[CONTRIBUTION FROM THE DEPT. OF CHEMISTRY, UNIVERSITY OF TORONTO]

REACTIONS OF GRIGNARD REAGENTS IN OPTICALLY ACTIVE SOLVENTS[1]

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Many chemists have attempted to prepare optically active substances from inactive reagents by use of an optically active solvent medium. Boyd (1) reduced benzoylformic acid in an aqueous solution of *dextro*-tartaric acid. Walden (2) used active amyl alcohol as a solvent in the hydrolysis of inactive chlorosuccinic acid. Kipping (3) used an alcoholic solution of *dextro*-camphor as a solvent in the benzoin condensation. Wedekind and Wedekind (4) used *dextro*-limonene, *levo*-menthol, and *levo*-chloromethyl menthyl ether as solvents for the addition of allyl iodide to N-methylbenzylaniline. All of these attempts led to optically inactive products.

In none of these instances is the optically active substrate thought to be associated with the inactive reagent to the extent that a coordinative solvent is associated with an organomagnesium compound. This latter favorable type of reagent was examined in 1940 by Betti and Lucchi (5). They reported the isolation of an optically active phenylmethylcarbinol from the reaction between a methyl iodide Grignard reagent and benzaldehyde, using *dextro*-bornyldimethylamine as the solvent. Similar results were reported for the reaction between phenylmagnesium bromide and acetaldehyde in the same solvent.

Tarbell and Paulson (6), in attempting to repeat this work, were unable to prepare a methyl iodide Grignard reagent directly in *dextro*-bornyldimethylamine. By first preparing the Grignard reagent in diethyl ether, and then displacing the ether under a vacuum with bornyldimethylamine, they obtained a suspension of the Grignard reagent in the active amine. While an optically active substance could subsequently be isolated, it evidently involved the solvent, since it was produced whether or not benzaldehyde was added to the suspension. Tarbell and Paulson therefore concluded that an optically active carbinol had not been produced. They reported also that the identical Grignard reactions carried out in partially resolved methyl *sec*-butyl ether also produced inactive carbinols.

We have succeeded in the preparation of 2,3-dimethoxybutane, which we believe to be enantiomerically pure, by methylation with sodium hydride and dimethyl sulfate of the optically active 2,3-butandiol, $[\alpha]_D^{20}$ $-13.09°$, which was kindly furnished to us by the National Research Council of Canada. The specific rotation of our ether at 23° is $+3.72° \pm 0.02°$. Helmkamp and Lucas (7) have recently reported the preparation of this ether with the specific rotation $+3.37°$. The higher rotation which we have obtained is not in itself a reliable criterion of higher purity, since rotation of this ether is strongly affected

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by solvent impurities. Thus the specific rotation of a 16.9% solution in benzene at 23° is −7.70°. We base our criterion of purity on a fractional crystallization at the freezing point of −84°. Each of four fractions comprising the whole sample gave rotations identical with the original. Our product is therefore chemically pure. It is also enantiomerically pure if *dd,ll*-dimethoxybutane is a racemic compound.

Dioxane is the only diether which has previously been examined thoroughly as a medium for Grignard reagents, and it is unsatisfactory because it precipitates the reagent. Neither 2,3-dimethoxybutane nor 1,2-dimethoxyethane suffers from this defect. We have had more experience with the latter solvent, since it is relatively more available than dimethoxybutane. The properties of dimethoxyethane as a medium for Grignard reagents will therefore be described in detail, with the understanding that dimethoxybutane behaves like a higher homologue.

TABLE I

YIELDS OF GRIGNARD REAGENTS IN DIETHYL ETHER (I) AND IN 1,2-DIMETHOXYETHANE (II)

HALIDE	YIELD BY TITRATION		YIELD OF DERIVATIVES	
	in I	in II	in I	in II
1-Chlorobutane	98	92	92	89
2-Chlorobutane	94	100	86	93
Bromobenzene	95	89		88
2-Bromooctane	95	97		
Benzhydryl chloride	28	30		
β-Bromostyrene	60	90		

In Table I are shown yields of several Grignard reagents and their derivatives with carbon dioxide and phenyl isocyanate in diethyl ether and in 1,2-dimethoxyethane. These experiments have not always been carried out under optimum, but certainly under comparable conditions. It may be seen that yields are at least as good, and sometimes better, in dimethoxyethane than in diethyl ether.

However these results do not show the fact that the formation of reagent is much slower in 1,2-dimethoxyethane than in diethyl ether when the ordinary preparative conditions of glass blade or magnetic stirring are employed. This retardation is caused by the precipitation of magnesium halide (demonstrated in one instance by the x-ray powder diffraction pattern of the hydrate of magnesium bromide), which coats the metallic particle. Because of this coating the reaction rate may be retarded to 0.1–0.05 of the rate in diethyl ether. If the system is heated (maximum 82°, reflux temperature), the coating is dissolved and the rate then approximates to that observed in diethyl ether. However the yield in this case is reduced by at least 10% from the optimum by the occurrence of side reactions such as coupling. It is of interest in this connection that less side reaction is obtained by slow consumption of badly-coated metal at 25° than by rapid consumption of bright clean metal at 82°. The behavior of magnesium in dimethoxyethane thus differs from that of sodium in petroleum ether (8, 9).

Thus it may be seen that Grignard reactions in 1,2-dimethoxyethane are not as satisfactory as those in diethyl ether when conditions suitable for the latter solvent are employed. However we have found that replacement of the ordinary glass mechanical or magnetic stirrer by a sharpened stainless steel blade, rotating at least 600 r.p.m., will keep the magnesium sufficiently clean so that reaction rates and yields at 25° in 1,2-dimethoxyethane are comparable with those in diethyl ether. Actually one might expect that dimethoxyethane would be superior (its dipole moment is 7.6 compared with 3.4 for diethyl ether), and in one instance this superiority has been demonstrated. Thus 6-chloro-2,6,6-trimethylcyclohexanone forms a Grignard reagent with magnesium in dimethoxyethane but not in diethyl ether (10).

