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Asymmetric Reactions. II. Anomalous Stereoselectivity of the Grignard Reaction with *N*-Benzyl-2,3-*O*-isopropylidene-D-glyceraldimine

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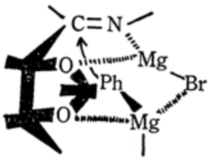
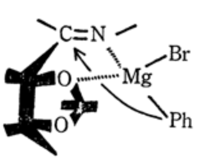
Stereoselectivity of the organomagnesium reaction with *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldimine was examined under various conditions (change of molarity, solvent, and composition ratio of reagents). The selectivity was not effected by the molarity of the reagents but by the solvent. When the substrate was treated with a mixture of various ratio of magnesium bromide and diphenylmagnesium, a remarkable effect of the ratio on the stereoselectivity was observed. Maximum ratio of *erythro*/*threo* was obtained at the point of equimolar mixture of magnesium bromide and diphenylmagnesium in ether. The structure of the transition intermediate was discussed.

The authors have reported the difference in stereoselectivity between the Grignard and alkyllithium reactions of *N*-phenyl-3,4;5,6-di-*O*-isopropylidene D-glucosaminonitrile,¹⁾ *N*-substituted 3,4-*O*-isopropylidene-D-tetrosaminonitriles, 2,3-*O*-isopropylidene-D-glyceraldimines,²⁾ and 2,3-*O*-isopropylidene-D-glyceraldehyde,³⁾ in which the configuration of the major product in the Grignard reactions was inconsistent with that deduced from Cram's rigid model.⁴⁾ This stereoselectivity of the Grignard reaction was explained by two possible models A and B.



A



B

A similar steric difference was observed by Stocker *et al.* between phenyllithium and phenylmagnesium halide reactions with α-hydroxyketones or α,β-diketones.⁵⁻⁷⁾

The composition of the Grignard reagents under the reaction condition seems to play an important role on such an anomaly. Although the structure of the crystalline Grignard reagent prepared from magnesium and bromobenzene or ethyl bromide in ether was formulated by X-ray diffraction method as $RMgBr \cdot 2Et_2O$ (R=phenyl or ethyl),⁸,⁹⁾ the reagent in the solution exists as an equilibrium mixture of several species as follows. Molecular weight determination by ebullioscopic method showed that the Grignard reagents exist as monomeric species in low molarity in ether solution (10^{-2} M concentration) and are apt to associate in higher molarity,¹⁰,¹¹⁾ while in tetrahydrofuran they exist as monomers even in a higher molarity.¹²⁾ IR spectroscopic data suggested that species of the Grignard reagent changes considerably with varying solvent, the nature of the organic part and halogen atom.¹³⁾

The authors examined the effect of the reaction conditions (*i. e.*, change of molarity, solvent and composition ratio of reagents) on the above mentioned stereoselectivity in the reaction of the Grignard reagent with *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldimine (I), in order to obtain information on the structure of the transition state. Model (A) was found to be more probable.

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1) J. Yoshimura, This Bulletin, **35**, 536 (1962).

2) Asymmetric Reactions. I: J. Yoshimura, Y. Ohgo and T. Sato, *J. Am. Chem. Soc.*, **86**, 3858 (1964).

3) This was presented at the 17th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1964.

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6) J. H. Stocker, *J. Org. Chem.*, **29**, 3593 (1964).

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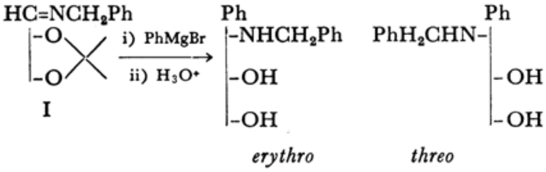
11) E. C. Ashby and M. M. Smith, *J. Am. Chem. Soc.*, **86**, 4363 (1964).

12) E. C. Ashby and W. E. Becker, *ibid.*, **85**, 118 (1963).

13) R. M. Salinger and H. S. Mosher, *ibid.*, **86**, 1782 (1964).



Results

Effects of Concentration and Solvent. I was treated with 3 molar equivalent of organomagnesium compounds under various conditions followed by hydrolysis to give a diastereoisomeric mixture of 1-benzylamino-1-deoxy-1-*C*-phenyl-*threo*- and -*erythro*-D-glyceritols. Diastereoisomeric ratios (*erythro*/*threo*) were calculated from the optical rotations as previously reported.[2]

The results obtained by changing solvent and molarity are shown in Table 1.

