

Asymmetric Synthesis with Carbohydrates. Part 2.¹ Asymmetric Grignard Addition Reactions conditioned by Chiral Magnesium Alkoxides

By Neil Baggett * and Richard J. Simmonds, Department of Chemistry, University of Birmingham, P.O. Box 363, Birmingham B15 2TT

Enantioselective Grignard addition reactions are described in which magnesium alkoxides derived from 1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose and 1,6-dideoxy-3,4-*O*-isopropylidene-2,5-di-*C*-methyl-*L*-*threo*-hexitol are used to provide chiral complexation of the Grignard reagent. A stereochemical interpretation of these and other results is presented.

THE enantioselective synthesis of chiral tertiary alcohols by addition of achiral Grignard reagents to achiral ketones in the presence of chiral auxiliary substances has been studied intermittently for 25 years²⁻⁸ but no convincing rationalisation of the results has appeared. During the same period asymmetric syntheses of chiral secondary alcohols by reduction of achiral ketones with chiral Grignard reagents have been achieved and in this case the results have been rationalised.⁹ Until recently there has been no agreement in the literature on the structure of Grignard reagents and this, no doubt, has deterred most authors from a detailed speculation on the stereochemical course of asymmetric Grignard addition reactions. The structure of Grignard reagents is now better understood¹⁰ and many features of their addition reactions to ketones are known¹¹ so that it is now appropriate to extend the study of this class of reaction and we now report some of our efforts in this direction. Our objectives have been to attempt to find new chiral conditioning reagents based on carbohydrates giving high enantioselectivity and to develop a convincing model in order to rationalise the stereochemical outcome of asymmetric Grignard addition reactions. In addition, results from such experiments may be used as a subtle mechanistic probe because any theory regarding mechanism of Grignard reactions may be tested for its degree of concordance.

RESULTS AND DISCUSSION

Some of the most enantioselective syntheses in this area have used^{5,7} an alkoxy magnesium halide, derived from a chiral alcohol and a Grignard reagent, which may then complex further Grignard reagent. For example, markedly enantioselective Grignard addition reactions were observed⁵ in the presence of the carbohydrate derivative 1,2:5,6-di-*O*-isopropylidene- α -D-glucopyranoside (DAG), and evidence was obtained for complexation of Grignard reagent to the chiral alkoxy magnesium halide as has been proposed during the late stages of Grignard addition reactions. Complexes involving one alkoxide moiety for two magnesium atoms and two alkoxide moieties for three magnesium atoms have been proposed,¹² with ether solvent molecules completing the co-ordination sphere for the magnesium atoms. In principle, a carbohydrate derivative could act as a

polydentate ligand with carbohydrate ether or acetal oxygen atoms playing the role usually fulfilled by solvent ether molecules and co-ordinating to magnesium. It is known that bicyclic acetals derived from α -*erythro*-diols are more stable than those derived from α -*threo*- or β -*threo*-diols¹³ and consequently it could be argued by analogy that 1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose (DAA), in which there is an *erythro*-relationship between the free hydroxy-group and other oxygen atoms in the molecule, could be involved in more stable bidentate complexing than is possible with DAG, in which there is a *threo*-relationship between the free hydroxy-group and adjacent oxygen atoms.

The ability of DAA to act as a chiral conditioning agent was explored under conditions identical with those which gave⁵ the highest optical yields when using DAG. Thus when a solution of methylmagnesium iodide was added to DAA in diethyl ether solution followed by ethyl phenyl ketone to give a mixture in the molecular proportions of 3.5:2:1 respectively, the resulting 2-phenylbutan-2-ol was optically active; this indicated selective formation of the *S*-enantiomer in 6% optical yield. This result may be compared with 24% optical yield of the *R*-enantiomer using DAG as the chiral auxiliary agent.⁵ Thus, in this case, the apparent possibilities for more effective complexation of the Grignard reagent do not, in practice, result in higher optical yields.

