Mechanisms of Hydrogenation. Part IX.† Induced Asymmetry in Homogeneous Hydrogenation at a Rhodium Complex by the Use of Optically Active Amide Ligands

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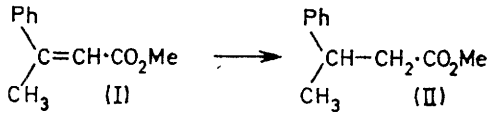
Homogeneous hydrogenation of methyl *trans*- or *cis*-3-phenylbut-2-enoate at a rhodium complex in presence of a series of optically active amides yields methyl 3-phenylbutanoate showing an appreciable degree of optical activity depending on the amide. The asymmetry of the methyl 3-phenylbutanoate formed is correlated with the chirality of the amide ligand in the complex.

We have described [1] a system for homogeneous hydrogenation from which a catalytically active complex, $(py)_2Rh(dmf)Cl_2(BH_4)$, carrying dimethylformamide (dmf) as a ligand has been isolated. This observation suggested the possibility of using an optically active amide ligand in place of dimethylformamide as a means of inducing asymmetric hydrogenation of a suitable olefin. This concept has been verified [2] by the hydrogenation of methyl 3-phenylbut-2-enoate (I)



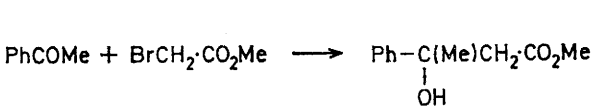
with $(py)_3RhCl_3$–$NaBH_4$ and hydrogen in the presence of the amides listed in the Table to give methyl 3-phenylbutanoate (II) of various degrees of optical activity.

Initially the optically active amide was used as the solvent, *i.e.* it replaced the dimethylformamide previously used as reaction medium with this catalyst system.[1] This procedure is, however, objectionable in that it limits the choice of amide to liquid materials, and more seriously through the possibility that the induced asymmetry could arise not *via* a specific amide–rhodium complex, but simply as a result of solvation in the asymmetric medium. However, since the induced optical activity could be reproduced quantitatively by using the amide in dilute solution in diethylene glycol monoethyl ether (digol, $EtOCH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2OH$), or in this solvent with a little water the results must be ascribed to the amide acting as an asymmetric ligand and in *cis* relation to the reaction site for hydrogenation.

† Part VIII, preceding paper.

[1] I. Jardine and F. J. McQuillin, *Chem. Comm.*, 1969, 477.
[2] P. Abley and F. J. McQuillin, *Chem. Comm.*, 1969, 477.

Pure methyl 3-phenylbutanoate shows an optical rotation [3] of ±58°. The best values observed for induced asymmetry therefore correspond to an optical yield of *ca.* 60%, which represents a useful advance on previous examples of this type reported for heterogeneous [4] or homogeneous hydrogenation.[5]

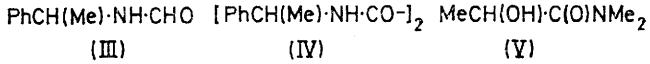


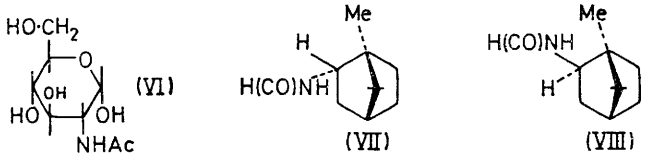
Methyl 3-phenylbut-2-enoate prepared [6] by sequence (1) was shown (n.m.r. spectrum) to contain the *cis*- (Ia) and *trans*- (Ib) isomers in a ratio of 1 : 9. Hydrogenation of this mixture and of the pure *trans*- and *cis*-isomers was examined.

Methyl 3-phenylbut-2-enoate (0·1M) with $(py)_3RhCl_3$–$NaBH_4$ ($4·5 \times 10^{-3}$M)

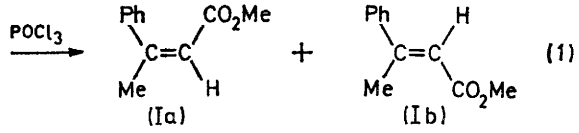
Amide		Solvent *	Product (II)
(+)-(III), $[\alpha]_D$	+180°	(*a*)	$[\alpha]_D$ +33°
(−)-(III)	−170	(*a*)	−28
(+)-(III)	+180	(*b*)	+32
(+)-(IV)	+175	(*c*)	+26
(−)-(V)	−0·55	(*a*)	−9
(+)-(VI)	+40·7	(*c*)	−8
(−)-(VII)	−42	(*b*)	+26
With *cis*- (Ia) ester		(*b*)	+23
With *trans*- (Ib) ester			
(−)-(VIII)	−25		
With *cis*- (Ib) ester			+16
With *trans*- (Ib) ester		(*b*)	+13

* (*a*) With amide as solvent at 60°. (*b*) With amide as a 5% solution in ethyl digol. (*c*) With a 5% solution in ethyl digol–water (10 : 1).