TABLE 1. EFFECT OF SOLVENT AND MOLARITY ON THE STEREOSELECTIVITY

Run	Solvent	Molarity	E/T
1	Ether	1.5 M	3.5[2]
2	Ether	0.081 M	3.4
3	THF	1 M	1.6
4	Benzene	1 M	4.26
5	Ether+TEA[a]	1.7 M	3.0
6	Ether+TEA[b]	1.6 M	2.9
7	Ether+TEA[c]	1.1 M	2.9

a) A mixture of ether (40 m*l*) and triethylamine (3.2 m*l*).
b) A mixture of ether (40 m*l*) and triethylamine (6.4 m*l*).
c) A mixture of ether (40 m*l*) and triethylamine (26 m*l*).

TABLE 2. EFFECT OF THE MOLAR RATIO ($MgBr_2/Ph_2Mg$) ON THE STEREOSELECTIVITY

Run	Reagent (moles/mole substrate) Ph_2Mg	Reagent (moles/mole substrate) $MgBr_2$	E/T
8	2.15	0	1.56
9	1.29	0.5	3.0
10	1.29	1	4.4
11	1.29	2	5.45
12	1.29	3	4.87
13	1.29	5	3.76
14	1.29	10	2.9

As was shown in runs 1, 2, 5, 6 and 7, the stereoselectivity was not effected by the molarity of the reagents. However, it is worth mentioning that a remarkable difference was found between stereoselectivity in THF solution and in ether solution of lower molarity. No remarkable effect was observed by addition of triethylamine.

Effect of Composition of the Grignard Reagent. I was treated with a mixture of various ratio of magnesium bromide to diphenylmagnesium in ether.

The results are shown in Table 2 and Fig. 1. Figure 1 was obtained by plotting E/T against the molar ratio of magnesium bromide to diphenylmagnesium. It shows that E/T increases steeply with the increase of the ratio of $MgBr_2/Ph_2Mg$ until the ratio reaches about 1, and then begins to decrease gradually with a further increase of the ratio of $MgBr_2/Ph_2Mg$ (>1). Maximum E/T (>5.45) was much greater than that previously obtained by conventional Grignard reagent ($E/T=3.5$).[2]

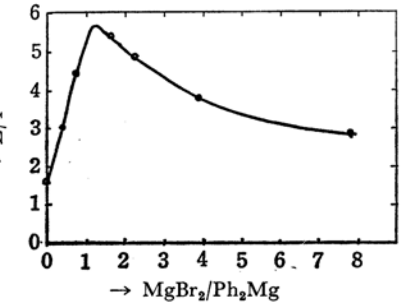


Fig. 1. The effect of the ratio of $MgBr_2/Ph_2Mg$ on the stereoselectivity.

Composition of the Complex formed in the Reaction and the Stereoselectivity by Reverse Addition Mode. In the ordinary Grignard reactions in which the solution of the substrate is added into the Grignard solution, it is observed that a white precipitate appears instantly and then disappears probably on account of being dissolved by excess Grignard solution. If so, a reverse mode of addition in which the reagent is added into the substrate solution should cause precipitation. As expected, the precipitate appeared and increased with the amount of the reagent added till about 1—1.5 equivalent to the substrate, and then began to dissolve with further addition. At the point of the equivalent molar ratio, the precipitate was separated from the solution. The molar ratio of phenylmagnesium bromide to the substrate in precipitate and that in the solution were determined from the content of magnesium and bromide to be 1.5 and 0.16 respectively. This shows that the reagent is considerably concentrated in the precipitate.

TABLE 3. THE STEREOSELECTIVITIES OBTAINED BY THE REVERSE ADDITION MODE

Run	PhMgBr (moles/mole substrate)	Product E/T
15	1	2.7
16	2	3.16

Two examples of E/T in the reverse addition mode are shown in Table 3. The results show that the stereoselectivity decreased as a whole to some extent, and is apt to increase with an increased amount of the reagent (compare runs 15, 16 and 1).