In a further attempt to achieve bidentate complexing of the Grignard reagent attention was turned to use of chiral diols. Inch and his co-workers⁵ used methyl 4,6-*O*-benzylidene- α -D-glucopyranoside as a conditioning agent but the complexity of this case precludes a stereochemical analysis. The use of symmetrical chiral diols can simplify the stereochemical analysis.¹ The magnesium atom in a Grignard reagent which is engaged in bidentate complexation with an unsymmetrical diol is a chiral centre which will be undergoing relatively rapid stereomutation involving interconverting diastereoisomers and this fact complicates any attempt to rationalise the stereochemical outcome of any reaction involving such a Grignard reagent. However if the chiral bidentate complexing agent has an axis of symmetry this simplifies the analysis because the number of diastereoisomeric arrangements is reduced. Therefore, to study the effect of a diol in asymmetric synthesis with Grignard reagents we have used 1,6-dideoxy-3,4-*O*-isopropylidene-

2,5-di-*C*-methyl-*L*-threo-hexitol (DIMTH). This diol was easily made from (+)-tartaric acid in reasonable yield by reaction with 2,2-dimethoxypropane followed by reaction with methylmagnesium iodide. The preparation and use in asymmetric synthesis of other compounds derived from tartaric acid has been described.¹⁴

When methylmagnesium iodide (3 mol equiv./mol equiv. of diol) was added to *ca.* 0.1M-solution of DIMTH in dry ether a thick syrup separated from solution. Addition of ethyl phenyl ketone gave preferentially (*S*)-2-phenylbutan-2-ol in 13.5% optical yield. When the experiment was repeated using more dilute solution (*ca.* 0.03M-solution of DIMTH) a thick syrup was also formed and the optical yield (13%) was not significantly changed. However, when a mixture of methylmagnesium iodide and diol (4 mol equiv. of MeMgI/mol equiv. of diol) was allowed to react with 0.55 mol equiv. of ethyl phenyl ketone the optical yield (3.4%) was considerably reduced although (*S*)-2-phenylbutan-2-ol was still formed preferentially. Since this result might have been due to only half of the unchanged Grignard reagent present being attached to the chiral template, the addition reaction then proceeding principally *via* achiral ether solvated Grignard reagent, the reaction was repeated using 1.3 mol equiv. of ethyl phenyl ketone per mol equiv. of diol. The expectation was that an increased optical yield due to reaction of an increased proportion of chiral conditioned Grignard reagent would result. However, despite the apparent complete use of Grignard reagent (some ketone was recovered) the optical yield (2.5%) remained almost unchanged. This result may, therefore, be taken as evidence that a complex is involved in which all of the Grignard reagent present is complexed and that its structure is different from that of the complex involving only 3 mol equiv. of Grignard reagent per mol equiv. of diol.

Addition of methylmagnesium iodide to cyclohexyl phenyl ketone in the presence of DIMTH using a molar ratio of Grignard reagent, diol, and ketone equal to 3 : 1 : 0.55 respectively at a concentration of *ca.* 0.03M of diol in ether produced (*S*)-1-cyclohexyl-1-phenylethanol with an optical yield of 24.4%. This may be compared with the reported⁵ synthesis of the (*R*)-enantiomer in 65% optical yield by using DAG.

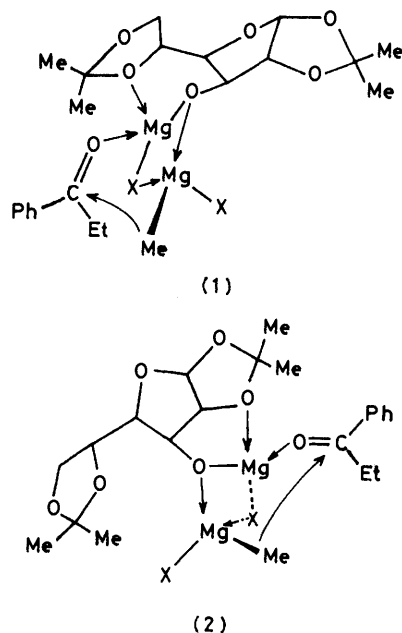
Stereochemical Interpretation.—In most investigations, Grignard reagents have been shown¹⁵ to be dimeric, solvated species with a tetrahedral arrangement of the groups around magnesium. In solution the RMgX may be involved in disproportionation reactions (the Schlenk equilibrium) as well as oligomerisation. Fairly recently, it has been recognised¹¹ that a further complicating feature in many Grignard addition reactions is that the magnesium alkoxides produced during the reaction form strong complexes with the original Grignard reagent. In the reactions described here the situation is much simplified because a complex is immediately created from the conditioning alcohol and Grignard reagent and the involvement of this strong complexation obviates the need for consideration of disproportionation