The purchase, purification, recovery, and application to Grignard reagent preparation of 1,2-dimethoxyethane present little difficulty. None of these advantages apply to *dextro*-2,3-dimethoxybutane. Especially troublesome is the voluminous precipitate of magnesium halide which is formed during reaction. However this precipitate may be avoided entirely, with additional economy of the diether, by application of Tchelinzev's use of benzene or toluene as the principal solvent (11–13). Under these conditions a molar equivalent of the diether per mole of organic halide suffices for rapid Grignard reaction with high yield. The optically active medium can be separated readily from the reaction products obtained with 1-chlorobutane Grignard reagent and phenyl isocyanate. The optical inactivity of the pentanoylanilide, and of the pentanoic acid derived from it by hydrolysis, shows that no contamination occurs with any optically active decomposition products which might have been formed from the ether.

When *d,l*-2-chlorobutane Grignard reagent, prepared in pure *dextro*-2,3-dimethoxybutane, is treated with phenyl isocyanate, the 2-methylbutanoylanilide obtained in this manner is slightly optically active. The 2-methylbutanoic acid derived from it shows a specific rotation of +0.29° ± .02°, or about 2% of the rotation of the pure enantiomer. Thus it seems apparent that a suitable optically active medium can influence the enantiomeric configuration of Grignard reaction products.

When this reaction with a 2-chlorobutane Grignard reagent is carried out in benzene containing only one equivalent of dimethoxybutane, the anilide and the acid derived from it have, within experimental error, the same specific optical rotations as those which are obtained when dimethoxybutane, as the pure solvent, is in large excess. This result shows that the observed optical activity in the product is due only to a coordination complex between the Grignard reagent and a molar equivalent of the active solvent. Any active solvent in excess of this amount merely acts as a diluent; as such it can be replaced by any noncoördinative solvent such as benzene.

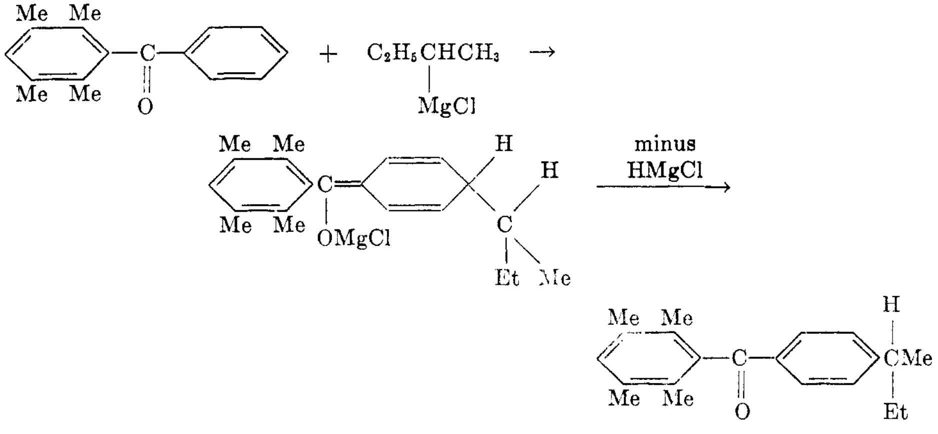
In order to find the most suitable characterizing reagent for study of the Grignard reagent-active solvent complex, a series of reactions has been carried out in the benzene-dimethoxybutane mixture with inactive 2-chlorobutane as the halide. In order to avoid the formation of diastereomeric mixtures, those characterizing reagents have been chosen which would not introduce a second asymmetric center in the product. Symmetrical ketones have been avoided for characterization because of the low yields of tertiary alcohols which are reported when ketones react with secondary Grignard reagents (14). The reagents which were tried are shown in Table II.

TABLE II

REACTION OF 2-CHLOROBUTANE GRIGNARD REAGENT IN (+) 2,3-DIMETHOXYBUTANE WITH CHARACTERIZING SUBSTANCES

CHARACTERIZING REAGENT	PRODUCT	YIELD, %	SPECIFIC ROTATION
Phenyl isocyanate	Methylbutanoylanilide	80	+0.34 ± 0.04°
Carbon dioxide gas	Methylbutanoic acid	85	−0.21 ± 0.02°
Benzoyldurene	4′-*sec*-Butyl-2,3,5,6-tetramethylbenzophenone	10	+0.44 ± 0.08°
Formaldehyde	2-Methylbutanol-1	18	+0.01 ± 0.02°
Mercuric chloride	Mercuri-*bis*-2-butane	20	+0.20 ± 0.08°

It may be seen from this table that only the results of the first two of the reactions are of more than qualitative significance. The value of the last three is limited firstly because the rotations of the pure enantiomers are not known, and secondly because the yields are low. These low yields may be a consequence of reaction in dimethoxybutane. The reaction of 2-chlorobutane Grignard reagent with benzoyldurene is reported to give a 60% yield of 4-*sec*-butyl-2,3,5,6-tetramethylbenzophenone (I) (15), which we were unable to duplicate.

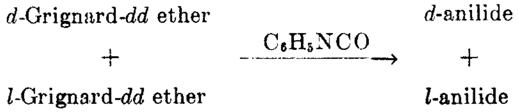


I

Despite the low yield which we have obtained, the product, because of its significant optical activity, shows the influence of the enantiomeric ether during its synthesis. The same may be said for the mercuri-*bis*-2-butane obtained when the Grignard reagent is treated with mercuric chloride; the low yield in this instance is probably owing to the insolubility of the mercury salt in the benzene-dimethoxybutane medium. The reaction of gaseous formaldehyde with the Grignard reagent (the pure diether being used as the medium) also gives a low yield, and in this case the 2-methylbutanol-1 is isolated as an optically inactive product. This experiment would indicate that the influence of the active ether is not general, but is specific to the mechanism of each individual Grignard addition.

The reactions with carbon dioxide and with phenyl isocyanate are most definitive. The yields are high; the anilide is easily purified and easily converted to 2-methylbutanoic acid. This acid, also obtained by carbonation of the Grignard reagent, is conveniently purified through its silver salt. By reference to the pure enantiomer its optical purity is known. Since the rate of carbon dioxide addition is less amenable to control than that of phenyl isocyanate, the principal evaluating variations have been carried out with the latter reagent.