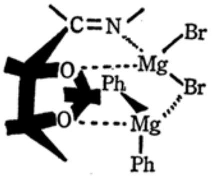
Discussion

The monomeric Grignard reagent in ether solution [run 2, $E/T=3.4$] gives the same results as the dimeric Grignard ethereal solution [run 1, $E/T=3.5$]. But the result is quite different in THF solution [run 3, $E/T=1.6$] in which the Grignard reagent exists also in monomeric form. This marked difference suggests that species in THF solution differ from those in ether solution, or stronger coordination ability of THF prevents magnesium from bridging between N and C_2-O. The former agrees with the infrared spectroscopic data presented by Salinger and Mosher.[13]

Monomeric species in the Grignard reagent should be diphenylmagnesium, magnesium bromide and phenylmagnesium bromide. In the devised Grignard reaction in which the two monomeric species (magnesium bromide and diphenylmagnesium) are freshly mixed, E/T value increased sharply and linearly with increasing amount of magnesium bromide in the ratio of $MgBr_2/Ph_2Mg<1$ and decreased gradually with increasing amount of magnesium bromide in the region of the ratio >1. The maximum E/T value at $MgBr_2/Ph_2Mg\simeq 1$ was considerably greater than that in the conventional Grignard solution. This result implies that the equimolar mixture of diphenylmagnesium and magnesium bromide is of greater importance than phenylmagnesium bromide to give *erythro* product, and also that alkyl-bromine exchange is not so rapid under the reaction conditions because results with a mixture of magnesium bromide and diphenylmagnesium should be identical with that of conventional Grignard reagent if the exchange is rapid.

From these facts, it may be inferred that the transition state based upon the coordinative interaction (A) plays a greater role for governing the steric direction of the Grignard reaction than that based upon the electrostatic repulsion (B). Here, we must infer a more detailed structure of the possible transition state; which component forms a bridge between C_2-O and nitrogen, and which component coordinates to C_3-O (magnesium bromide or diphenylmagnesium).

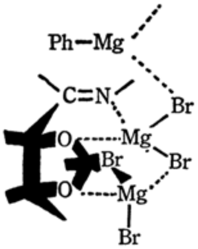
Magnesium bromide is more acidic than diphenylmagnesium. Therefore it can be assumed that at first magnesium bromide preferentially makes a bridge between nitrogen and C_2-O by coordination and then diphenylmagnesium coordinates with C_3-O and bromine of the magnesium bromide as shown by C.



C

Model C explains that an equimolar mixture of magnesium bromide and diphenylmagnesium gives the highest yield of *erythro* derivative, because there is no phenyl group above the five membered ring made by N, C_1, C_2, O and Mg, but under the ring. This model is also in agreement with the results obtained by the reverse addition made. The ratio (reagent/substrate)$=1.5$ in the precipitate implies that half of the substrate is coordinated with dimeric species or two magnesium. It may be considered that the ratio of the substrate coordinated with the dimeric Grignard species increases further on increasing the amount of reagent. Therefore, the stereoselectivity is apt to increase with an increased amount of the reagent (run 15, 16 and 1).

The effect of excess magnesium bromide to lower the E/T can also be explained as follows. When the ratio of magnesium bromide to diphenylmagnesium becomes larger, magnesium bromide will coordinate with C_3-O competitively, and then, Ph-Mg species must approach from above the ring as is shown in diagram D. Consequently, excess magnesium bromide acts to lower the E/T value (run 12, 13, 14 and Fig. 1).



D

Cram *et al.* have explained reversal of the stereoselectivity of phenylmagnesium bromide reaction *vs.* phenyllithium reaction with α,β-diketones or hydroxyketones (Stocker's observation) by dipolar model.[14] However, it cannot be explained by the dipolar model that the reaction with low molar concentration of the Grignard reagent in ether (monomeric reagent) gave almost the same value as that with high molar concentration of the ethereal Grignard reagent (run 1 and 2), and

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[14] a) D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1963); b) J. W. Cornforth, R. H. Cornforth and K. K. Maphews, *J. Chem. Soc.*, **1959**, 112.

TABLE 4. SPECIFIC ROTATIONS OF DIASTEREOMERIC MIXTURES

Run	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
$[\alpha]_D$	+34	+10.5	+39	+31	+30	+30	+9	+31.5	+41	+45	+43	+37	+30	+28	+32

Each specific rotation was measured in ethanol (c=1.0, l=1).

also that excess of magnesium bromide disturbs formation of *erythro* derivative (Table 2 and Fig. 1).

Experimental

Preparation of the Grignard Reagent in Various Solvent. The Grignard reagent in ether or tetrahydrofuran was prepared as follows.

To a suspension of 1.7 g (0.07 g atom) of magnesium in 100 m*l* of ether or 70 m*l* of tetrahydrofuran was added dropwise a solution of 7.2 m*l* (0.069 mol) of bromobenzene in ether on heating.

The ethereal Grignard solution in low molarity (0.083 M concentration) was prepared by dilution of the above solution with ether (about 700 m*l*; to the final volume of 850 m*l*).