or oligomerisation of the Grignard reagent. Structures for these complexes can be envisaged which are analogous to the complexes proposed¹¹ by Ashby except that acetal oxygen atoms in the carbohydrate as well as solvent co-ordinate to magnesium.

For simplicity it may be assumed that the next step in the Grignard addition reaction is co-ordination of the ketone to magnesium involving displacement of a ligand rather than expansion of the co-ordination shell. In these cases there are usually ligand positions occupied by relatively weakly co-ordinated solvent molecules which are obvious favourites for displacement. It is reasonable to assume that the ketone is complexed to the magnesium which is a stronger Lewis acid (the alkoxide magnesium) which therefore results in the alkyl group being transferred in a six-centred process.

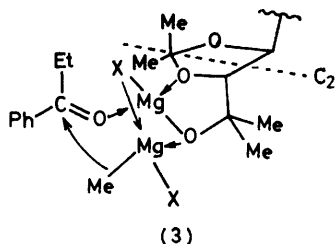
The remaining choices concern the geometry of co-ordination of the carbonyl group to magnesium. It is assumed that the phenyl rather than the ethyl group prefers¹⁶ the position opposite to the magnesium atom, *i.e.* that the *E*-configuration around the co-ordinated carbonyl group is preferred and that the *anti*-conformation at the new O-Mg bond is preferred.

Taking these points into consideration, structures (1) and (2) are proposed as transition-state models to rationalise the observed stereoselectivity of methylmagnesium iodide addition reactions to ethyl phenyl ketone in the presence of DAG and DAA respectively. In (1) the methyl group is arranged for addition to the *si*-face of the carbonyl group in a chair-like transition state to give the *R*-product and *via* (2) the *S*-product will result by addition of the methyl group to the *re*-face of the carbonyl group.

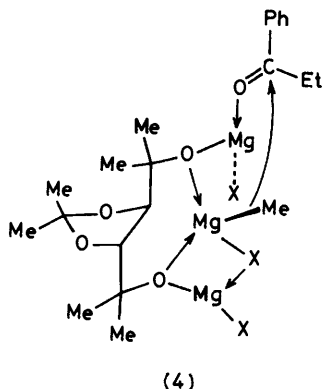


In the reactions conditioned by DIMTH two transition-state models are required to account for differences observed when the ratio of diol to Grignard reagent was

varied. For the complex resulting from admixture of 4 mol equiv. of Grignard reagent per mol equiv. of diol an axially symmetrical arrangement that is structurally analogous to the models above can be assumed. Co-ordination of the ketone, in the *anti,E*-conformation at the magnesium of the alkoxide then allows transfer of the methyl group in a six-centred process to the *re*-face of the carbonyl group to give the *S*-product as observed and as shown in structure (3).

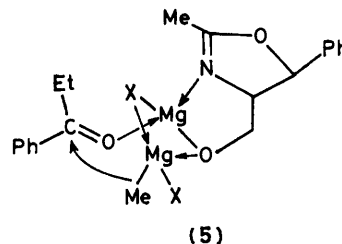


When 3 mol equiv. of Grignard reagent are added per mol equiv. of diol an axially symmetrical complex is impossible. A pseudosymmetrical complex can be envisaged however, since the magnesium atom of the unchanged Grignard reagent is undergoing¹⁷ rapid inversion of configuration which exchanges the environments of the two alkoxide magnesium atoms so that their time-averaged environments are stereochemically equivalent (homotopic). Co-ordination of the ketone, in the *anti,E*-conformation, at either alkoxide magnesium then allows transfer of the methyl group in a six-centred process to the *re*-face of the carbonyl group to give the *S*-product as observed and as shown in structure (4).