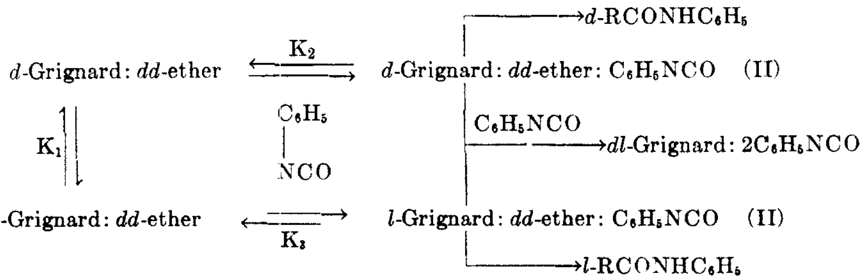
It is generally accepted that an optically active Grignard reagent cannot be prepared in diethyl ether from an enantiomeric halide in which the reactive linkage involves the asymmetric center (16–18). Letsinger found some retention of configuration in a *trans*-metalation reaction at −72°, but the resultant organolithium compound lost its enantiomeric specificity when the solution was warmed to 0° (19). We have demonstrated this principle again by the expedient of adding 0.5 equivalent and also 1 equivalent of phenyl isocyanate to a 2-chlorobutane Grignard reagent containing the active ether. The anilides obtained from these two experiments, and the acids derived from them, have the same optical rotation within limits of experimental error. If the organometallic compound had retained its configuration, then the two diastereomeric coördination complexes would be expected to compete at different rates for a deficiency of the isocyanate



$$\begin{array}{c} d\text{-Grignard-}dd\text{ ether} \\ + \\ l\text{-Grignard-}dd\text{ ether} \end{array} \xrightarrow{C_6H_5NCO} \begin{array}{c} d\text{-anilide} \\ + \\ l\text{-anilide} \end{array}$$

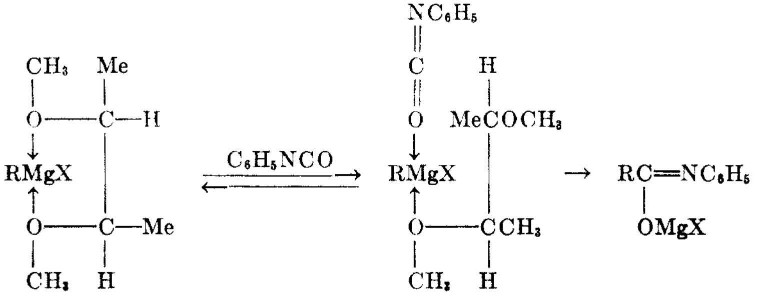
to give an enantiomeric excess of one anilide over the other. Of course if sufficient phenyl isocyanate were present, both diastereomers would react completely, and the anilide would then be optically inactive. The identical rotation in the anilides actually produced under these different conditions shows that the C-Mg linkage in the Grignard reagent is labile.

This lability is implicit in the equilibrium K_1 which is included in the following expression.



According to this expression four factors will affect the enantiomeric preponderance in the anilide: (a) the position of the equilibria K_1, K_2, and K_3, (b) the rate of attainment of these equilibria, (c) the relative rate at which the ether: Grignard:phenyl isocyanate complex decomposes irreversibly to the magnesium salt of the anilide, and (d) the extent to which the optically active ether is replaced entirely by phenyl isocyanate, leading to an inactive product.

The reaction equilibria K_2 and K_3, and the irreversible reactions which occur subsequently may be represented structurally as follows:



II

The significance of the partial displacement of the coördinative ether linkage in the complex II (as contrasted to the complete replacement of a mono-functional ether) is not apparent to us at present. We believe it to be important, since we have been unable to prepare products showing the slightest optical activity by use of the monofunctional menthyl methyl ether. This negative result, together with those of Tarbell and Paulson, indicate that the bifunctional nature of 2,3-dimethoxybutane may be necessary for the formation of an optically active product.

In order to evaluate the four factors mentioned above, a series of experiments were carried out wherein reaction temperature and mode of addition were varied. In this series 1-chloro-1-phenylethane Grignard reagent was used in addition to the reagent obtained from 2-chlorobutane. The results of these experiments are shown in Table III.

Firstly it may be seen that by use of "normal" addition (when phenyl isocyanate is added slowly to the Grignard reagent) the yield and optical rotatory product is about the same whether the reaction temperature is 0° or −72°. One may assume from this result that the temperature coefficients of reaction K_2 and K_3 are approximately equal, while K_1 is not significant to over-all reaction conditions involving a large amount of Grignard reagent and a small amount of isocyanate. When these relative amounts of reactants are reversed (inverse addition, wherein a small amount of Grignard reagent combines with a large amount of isocyanate), then both the position of equilibrium K_1 and its rate of attainment become important. It may be seen from Table III that inverse addition of 2-chlorobutane Grignard reagent decreases the rotatory power of the product by about half; the direction of rotation actually is reversed by addition of 1-chloro-1-phenylethane Grignard reagent to the isocyanate. As might be expected if equilibrium K_1 is preponderant in one diastereomer and its rate of attainment is retarded by low temperature, the decrease in rotation of product from 2-chlorobutane Grignard reagent added "inversely" at 0° is accentuated when it is added inversely at −72°.

The explanation just presented seems to be reasonable for the reaction between the Grignard reagents of the organic chlorides cited and phenyl isocyanate. It may not be true, and at best it does not suffice to explain all the facts. The inactivity of the methylbutanol obtained from formaldehyde and the 2-chlorobutane Grignard reagent has been mentioned above. This inactivity may be caused by complete exclusion of the optically active ether in favor of the strongly coördinating effect of two molecules of formaldehyde. Also inactive is the anilide obtained from 2-bromobutane Grignard reagent and phenyl isocyanate under conditions where 2-chlorobutane gives a *dextro* anilide (Table III). Several explanations based on the lesser electronegativity of bromine *versus* chlorine may be suggested, but best are deferred until the structure of Grignard reagents is better understood.