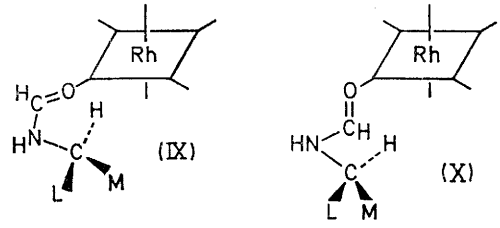




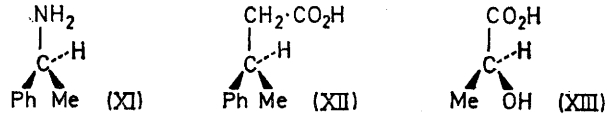
Although there are clear exceptions,[7] amides are generally regarded as being co-ordinated through the carbonyl oxygen [8] which, in a case such as PhCH(Me)·NH·CHO places the optically active centre five atoms removed from the centre of induced asymmetry. However, in the reactions of glyoxylic esters with Grignard reagents asymmetry is induced over a separation of four atomic centres,[9] and in the amides the bond order places some limitation on rotation about the –NH–CO bond.[10] Further, in considering the rotational preference at the asymmetric carbon centre of the complexed amide we suppose that an arrangement

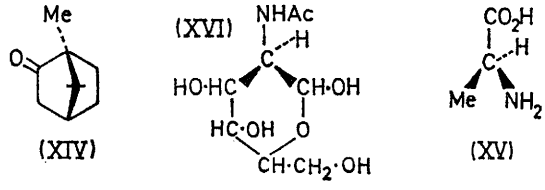


(IX) or (X) with the smallest substituent directed towards, and the larger groups L and M, directed away from the rhodium complex will represent a state of minimal compression.



The stereochemistry of (*S*)-(−)-1-phenylethylamine (XI) has been related to that of (*R*)-(−)-3-phenylbutanoic acid (XII) *via* (*S*)-(+)-hydratropic acid.[4,11] The *NN*-dimethyl-lactamide (V) used was obtained from (+)-lactic acid (XIII).[12] The bornyl- and isobornylamides were prepared [13] from (+)-camphor [14] (XIV), and have therefore the absolute configurations shown in (VII) and (VIII). The configuration of C-2 of (+)-*N*-acetyl-α-D-glucosamine has been correlated [15] with (+)-alanine (XV) in which the methyl group is derived from C-1 of the glucosamine. The *N*-acetyl glucosamine therefore has the configuration (XVI).





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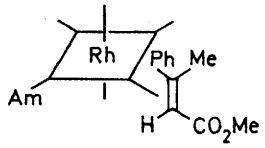
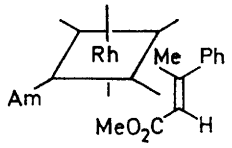
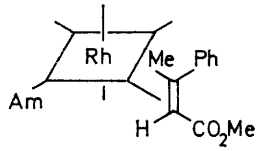
The resultant chirality of the methyl 3-phenylbutanoate which is formed in hydrogenation could be determined either by the sense (XVIIa and b) for the *trans*- and (XVIIIa and b) for the *cis*-ester, in which the methyl 3-phenylbut-2-enoate is co-ordinated, or at the subsequent stage of hydrogen transfer. Since, however, the *cis*- and *trans*-isomers (Ia) and (Ib) give almost exactly the same degree of induced asymmetry it seems likely that at the decisive stage the molecule has lost the olefin geometry. This may imply that the hydrogen-transfer step determines the induced asymmetry, or that of the arrangements (a) and (b) in (XVII) and (XVIII), one is very much preferred.