When this hypothesis of a six-centred process for Grignard addition reactions conditioned by chiral alkoxides is extended to the hydroxymethyloxazolines used by Meyers and Ford⁷ a transition-state model, structure (5), is obtained and the reported enantioselectivity is explained qualitatively. By using transition-state models similar to (5) and (1) and by assuming that the tendency of the groups on the ketone to adopt the *anti*-position with respect to the magnesium atom is in the order¹⁶ phenyl > cyclohexyl > hexyl or butyl > ethyl > methyl > hydrogen, then all the seven remaining results of Meyers and Ford and five of the eight

remaining results of Inch and his co-workers are qualitatively explained.



EXPERIMENTAL

Grignard reagents were prepared from 'magnesium turnings for Grignard reaction' using thoroughly dried methyl iodide and solvents under oxygen-free nitrogen. Grignard addition reactions were performed by addition of the dried ketone under oxygen-free nitrogen. G.l.c. was performed on a Pye series 104 chromatograph with an SE-30 column. N.m.r. spectra were recorded at 100 MHz on a Perkin-Elmer R 14 instrument under the normal working conditions using deuteriochloroform solutions with tetramethylsilane as internal reference. Optical rotations were determined using a Perkin-Elmer 141 polarimeter with a 10-cm cell. Light petroleum refers to the fraction having b.p. 40–60 °C. T.l.c. was carried out by upward irrigation on silica gel (Merck type 7731) and detection was by iodine vapour or by fluorescence quenching. Column chromatography was effected by downward irrigation on silica gel (Merck 7734).

Addition of Methylmagnesium Iodide to Ethyl Phenyl Ketone in the Presence of DAA.—A solution of DAA (1.43 g, 5.5 mmol) in dry ether (25 ml) was added dropwise with stirring to methylmagnesium iodide [(10 mmol) from magnesium (0.244 g) and methyl iodide (1.42 g)] in dry ether (10 ml). After the mixture had been stirred for 0.5 h ethyl phenyl ketone (0.36 g, 2.7 mmol) in dry ether (25 ml) was added dropwise and stirring continued at ambient temperature for 60 h. Saturated aqueous ammonium chloride (200 ml) was added to the mixture which was then stirred for a further 0.5 h. The ether layer was then separated off and combined with an ether extract of the aqueous layer. The ethereal solution was washed with water, dried, and concentrated; the residue upon evaporation of the latter was then triturated with light petroleum. The mixture was filtered to recover DAA and the filtrate was concentrated and chromatographed on silica gel. Elution with benzene gave pure 2-phenylbutan-2-ol (0.21 g, 52%), $[\alpha]_D -1.04^\circ$ (*c* 10.4 in CHCl_3) {lit.,¹⁸ $[\alpha]_D 17.45^\circ$ for the pure *R*-enantiomer}.

1,6-Dideoxy-3,4-O-isopropylidene-2,5-di-C-methyl-L-threo-hexitol (DIMTH).—To methylmagnesium iodide (0.5 mol) [preparation from magnesium (12.2 g, 0.5 mol) and methyl iodide (71 g, 0.5 mol) in dry ether (300 ml)] was added dimethyl 2,3-*O*-isopropylidene-*L*-threarate¹⁹ (15 g, 0.07 mol) in dry ether (100 ml) at a rate sufficient to maintain gentle reflux. Stirring was maintained for 3 h and the reaction mixture subsequently poured into ice-water (1 l) containing ammonium chloride (50 g). After the mixture had been stirred for 1 h the organic layer was separated and the aqueous one extracted with ether (3 × 300 ml). The combined ethereal solutions were washed with water, dried, and evaporated to yield a white solid (12.3 g). This was recrystallised from dichloromethane to yield the *title product*

(10 g, 67%), m.p. 154–156 °C, $[\alpha]_D +5.3^\circ$ (*c* 0.9 in EtOH), δ 2.27, 2.31, 2.37 [18 H, 3 s, C(CH₃)₂], (2 H, s, exchangeable with D₂O, OH), and 3.74 (2 H, s, H-3, H-4) (Found: C, 60.7; H, 9.9. C₁₁H₂₂O₄ requires C, 60.5; H, 10.2%).