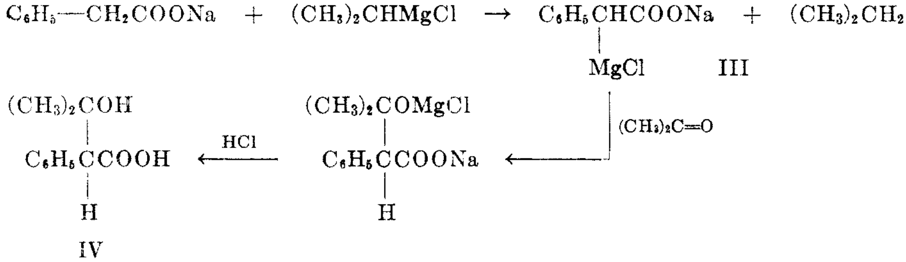
TABLE III

EFFECT OF TEMPERATURE AND MODE OF ADDITION ON GRIGNARD REACTION WITH PHENYL ISOCYANATE AND 2,3-DIMETHOXYBUTANE

GRIGNARD REAGENT FROM:	MODE OF ADDITION	DILUENT MEDIUM	TEMP., °C.	YIELD OF		SPECIFIC ROTATION OF ACID
				Anilide	Acid	
2-Chlorobutane	Normal ←	Benzene	0	72	59	+0.29° ± 0.03°
2-Chlorobutane	Inverse →	Benzene	0	42	35	+0.18° ± 0.02°
2-Chlorobutane	Normal ←	Toluene	−70	60	50	+0.30° ± 0.04°
2-Chlorobutane	Inverse →	Toluene	−70	48	45	+0.07° ± 0.03°
1-Chloro-1-phenylethane	Normal ←	Benzene	0	12	7	+2.20° ± 0.08°
1-Chloro-1-phenylethane	Inverse →	Benzene	0	—	16	−0.67° ± 0.08°
2-Bromobutane	Normal ←	Benzene	0	70	—	+0.01° ± 0.02°

The coupling reaction observed during Grignard reagent formation and interaction is thought by some to involve free radicals (20, 21). The optical inactivity of the coupling product found in the 1-chloro-1-phenylethane Grignard reagent prepared in 2,3-dimethoxybutane does not contradict this opinion. This coupling product, 2,3-diphenylbutane, can easily be separated from the other products of the reaction because it is insoluble in concentrated sulfuric acid. Separation of the *dd,ll* and *dl,ld*-diastereomers can be achieved, and the specific rotation of the *dd*-enantiomer (+96°) is known (22). When *dd,ll*-2,3-diphenylbutane is separated from the *meso*-diastereomer in the coupling product, it is entirely inactive. The same inactivity is observed in the *dd,ll*-diastereomer when coupling is carried out deliberately by boiling the 1-chloro-1-phenylethane Grignard reagent with excess of the halide until a negative Gilman test is obtained, or by treating it with silver bromide. A further test of the coupling reaction has been effected by boiling the same Grignard reagent with benzyl chloride until a negative Gilman test is obtained. *meso*-Diphenylbutane is separated by filtration from the hydrocarbons insoluble in concentrated sulfuric acid. The remaining oil, which must consist of *dd*,*ll*-diphenylbutane, biphenyl, and 1,2-diphenylpropane, has been separated into fractions, none of which shows any significant optical activity. It may be concluded that the active solvent does not partake in these several coupling reactions. This view is not incompatible with the concept that coupling products are formed by radical combination.

We have found in the Ivanov reagent a possible exception to this observation that the optically active medium cannot affect enantiomerism in a coupling product. Ivanov (23) prepared a Grignard reagent from sodium phenylacetate and a 2-chloropropane Grignard reagent.



$$C_6H_5{-}CH_2COONa + (CH_3)_2CHMgCl \rightarrow \underset{\substack{|\\ MgCl}}{C_6H_5CHCOONa} + (CH_3)_2CH_2$$

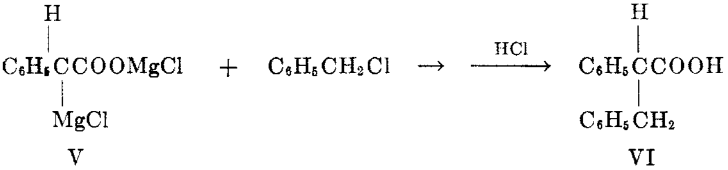
III

$$\overset{\substack{(CH_3)_2COH\\ |}}{\underset{\substack{|\\ H}}{C_6H_5CCOOH}} \xleftarrow{HCl} \overset{\substack{(CH_3)_2COMgCl\\ |}}{\underset{\substack{|\\ H}}{C_6H_5CCOONa}} \xleftarrow{(CH_3)_2C=O}$$

IV

The derived Grignard reagent (III) reacted readily with carbonyl-containing compounds such as acetone, to give substances such as 3-hydroxy-3-methyl-2-phenylbutanoic acid (IV). We have repeated this procedure in the medium *dextro*-dimethoxybutane-benzene. Reaction occurs even though the organometallic compound (III) is insoluble in this medium; the acid (IV) has a specific rotation of +2.94° ± 0.09°.

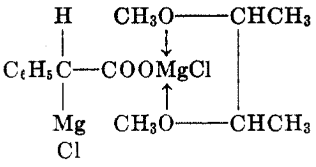
The Ivanov reagent in dimethoxybutane-benzene medium will not react with methyl sulfate or methyl iodide. However we have obtained coupling with benzyl chloride of a similar reagent (V) prepared from phenylacetic acid and two moles of the 2-chloropropane Grignard reagent.



$$\overset{\substack{H\\ |}}{\underset{\substack{|\\ MgCl}}{C_6H_5CCOOMgCl}} + C_6H_5CH_2Cl \rightarrow \xrightarrow{HCl} \overset{\substack{H\\ |}}{\underset{\substack{|\\ C_6H_5CH_2}}{C_6H_5CCOOH}}$$

V VI

The 2,3-diphenylpropanoic acid (VI) so obtained in 12% yield has a specific rotation of +1.52° ± 0.04°. This result would seem to contradict our opinion that the mechanism of the coupling reaction precludes an enantiomeric orienting effect by the reaction medium. However the Ivanov type of reagent differs because it contains a metallic linkage separated from the Grignard reactive linkage. If dimethoxybutane is presumed to coördinate with the salt linkage the resulting complex (VII) is undoubtedly not



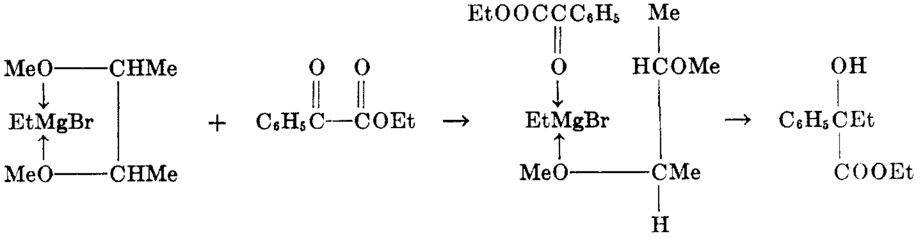
VII

freely ionic, since it is insoluble in the reaction medium. It may then be expected to give optically active coupling products quite independently of the mechanism of the Grignard coupling reaction. In this sense it might resemble the reactions of McKenzie and his co-workers with Grignard reagents and *l*-menthyl benzoylformate which lead to optically active products (24).

