bp 84-90° (10 mm) and no. 4, 2.8 g , bp 100-110° (10 mm). Preparative glpc of Fraction no. 2 provided trifluoromethylphenylcarbinol, α_D^{24} -1.51° (neat, 1 = 0.5).

R-3-Cyclohexyl-1-butoxymagnesium Iodide, R-(130), in Ether-Benzene. The alcoholate was prepared from a solution of methylmagnesium iodide in ether (14 ml, 2.3 N, 0.032 mole), R-(+)-3-cyclohexyl-1-butanol, α_D^{30} +4.66° (neat, 1 = 0.5), (5.30 g, 0.034 mole) and dry benzene. Trifluoromethyl phenyl ketone (5.40 g, 0.031 mole) in benzene was added to provide a clear solution which became cloudy during the 16 hours the

mixture was stirred. Distillation provided 4.3 g, bp 50-95° (16 mm), and ca. 5 g of pot residue. Preparative glpc of the distilled products furnished trifluoromethylphenylcarbinol, α_D^{28} +0.54° (neat, 1 = 0.2).

R-4-Phenyl-1-pentoxymagnesium Bromide, R-(131), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (19 ml, 1.6 N, 0.030 mole), R-(-)-4-phenyl-1-pentanol, α_D^{29} -9.0° (neat, 1 = 0.5), (5.10 g, 0.031 mole) and benzene. Trifluoromethyl phenyl ketone (5.00 g, 0.029 mole) in dry benzene was added and the mixture was stirred for 16 hours. Distillation of the products provided two fractions: no. 1, 0.6 g, bp 40-80° (16 mm); no. 2, 3.5 g, bp 80-100° (16 mm); and ca. 5 g of pot residue. Preparative glpc of Fraction no. 2 provided trifluoromethylphenylcarbinol, α_D^{27} +0.25° (neat, 1 = 0.2).

R-4-Cyclohexyl-1-pentoxymagnesium Bromide, R-(132), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (20 ml, 1.6 N, 0.032 mole), R-(+)-4-cyclohexyl-1-pentanol, α_D^{28} +4.86° (neat, 1 = 0.5), (5.80 g, 0.034 mole), and dry benzene. Trifluoromethyl phenyl ketone (5.40 g, 0.031 mole) in dry benzene was added and the reaction mixture was stirred for 16 hours. Distillation of the products provided two fractions: no. 1, 0.9 g, bp 30-80° (16 mm); no. 2, 6.5 g, bp 80-105° (16 mm) and ca. 7 g of pot residue. Preparative glpc of Fraction no. 2 provided trifluoromethylphenylcarbinol, α_D^{28} -0.065° (neat, 1 = 0.2).

Reductions of Other Carbonyl Compounds

2-Methylbutanal with 2,2,2-Trifluoro-1-phenylethoxymagnesium Bromide-1-d, (94), in Ether-Benzene. The alcoholate was prepared from 2,2,2-trifluoro-1-phenylcarbinol-0,1-d_2, (5.00 g, 0.0284 mole) containing 21% hydrogen at the carbinol

position, n-propylmagnesium bromide (18 ml, 1.7 N, 0.030 mole) and dry benzene. 2-Methyl-1-butanal (Aldrich Chemical Co.) (4.90 g, 0.057 mole) in dry benzene was added and the mixture was stirred for 36 hours. The IR spectrum of the crude product mixture showed that both trifluoromethylphenylcarbinol and 2-methylbutanol were present. Distillation of the products provided 4.3 g of liquid, bp 70-76° (10 mm), which on preparative glpc furnished a sample of trifluoromethylphenylcarbinol which was shown by repeated integration of its nmr spectrum to contain 25% hydrogen at the carbinol position (30 integrations).