The Grignard benzene solution was prepared by addition of benzene (70 m*l*) to the syrup obtained by removal of ether from ethereal reagent described above.

The Grignard solution with a mixed solvent of ether and triethylamine was prepared by addition of 3.2 m*l*, 6.4 m*l* or 26 m*l* of triethylamine into the ethereal solution described above.

0.25 M Diphenylmagnesium Solution. Diphenylmagnesium was prepared according to the Schlenk method,[15] by shaking 148 g of diphenylmercury and 110 g of magnesium in 1700 m*l* of ether under nitrogen atmosphere for 30 days. Molarity was determined by residual titration with alkali.

2.5 M Magnesium Bromide Solution. An ether solution of magnesium bromide was prepared by the reaction of magnesium with ethylene bromide in ether.[16] The reaction mixture was filtered through glass filter under dried nitrogen atmosphere. The reagent was analyzed by titrating bromine with 0.5 N $AgNO_3$ solution using K_2CrO_3 as an indicator.

A Mixture of Diphenylmagnesium and Magnesium Bromide. In runs 8—14, 120 m*l* of 0.25 M diphenylmagnesium solution was mixed with 4.5 m*l*, 9 m*l*, 18 m*l*, 27 m*l*, 45 m*l* or 90 m*l* of 2.5 M $MgBr_2$ solution respectively, just before the reaction.

General Procedure for the Reaction of *N*-Benzyl-2,3-*O*-isopropylidene-D-glyceraldimine with Various Grignard Reagents. An ether solution of 5 g (0.0228 mol) of *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldimine was added at 0—5°C under nitrogen atmosphere to the Grignard solution described above. The reaction mixture was stirred at 0—5°C for 1 hr, and then refluxed with stirring for 6—10 hr. It was poured into ice-water containing ammonium chloride covered with 100 m*l* of ether. Ether layer was separated, washed with water, dried, and concentrated *in vacuo* to a syrup. The syrup was treated with 6 N hydrochloric acid (20 m*l*) at 100°C for 3 hr. An insoluble residue was removed by filtration through activated carbon. The filtrate was decolorized with activated carbon, and then extracted four times with 50 m*l* portions of ethyl acetate, after adjustment of the pH to about 10 with sodium hydroxide solution. The combined ethyl acetate solution was washed with water and dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure to give a diastereoisomeric mixture of the crude 1-benzylamino-1-deoxy-1-*C*-phenyl-D-glyceritol. Thin layer chromatography of each raw product gave a single spot (R_f: 0.63±0.01; solvent=ethanol - benzene mixture (7 : 3)) identical with authentic sample. Analytical values in every case were in agreement with that calculated for $C_{16}H_{19}O_2N$. The specific rotations of the crude products were measured and the results were summarized in Table 4. The mixture was fractionally crystallized from ethanol - acetone to isolate the two pure diastereoisomers. 1-Benzylamino-1-deoxy-1-*C*-phenyl-*threo*-D-glyceritol [mp 101—102°C, $[\alpha]_D$ −81 (c 1, ethanol)] and 1-benzylamino-1-deoxy-1-*C*-phenyl-*erythro*-D-glyceritol [mp 89—90°C, $[\alpha]_D$ +68 (c 1, ethanol).[2]

Reaction by Reverse Addition Mode. To an ethereal solution of 5 g (0.0228 mol) of I was added an equimolar or two molar equivalent Grignard solution in ether. The reaction mixture was treated by the same procedure as above.

The precipitate appeared on addition of equimolar amount of the reagent (0.00137 mol) into an ethereal solution of I (0.00137 mol) was separated from the solution and washed with ether. The precipitate was dried which weighed 3.15 g. The ether solution was concentrated *in vacuo* to give 1.25 g of a syrup. Combustion of 0.2090 g of the precipitate gave 0.0255 g of magnesium oxide. The ratio of the reagent to the substrate was calculated from this value. The calculated ratio (magnesium/substrate) was 1.5. Similar results were obtained by determination of bromine (using 0.5 N $AgNO_3$ solution). The molar ratio (bromine/substrate) was 1.47.

On the other hand, the ratio (reagent/substrate) in the syrup obtained from the solution was 0.16 by combustion analysis, and 0.35 by bromine determination

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[15] W. Schlenk, jun., *Ber.*, **64**, 736 (1931).

[16] H. O. House, D. D. Traficante and R. A. Evans, *J. Org. Chem.*, **28**, 348 (1963).