The reactions discussed thus far have all been of the "resolution" type in which an equal mixture of two enantiomers reacts at different rates. On the other hand the reactions with *l*-menthyl benzoylformate described by McKenzie (24) involve the creation of a new asymmetric center and are known as "asymmetric syntheses" or "inductions". It seemed desirable to ascertain whether the effect of an optically active medium on the reagents would be similar to the effect of an asymmetric radical such as *l*-menthyl within the molecule.

Accordingly ethyl benzoylformate (IX) has been treated with a chloroethane Grignard reagent in benzene-*dextro*-dimethoxybutane medium. The product, ethyl 2-hydroxy-2-phenylbutanoate (XI) obtained in 30% yield, has been hydrolyzed to the corresponding acid with specific *dextro* rotation of +1.18° ± 0.03°. This respresents asymmetric synthesis to the extent of about 5%. The 2-hydroxy-2-phenylbutanoic acid obtained by the comparable reaction with a bromoethane Grignard reagent shows a lower specific *dextro* rotation of +0.37° ± 0.02°. This value is essentially the same when the reaction with a bromoethane Grignard reagent is carried out in pure *dextro*-2,3-dimethoxybutane.

Since a single equivalent of the bifunctional ether is as effective in asymmetric synthesis as is a large excess, it must be acting as a coördination complex (VIII) with the organometallic compound rather than by interaction of the van der Wals type with the ethyl benzoylformate. Since elements of asymmetry are absent in the organometallic compound as such, the presence of a Grignard reagent:dimethoxybutane:ethyl benzoylformate complex (X) is indicated. This type of complex is that



VIII IX X XI

which has been postulated for the resolution type of reaction. Therefore we believe that there is no essential difference between the cause of optical activity in the products from the resolution and synthesis types of reaction.

EXPERIMENTAL

Melting points have been corrected against reliable standards.

Halides were washed successively with concentrated sulfuric acid, aqueous sodium carbonate, and saturated aqueous sodium chloride, then dried with calcium chloride and distilled.

Magnesium was either Merck grade "For Grignard Use" or else sublimed magnesium supplied by courtesy of the Dominion Magnesium Company, Haley, Ontario.

Composition of Grignard reagents in 1,2-dimethoxyethane. The Grignard reagent prepared from 0.02 mole of bromobenzene in dimethoxyethane was centrifuged in a nitrogen-filled bottle, and the supernatant solution was decanted off. The solid substance thus removed from the original suspension was twice washed by re-suspension and centrifugation. It was then exposed to air for 1 day. Analysis showed that 4% of free base (as magnesium hydroxide) was present. An x-ray diffraction pattern showed that the suspended material after hydration was chiefly magnesium bromide hexahydrate.

The supernatant solution from centrifugation was titrated for Grignard reagent content, and then was analyzed for halogen content. The ratio of phenylmagnesium bromide to the total phenylmagnesium linkage, *i.e.* $C_6H_5MgBr/[C_6H_5MgBr + (C_6H_5)_2Mg]$, was found to be 0.45. The comparable ratio in the centrifuged clear solution of 1-chlorobutane Grignard reagent in 1,2-dimethoxyethane was found to be 0.24.

dextro-2,3-Dimethoxybutane. Distilled *levo*-2,3-butanediol (b.p. 69°/10 mm. $[\alpha]_D^{20}$ −13.09°) (900 g., 10 moles) was added dropwise during 90 minutes to a suspension of 528 g. (22 moles) of sodium hydride in 8.5 liters of anhydrous ether stirred in an ice-water-cooled 12-liter three-necked flask equipped with a 0.25-inch stainless wide-sweep stirrer and an efficient reflux condenser. Hydrogen evolution ceased after the viscous mass was stirred for 30 hours. Stirring was continued while 2.52 kg. (20 moles) of practical dimethyl sulfate was added during 5 hours. After 6 hours of continued stirring the ethyl ether was distilled off on a water-bath.

The flask was then made vacuum-tight and equipped for downward distillation through a water-cooled condenser into an ice-cooled receiver to which a Dry Ice-cooled reflux condenser was attached. While a vacuum was maintained at about 30 mm. pressure, the temperature of a heating mantle was gradually raised during 8 hours to about 150°. At the end of this period the internal temperature was 130°.

The distillate was fractionated through a 10-plate column to remove residual ether. The residue (*ca.* 1 liter, which gave a negative test with dinitrophenylhydrazine reagent) was treated with 100 g. of sodium hydride and then distilled entirely under 150 mm. pressure after the vigorous reaction had subsided. The distillate was boiled under reflux with sodium in a nitrogen-filled flask for 2 hours; then 2 g. of benzophenone was added. Within 10 minutes the liquid turned blue and was distilled, b.p. 109–110°/750 mm., wt. 885 g. (75%), $[\alpha]_D^{20}$ +3.72°, d_4^{20} 0.854, n_D^{20} 1.3937, m.p. −84.2° to −83.5°.

After a sample of the purified ether had been caused to crystallize partially under dry nitrogen by cooling in a liquid-air bath, the liquid portion was removed by decantation. This process was repeated 3 times. All 4 fractions had the same specific rotation as the starting material.

Optically active 2-methylbutanoylanilide. After 5 ml. of a solution of 4.6 g. (0.05 mole) of 2-chlorobutane in 40 ml. of *dextro*-2,3-dimethoxybutane was added to 1.25 g. (0.05 atom) of sublimed magnesium under nitrogen, the mixture was heated until reaction was apparent (*ca.* 5 minutes). The remainder of the solution was added dropwise to the stirred suspension during 1 hour, then stirred subsequently at 60° for 1 hour. Titration of an aliquot indicated a yield of 68% of Grignard reagent. Alternatively when the reaction medium comprised 35 ml. of benzene or toluene with 6.0 g. (0.05 mole) of *dextro*-2,3-dimethoxybutane, the homogeneous solution (no precipitated magnesium halide) indicated by titration a Grignard reagent content of 75%.