t-Butyl Phenyl Ketone with S-2-Methyl-1-butoxymagnesium Bromide, S-(93), in Ether-Benzene. The alcoholate was prepared from n-propylmagnesium bromide (30 ml, 1.7 N 0.051 mole), S-(-)-2-methyl-1-butanol, α_D^{25} -1.65° (neat, 1 = 1), 34% e.e., (4.85 g, 0.055 mole) and dry benzene. t-Butyl phenyl ketone (8.1 g, 0.050 mole) in dry benzene was added to provide ca. 80 ml of a clear, homogeneous solution. Aliquots of the solution were withdrawn by syringe after the mixture had been stirred for 2 hours, 6 hours, 24 hours, 2 days and 2 weeks. Each aliquot was hydrolyzed and the crude products analyzed by IR and analytical glpc. After two weeks at room temperature only ca. 3% reduction had occurred. The mixture was then heated at reflux for 2 days, hydrolyzed and worked up in the normal manner. Analytical glpc showed that ca. 20% reduction had taken place. The crude products were subjected to preparative glpc (CW-20-M, 180°, only) to provide a sample of t-butylphenylcarbinol, $[\alpha]_D^{28}$ -0.23°, α_D^{28} -0.060° (c = 26.20, benzene, 1 = 0.5).

Isopropyl Phenyl Ketone with (+)-2-Phenyl-1-butoxymagnesium Bromide, (+)-(90), in Ether-Benzene. The alcoholate was prepared from a solution of ethylmagnesium bromide in ether (ca. 0.05 mole), (+)-2-phenyl-1-butanol

(7.50 g, 0.050 mole) and dry benzene. By trial and error it was determined that a mixture of benzene and ether (ca. 5:1) provided a clear solution of alcoholate, while addition of either of the pure solvents led to precipitation. Isopropyl phenyl ketone (7.4 g, 0.050 mole) in 5:1 benzene-ether was added, and the homogeneous mixture was allowed to stand under nitrogen for three days. Distillation of the products provided 13.6 g of liquid, bp 57-68° (0.3 mm), which contained isopropylphenylcarbinol detectable by analytical glpc.

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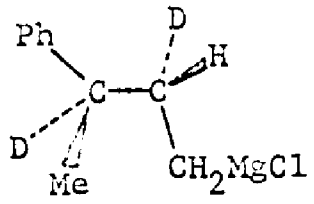
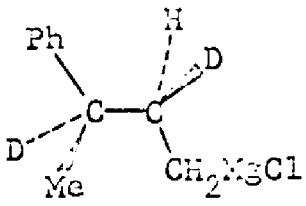
SUMMARY

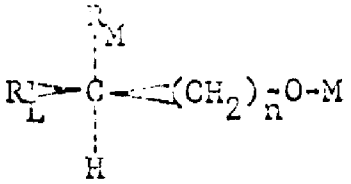
Long range asymmetric reductions of representative alkyl phenyl ketones by γ- and δ-asymmetric Grignard reagents prepared from optically active 1-halo-3-phenylbutanes and 1-chloro-4-phenylpentane were studied. The "normal" deuterium isotope effects for these reductions were determined. The stereochemical behavior of the diastereotopic hydrogens transferred from the β-carbon during γ-asymmetric Grignard reductions was studied by means of stereospecifically deuterium labeled reagents of the type:





A clear preference for the reaction of one of the hydrogens was detected, and the degree of preference was found to depend upon the particular ketone reduced. A stereochemical model for γ-asymmetric Grignard reductions is discussed which can be used to rationalize the experimentally observed results of these reactions.

Trifluoromethyl phenyl ketone was shown to undergo a facile and essentially irreversible Meerwein-Ponndorf-Verley reduction with magnesium alcoholates but not with salts of aluminum, sodium or lithium. This ketone was reduced with a number of chiral alcoholates of the type:



n = 0,1,2,3

M = Metal or Substituted Metal

The effect of solvent, length of the methylene chain and substituents on the asymmetric center was studied. In all cases tested these alcoholates provided reduction products with appreciable optical activity.

The anomalous behavior of perfluoroalkyl carbonyl compounds toward reduction is discussed from the standpoint of mechanism, deuterium isotope effects, and stereochemistry. A nonplanar cyclic transition state model is proposed for asymmetric reductions of these compounds.

Widely divergent trends were noted in long range asymmetric reductions by reagents containing aromatic substituents as compared to those containing only saturated substituents. This behavior is discussed in terms of competitive reduction by an equilibrating mixture of intramolecularly complexed and uncomplexed reducing agent of the type shown below.