Addition of Methylmagnesium Iodide to Ethyl Phenyl Ketone in the Presence of DIMTH.—(a) A solution of DIMTH (2.0 g, 9.2 mmol) in dry ether (45 ml) was added dropwise to methylmagnesium iodide [from magnesium (0.66 g, 27.4 mmol) and methyl iodide (3.89 g, 27.4 mmol) and dry ether (35 ml)] with stirring. Stirring was continued for 1.5 h and then ethyl phenyl ketone (0.67 g, 5 mmol) in dry ether (10 ml) was added dropwise to the cooled (0 °C) and stirred mixture. After being stirred for a further 3 h the mixture was allowed to come to room temperature overnight. Saturated aqueous ammonium chloride was added, and the ether layer was separated and combined with an ether extract of the aqueous layer. The combined ethereal solutions were washed with water, dried, and evaporated. The residue was triturated with light petroleum and DIMTH (1.3 g, 65%) was recovered by filtration. The filtrate was evaporated and distilled to give an oil (0.36 g), b.p. 70–85 °C at 1 mmHg, $\alpha_D -0.17^\circ$ (*c* 13.6 in CHCl₃). G.p.c. analysis showed the presence of DIMTH (3.7%), ethyl phenyl ketone (35%), and 2-phenylbutan-2-ol (61.3%); corrected $[\alpha]_D -2.36^\circ$ {lit.,¹⁸ $[\alpha]_D 17.45^\circ$ for the pure *R*-enantiomer}.

(b) The experiment was repeated as in (a) except that a greater volume (200 ml) of dry ether was used. This gave recovered DIMTH (1.7 g, 85%) and an oil (0.47 g), $\alpha_D -0.138^\circ$ (*c* 20.4 in CHCl₃) containing (by g.p.c.) the DIMTH (1.1%), the starting ketone (66.4%), and 2-phenylbutan-2-ol (32.4%); corrected $[\alpha]_D -2.27^\circ$.

(c) The experiment was again repeated as in (a) using methylmagnesium iodide (36.2 mmol), DIMTH (9.15 mmol), and dry ether (200 ml); work-up gave recovered DIMTH (1.53 g, 75%) and an oil, $\alpha_D -0.045^\circ$ (*c* 19.4 in CHCl₃) containing (by g.p.c.) DIMTH (6.1%) and 2-phenylbutan-2-ol (93.8%); corrected $[\alpha]_D -0.59^\circ$.

(d) The experiment was again repeated as in (c) but using ethyl phenyl ketone (1.62 g, 12 mmol) to give recovered DIMTH (1.4 g, 70%) and an oil (0.99 g), $\alpha_D +0^\circ$ (*c* 46.0 in CHCl₃) containing (by g.p.c.) DIMTH (5.1%), ethyl phenyl ketone (34.3%), and 2-phenylbutan-2-ol (60.6%); corrected $[\alpha]_D -0.44^\circ$.

Addition of Methylmagnesium Iodide to Cyclohexyl Phenyl Ketone in the Presence of DIMTH.—The addition of a mixture of methylmagnesium iodide (27.4 mmol) and DIMTH (2.0 g, 9.15 mmol) to cyclohexyl phenyl ketone (0.95 g, 5 mmol) in dry ether (200 ml) was performed as in (b) above. Chromatographic purification of the product gave cyclohexyl-1-phenylethanol (0.11 g, 11%); $[\alpha]_D -5.02^\circ$ (*c* 5.05 in CHCl₃) {lit.,⁵ $[\alpha]_D -20.6^\circ$ in CHCl₃ for the pure *S*-enantiomer}.

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