A. "Normal" addition of phenyl isocyanate to reagent. While the stirred Grignard reagent was cooled in an ice-water bath, 4.3 g. (0.38 mole) of phenyl isocyanate in 10 ml. of benzene or 2,3-dimethoxybutane was added dropwise during 30 minutes. A Gilman test for Grignard reagent was then negative. After pouring the reaction mixture into cold dilute hydrochloric acid, the benzene layer was washed with water and dried with magnesium sulfate. Vacuum evaporation of solvent left 5.98 g. (90%) of oil which crystallized. Two crystallizations from 5 ml. of ethyl acetate plus 50 ml. of petroleum ether (b.p. 60–70°) gave 5.3 g. (78%) of methylbutanoylanilide, m.p. 111–112°, $[\alpha]_D^{20}$ +0.34° ± 0.04° (solution in acetone). An experiment which was identical, except that 2-bromobutane was used for preparation of the Grignard reagent, gave a product with no detectable optical activity.

B. "Inverse" addition of reagent to phenyl isocyanate. A solution of the Grignard reagent (0.035 mole) in 6 g. of dimethoxybutane and 40 ml. of anhydrous benzene was added dropwise to 8.4 g. (0.07 mole) of stirred phenyl isocyanate in 15 ml. of benzene during 60 minutes at 0°. Subsequent processing as before gave a 42% yield of 2-methylbutanoylanilide, m.p. 110–111°. Hydrolysis yielded 2-methylbutanoic acid (35%), $[\alpha]_D^{20}$ +0.18° ± 0.02°.

C. Reaction at −70°. These reactions were otherwise identical with those described in *A* and *B* except that toluene was used instead of benzene. The reaction was complete within 10 minutes following "normal" addition and immediately following "inverse" addition. Yields and rotations are recorded in Table III.

Optically active 2-methylbutanoic acid. A. By hydrolysis of the anilide. A mixture of the anilide (4.0 g.) and 20 ml. of 50 vol.-% aqueous sulfuric acid was boiled under reflux until it was homogeneous (8 hours). After dilution into 100 ml. of cold water, the acid was extracted with five 10-ml. portions of chloroform. The dried extract was distilled, b.p. 170–172°, 1.6 g. (75%).

B. By carbonation of Grignard reagent. The Grignard reagent from 2-chlorobutane was prepared as was described for the anilide (80%). The reaction system was cooled to 0° and the nitrogen atmosphere was replaced by dry gaseous carbon dioxide. A negative Gilman test was obtained within 30 minutes. After evaporation of the solvent under reduced pressure, the residue was treated with dilute hydrochloric acid, then extracted with ether; this extract was washed with two 10-ml. portions of sodium carbonate solution and discarded. The combined carbonate washings, boiled for 5 minutes, were acidified with dilute sulfuric acid and extracted with chloroform. This extract (dried) was distilled, finally at 171–173°, $[\alpha]_D^{20}$ −0.21° ± 0.02°, 3.4 g. (85%).

A solution of the sodium salt of this product in 15 ml. of water was boiled and then treated with 100 ml. of *N* silver nitrate solution. The silver salt was filtered off, vacuum dried, and decomposed by treatment with 100 ml. of 10% aqueous nitric acid. The regenerated acid was extracted with ether; this dried extract gave 2.2 g. (65% recovery) of 2-methylbutanoic acid, b.p. 172–173°, $[\alpha]_D^{20}$ −0.21° ± 0.02°.

Pentanoylanilide. When a 1-chlorobutane Grignard reagent was prepared in *dextro*-2,3-dimethoxybutane by the procedure described for 2-chlorobutane, the yield was 60%. Treatment of this solution with one equivalent of phenyl isocyanate, followed by processing as described for the reaction with the 2-chlorobutane Grignard reagent, gave a 35% yield of pentanoylanilide, m.p. 61–63°. Hydrolysis of the anilide as described above gave a 20% yield of pentanoic acid, b.p. 184–186°. This product was optically inactive.

Ethyl 2-hydroxy-2-phenylbutanoate. A. From a chloroethane Grignard reagent. When a Grignard reagent was prepared from 4.2 g. (0.065 mole) of 2-chloroethane, 1.25 g. (0.05 atom) of magnesium, 6.0 g. (0.05 mole) of *dextro*-2,3-dimethoxybutane, and 40 ml. of benzene, a two-phase system was obtained. Both phases gave positive Gilman tests; titration of the stirred mixture showed that 0.032 mole (64%) of Grignard reagent was present. Within 10 minutes after this mixture had been added dropwise during 1 hour to a stirred solution of 5.7 g. (0.032 mole) of ethyl benzoylformate in 20 ml. of benzene, a negative Gilman test was obtained.

After hydrolysis with dilute hydrochloric acid the benzene phase was water-washed and dried with magnesium sulfate. The solvent was largely removed by distillation up to 120°; then nitrogen was bubbled through the residue at 120° under 30 mm. pressure for 30 minutes. Distillation under 10 mm. pressure then gave 2.5 g. (37%) of ethyl 2-hydroxy-2-phenylbutanoate, b.p. 124–124.5°, with a rotation of +1.18° ± 0.02. Hydrolysis of this ester with boiling 50 vol.-% aqueous sulfuric acid yielded 1.5 g. of 2-hydroxy-2-phenylbutanoic acid, m.p. 125.5–126.5°, $[\alpha]_D^{20}$ +1.30° ± 0.06° (50% solution in ethanol).

B. From a bromoethane Grignard reagent. The previous procedure was followed except that bromoethane was used as the halide. Again a two-phase system was obtained. The yield of ester was 2.1 g. (25%), $[\alpha]_D^{20}$ +0.36° ± 0.02°. The yield of 1-hydroxy-1-phenylbutanoic acid was 1.2 g., m.p. 124.5–125.5°, $[\alpha]_D^{20}$ +0.40° ± 0.04° (50% solution in ethanol).