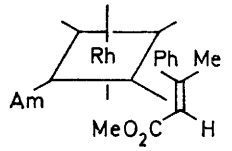
(XVIIa)



(XVIIb)



(XVIIIa)

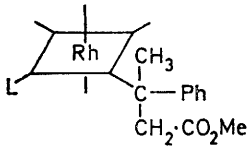


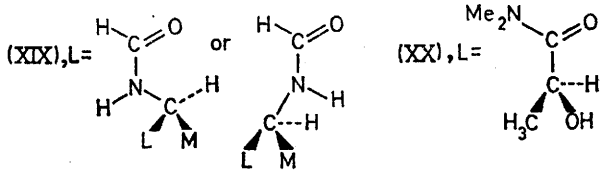
(XVIIIb)

Am = Amide ligand

The sequence of hydrogen addition is unknown, but on steric grounds addition to the tertiary centre should be the slow step. The converse order of addition would not materially alter the following reasoning, but development of the asymmetry of the product is most conveniently discussed in terms of a reaction complex (XIX) or (XX) based on the following considerations. (i) The amide is co-ordinated so that the smallest substituent group, hydrogen, projects towards the complex. (ii) The smaller groups of the butanoate, *i.e.* $CH_2{\cdot}CO_2Me$ or CH_3, will be projected so as to lie preferentially between the two smaller groups, H and M, of the asymmetric carbon centre, *i.e.* with the phenyl group remote.

Premise (i) minimises steric compression of the co-ordinated amide, and (ii) minimises steric compression between the amide and butanoate substituent groups. The activation energy to achieve (XIX) or (XX) is in this way minimised.

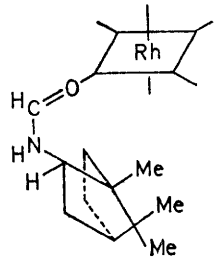


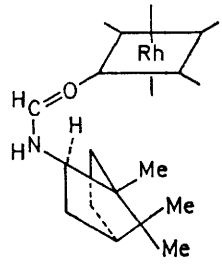


Hydrogenolysis of the rhodium–carbon bond, with retention of stereochemistry, leads to (*R*)-(−)-methyl 3-phenylbutanoate, which is in fact the predominant enantiomorph formed with (*S*)-(−)-1-phenylethylformamide, *i.e.* in the case (XIX; L = Ph, M = Me). For (−)-*NN*-dimethyl-lactamide: L = Me, and M = OH, and for (+)-*N*-acetyl-α-D-glucosamide: L = CH·OH·CH·OH and M = CH·OH–O–, which again should correspond with the formation of an excess of the (*R*)-(−)-methyl phenylbutanoate, as is observed. For (*R*)-(+)-PhCH(Me)·NH·CHO and the related (+)-oxamide (IV), the group sizes at the chiral centre lead to an arrangement entiomorphous with (XIX) in which the stereochemistry of the amide and butanoate ligands are inverted. Following the steric conventions (i) and (ii) the (*R*)-(+)-phenylethyl amides should then lead to the formation of a preponderance of (*S*)-(+)-methyl phenylbutanoate, as is observed. Thus the stereoselectivity of the complex derives from the effectiveness of the substituents L and M in the amide in determining the orientation in which the phenylbutenoic ester will more readily co-ordinate and react. The available data point to a correlation between the degree of induced optical activity and the size of the L and M groups in the amide.

The bornane ring system is less hindered on the *endo*-side,[16] *i.e.* remote from the $>C(CH_3)_2$ bridge and $-CH_3$ substituents. On these grounds (XXI) and (XXII) should represent preferred orientations for the bornyl- and isobornyl-formamide ligands respectively. In alternative rotamers of (XXI) and (XXII) there is greater hindrance between the bornyl residue and the –NH·CHO group, and also with the remainder of the rhodium-complex, although the energy advantage of (XXI) and

(XXI)





(XXII)

(XXII) over these alternatives is evidently not large. Inspection shows that both (XXI) and (XXII) should lead to the observed preponderance of (*S*)-(+)-methyl phenylbutanoate on hydrogenation. It is of interest that the bornylamine derivative proved rather the more effective. In the reaction of bornyl- and isobornyl-phenylglyoxalates with methylmagnesium iodide Prelog[17] observed a rather greater degree of asymmetric induction with the bornyl than with the isobornyl ester.

EXPERIMENTAL

Methyl 3-phenylbut-2-enoate. This was obtained as described in ref. 6, b.p. 142° at 1·2 mmHg, τ 3·90 and 3·16

[16] *Cf.* H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, 1966, **88**, 2811.