In a variation of this procedure the reaction medium comprised 40 ml. of dimethoxybutane to 10 ml. of tetrahydrofuran. The latter substance was included in order to make the reagent homogeneous. This solution was added dropwise during 1 hour to a stirred solution of 7.12 g. (0.04 mole) of ethyl benzoylformate in 30 ml. of 2,3-dimethoxybutane. The mixture was stirred subsequently at 60° for 90 minutes. The ethyl 2-hydroxy-2-phenylbutanoate showed a specific rotatory power of $[\alpha]_D^{20}$ +0.23° ± 0.03°. Hydrolysis of this ester (3.8 g., 46%) with hot aqueous alcoholic potassium hydroxide yielded the acid (3.02 g.) This acid was crystallized from 30 ml. of boiling water, m.p. 125.5–126.5°, $[\alpha]_D^{20}$ +0.24° ± 0.06° (3.02 g. in 0.82 g. of acetic acid).

2-Phenylpropanoic acid. Three ml. of a solution of 7.0 g. (0.05 mole) of 1-chloro-1-phenylethane in 6.0 g. (0.05 mole) of *dextro*-2,3-dimethoxybutane was added under nitrogen to 1.25 g. (0.05 atom) of sublimed magnesium under 3 ml. of benzene. Heating of the mixture for 10 minutes initiated the reaction. The remainder of the halide solution was added dropwise with stirring during a two-hour period. Titration of an aliquot showed a Grignard reagent yield of 55%.

A. "Normal" addition of phenyl isocyanate to Grignard reagent. To the cooled, stirred Grignard reagent was added 3.3 g. (0.23 mole) of phenyl isocyanate in 10 ml. of benzene during 1 hour. A Gilman test was then negative. After hydrolysis with dilute hydrochloric acid the non-aqueous layer was washed with water and dried with magnesium sulfate. After vacuum evaporation of the solvents the residue was boiled for 8 hours under reflux with 20 ml. of 50 vol.-% aqueous sulfuric acid. The reaction mixture was then diluted to 200 ml. with water and extracted with five 20-ml. portions of ether. The etherous solution was extracted with two 20-ml. portions of 5% aqueous sodium carbonate and then was dried prior to isolation of 2,3-diphenylbutane.

The alkaline solution was washed four times with chloroform, boiled 5 minutes with Norit, and filtered. The acidified filtrate was extracted with five 10-ml. portions of chloroform. The extract was water-washed and dried, then vacuum evaporated to leave 0.338 g. (9.8%) of 2-phenylpropanoic acid, b.p. 101–103° (0.3 mm.). A 30% solution in acetic acid gave a specific rotation $[\alpha]_D^{20}$ +2.20° ± 0.06°.

The carbonate-extracted etherous solution was evaporated and the residue dissolved in 15 ml. of purified petroleum ether. This solution was washed with 5-ml. portions of concentrated sulfuric acid until the extract was no longer colored. The petroleum ether solution was evaporated, and the residue (2.3 g.) was filtered to remove *meso*-2,3-diphenylbutane. The oily filtrate (1.7 g.) was distilled, b.p. 143–150° (12). After more *meso* diastereomer was filtered off, the liquid *dd,ll*-2,3-diphenylbutane (1.2 g.) was diluted to 2 ml. with benzene. This solution had no optical rotatory power.

B. "Inverse" addition of Grignard reagent to phenyl isocyanate. A solution of 0.03 mole of the Grignard reagent in 6.0 g. (0.05 mole) of *dextro*-2,3-dimethoxybutane and 40 ml. of benzene was added dropwise during 1 hour to a cooled, stirred solution of 7.2 g. (0.06 mole) of phenyl isocyanate in 15 ml. of benzene. The reaction mixture was processed as described above to yield 0.720 g. (16%) of 2-phenylpropanoic acid, b.p. 99–101° (0.15 mm.). This product, diluted to 2 ml. with benzene, showed a specific rotation $[\alpha]_D^{20}$ −0.67° ± 0.08°.

2,3-Diphenylbutane. A. With excess 1-chloro-1-phenylethane. To 0.03 mole of 1-chloro-1-

phenylethane Grignard reagent in 6.0 g. (0.05 mole) of *dextro*-2,3-dimethoxybutane and 40 ml. of benzene was added 4.2 g. (0.03 mole) of 1-chloro-1-phenylethane in 20 ml. of benzene. The mixture was heated to 60° for 1 hour, after which time a Gilman test was negative. Processing was carried out as described in *A*, above, to yield 2.4 g. (76%) of *dd*,*ll*-2,3-diphenylbutane, b.p. 130–132° (7 mm.). A 1:1 solution in toluene was optically inactive.

B. With silver bromide. When 0.03 mole of 1-chloro-1-phenylethane Grignard reagent in 6 g. of dimethoxybutane and 40 ml. of benzene was heated with 5.4 g. (0.03 mole) of freshly prepared dry silver bromide, heat was evolved and a gray-black precipitate formed. The mixture was processed as described above, yielding 1.5 g. (47%) of *dd*,*ll*-diastereomer which was optically inactive.

C. With benzyl chloride. When 3.8 g. (0.03 mole) of benzyl chloride in 10 ml. of benzene was added to a warm, stirred solution of 0.028 mole of 1-chloro-1-phenylethane Grignard reagent in 6 g. of dimethoxybutane and 40 ml. of benzene, a heavy gelatinous precipitate formed. After 30 minutes a Gilman test was negative. The mixture was processed as described above, yielding three fractions boiling under 7 mm. at 125–127° (0.9 g.), 127–129° (0.5 g.) and 129–132° (0.4 g.). None of these fractions was optically active.

4-sec-Butyl-2,3,5,6-tetramethylbenzophenone. When 5.6 g. (0.025 mole) of benzyldurene in 25 ml. of benzene was added dropwise during 1 hour to a stirred solution of 0.038 mole of 2-chlorobutane Grignard reagent in 6 g. of dimethoxybutane and 40 ml. of benzene, a ruby-red color was produced. After 2 hours at 60°, 10 ml. of water was added; the color was dispersed within 5 minutes. The benzene solution was decanted from the magnesium salts, dried with magnesium sulfate, and distilled to leave 5.6 g. of a viscous oil. Distillation gave 0.25 g. boiling at 120–150° (0.3 mm.) and 3.07 g. (60%), b.p. 154–156° (0.1 mm.), $[\alpha]_D^{20}$ +0.36° ± 0.05° (30% solution in benzene). This main fraction crystallized slowly and partially. The filtered solid (0.85 g.) was crystallized from 2 ml. of methanol to yield 0.715 g. (10%), m.p. 67–69°. A solution of this 4-*sec*-butyl-2,3,5,6-tetramethylbenzophenone (25% in benzene) showed the specific rotation of the product to be $[\alpha]_D^{20}$ +0.44° ± 0.08°.

2-Methylbutanol-1. A stream of gaseous formaldehyde (prepared by depolymerization of dry Merck paraformaldehyde at 200° in a stream of nitrogen) was passed over a cooled stirred solution of 0.032 mole of 2-chlorobutane Grignard reagent in 25 ml. of *dextro*-2,3-dimethoxybutane until the heavy gummy precipitate did not increase in quantity. After 30 minutes the Gilman test was negative. The solvents were evaporated under reduced pressure; ether and water were added to the residue. The etherous phase was dried and evaporated, leaving 3 g., b.p. 116–135°. This distillate was heated with 4 g. of 3-nitrophthalic anhydride and then extracted with boiling water. The residual crude nitrophthalate was dissolved in 50 ml. of 5% aqueous sodium carbonate. This solution was extracted with ether and then acidified. The 2-methylbutyl nitrophthalate was crystallized from 40 ml. of 50% ethanol:water, 1.67 g. (18%), m.p. 157–158°. After exact neutralization with alkali the aqueous solution of this salt in 10 ml. of water was optically inactive.

A solution of the 3-nitrophthalate in 25 ml. of 20% aqueous potassium hydroxide was boiled 2 hours under reflux. An etherous extract, distilled, yielded 0.5 g. (18%) of 2-methylbutanol-1, b.p. 129–130°. This sample in 0.5 ml. of dioxane was optically inactive.

Mercuri-bis-2-butane. Heat was evolved and a gray-black precipitate was formed when 0.033 mole of 2-chlorobutane Grignard reagent in 6 g. of dimethoxybutane and 40 ml. of benzene was treated during 30 minutes in small portions with 10.8 g. (0.04 mole) of pulverized mercuric chloride. The solvent was recovered under reduced pressure. The residue was eluted with 30 ml. of water at 4° and filtered cold to remove a dark gray powder. Five crystallizations from absolute ethanol left 2.0 g. (20%) of mercuri-bis-2-butane, m.p. 29.5–30.5°. A solution of this material in 3 g. of chloroform gave a specific rotation for the product of $[\alpha]_D^{20}$ +0.20° ± 0.08°.

3-Hydroxy-3-methyl-2-phenylbutanoic acid. A mixture of 1.25 g. (0.05 atom) of magnesium, 5 g. of *dextro*-2,3-dimethoxybutane, and a few drops of 2-chloropropane was heated with stirring until the formation of a precipitate and a positive Gilman test showed that Grignard reagent formation had commenced. After 5.8 g. more (total 0.09 mole) of active solvent, 40 ml. of benzene, and 4.8 g. (0.025 mole) of dried pulverized sodium phenylacetate had been added to the stirred mixture, a solution of 2-chlorobutane in 25 ml. of benzene was added dropwise during 1 hour. After 4 hours at 60° the system was still heterogeneous.

When 3.0 g. (0.05 mole) of acetone in 10 ml. of benzene was added to the mixture it became warm and much precipitate was formed. A Gilman test was negative within 30 minutes. After hydrolysis with dilute hydrochloric acid the non-aqueous phase was extracted with aqueous sodium carbonate. The alkaline extract was washed with benzene, decolorized with Norit, and acidified with dilute hydrochloric acid to yield 2.6 g., m.p. 87–91°. This product was crystallized from 20 ml. of carbon tetrachloride; 2.2 g. (42%) melted at 91–92°, $[\alpha]_D^{20}$ +2.94° ± 0.09° (30% solution in absolute ethanol).

2,3-Diphenylpropanoic acid. To a stirred Grignard reagent from 4 g. (0.05 mole) of 2-chloropropane in 10.8 g. (0.1 mole) of dimethoxybutane and 40 ml. of benzene was slowly added 2.72 g. (0.02 mole) of phenylacetic acid in 10 ml. of benzene. After stirring for 10 hours the derived Grignard reagent was entirely precipitated (the supernatant liquor gave a negative Gilman test). Within 1 hour after benzyl chloride (2.5 g., 0.02 mole) in 10 ml. of benzene had been added, the entire system gave a negative Gilman test. It was treated with water; the aqueous layer was separated and washed ten times with 10-ml. portions of benzene and twice with 10-ml. portions of chloroform. After having been decolorized by boiling with Norit, the solution was acidified with dilute hydrochloric acid to yield 0.55 g. (12%) of solid, m.p. 85–88°. This 2,3-diphenylpropanoic acid was crystallized from 10 ml. of carbon tetrachloride, 0.514 g., m.p. 88–89°, $[\alpha]_D^{20}$ −1.52° ± 0.05° (30% solution in ethanol).

Menthyl methyl ether as Grignard medium. Menthyl methyl ether was prepared by the procedure of Tarbell and Paulson (6) in 65% yield. It boiled at 200–201° and had a specific rotation of $[\alpha]_D^{20}$ −95.2°.

When a mixture of 4.6 g. (0.05 mole) of 2-chlorobutane, 8.5 g. (0.05 mole) of menthyl methyl ether, and 40 ml. of benzene was stirred with metallic magnesium, a heavy white precipitate began to form within 8 hours. After 4 days the supernatant liquor showed a Grignard reagent content of 72% by titration. It also contained halogen according to a test with aqueous silver nitrate acidified with nitric acid.

After 4.8 g. (0.04 mole) of phenyl isocyanate in 10 ml. of benzene had been added, the mixture was hydrolyzed with dilute hydrochloric acid, and then processed like the experiments in which dimethoxybutane was used. The yield of 2-methylbutanoylanilide (1.6 g., 25%, m.p. 109–110°) was hydrolyzed to 0.420 g. (11%) of 2-methylbutanoic acid, b.p. 171–173°. A toluene solution was optically inactive.

SUMMARY

1. *dextro*-2,3-Dimethoxybutane has been prepared in high enantiomeric purity.

2. Because of the coördination complex which this ether forms with Grignard reagents, it has been found possible to induce slight optical activity in adducts which the reagents form with carbonyl compounds.

3. Both "resolution" and synthesis types of reaction have led to optically active products.

4. The coupling of Grignard reagents in the optically active solvent with organic halides has resulted only in optically inactive products, except when activity can be induced by a functional group other than the organometallic linkage.

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