[17] V. Prelog and H. L. Meier, *Helv. Chim. Acta*, 1953, **36**, 320.

(vinyl proton) relative intensity 9 : 1, corresponding to the *trans*- and *cis*-isomers. Hydrolysis and recrystallisation of the acid from hexane gave *cis*- and *trans*-3-phenylbut-2-enoic acid, m.p. 131 and 98° respectively (lit.,[18] 131·5 and 98·5° respectively). Re-esterification with diazomethane gave the corresponding methyl esters.

(+)- *and* (−)-N-1-*Phenylethylformamide*. 1-Phenylethylamine was resolved [19] by means of (+)-tartaric acid to give the (+)- and (−)-enantiomorphs, $[\alpha]_D$ +39 and −37° (lit.,[19] $[\alpha]_D$ +39·1 and −40·3° respectively). The amine was heated under reflux with ethyl formate and the product was distilled to give (+)- and (−)-*N*-1-phenylethylformamide, b.p. 130° at 1·2 mmHg, $[\alpha]_D$ +180 and −172° (lit.,[20] −178°).

(+)-NN′-*Bis*-(1-*phenylethyl*)*oxamide*. This was obtained from (+)-1-phenylethylamine and diethyl oxalate on warming, m.p. 182° (lit.,[21] 180°), $[\alpha]_D$ +175°.

NN-*Dimethyl-lactamide*. (+)-Lactic acid (1·0 g) in tetrahydrofuran (20 ml) with triethylamine (1·1 g) was treated with ethyl chloroformate (1·3 g) with cooling. The precipitated triethylamine hydrochloride was filtered off and dimethylamine (0·5 g) was added to the filtrate. Distillation gave (−)-*NN*-dimethyl-lactamide, b.p. 62° at 1·2 mmHg, $[\alpha]_D$ −0·55° (lit.,[21,22] b.p. 56° at 0·6 mmHg, $[\alpha]_D$ −0·6°).

N-*Bornyl- and -isobornyl-formamides*. Camphor oxime, $[\alpha]_D$ −43°, was prepared from (+)-camphor, $[\alpha]_D$ +44°. Reduction of the oxime with sodium and pentyl alcohol gave (+)-bornylamine, m.p. 161°, $[\alpha]_D$ +43° (lit.,[13] m.p. 163°, $[\alpha]_D$ +47·2). Catalytic hydrogenation with platinum oxide in acetic acid gave isobornylamine, m.p. 182°, $[\alpha]_D$ −45° (lit.,[13] m.p. 184°, $[\alpha]_D$ −43·7°). The formyl derivatives were obtained by refluxing the amines with ethyl formate, *viz*: *N*-bornylformamide, m.p. 95°, $[\alpha]_D$ −40·3° (lit.,[13] m.p. 93°, $[\alpha]_D$ −42°), and *N*-isobornylformamide, m.p. 69°, $[\alpha]_D$ −26·2° (lit.,[13] m.p. 73°, $[\alpha]_D$ −25·8°).

Hydrogenations. Hydrogenations were carried out in a differential form of apparatus,[23] the olefin being introduced after the catalyst solution [$(py)_3RhCl_3NaBH_4$–amide–solvent] had been equilibrated with hydrogen (1 atmos.; 20°). The concentrations and conditions of use are indicated in the Table.

Asymmetric hydrogenations. A solution of $(py)_3RhCl_3$–$NaBH_4$ (4·5 mM) was prepared either (a) in the optically active amide, (+)- or (−)-(III), or (−)-(V), as solvent, or (b) in a 5% solution of the amide, (+)-(III), (−)-(VII), or (−)-(VIII), in ethyl digol, or (c) in a 5% solution of amide (+)-(VI) in ethyl digol and water (10 : 1). Methyl 3-phenylbut-2-enoate was added so as to give a 0·1 molar concentration and the mixture was shaken under hydrogen. In case (a) the solution was warmed to 60° to reduce the viscosity.

After uptake of the required volume of hydrogen, and testing of a sample (n.m.r.) for complete hydrogenation, the organic product was extracted into hexane. The hexane extract, washed with water and dried, gave a product which was distilled, b.p. 110° at 1·2 mmHg. The optical rotation of the distilled ester was measured directly, and also after alkaline hydrolysis and re-esterification with diazomethane. We observed no significant differences between these measurements.

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