Asymmetric Synthesis

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1 Introduction

In a paper entitled 'A Suggestion Looking to the Extension into space of the Structural formulas at Present Used in Chemistry, and a Note upon the Relation between the Optical Activity and the Chemical Constitution of Organic Compounds' van't Hoff laid down a fundamental concept of stereochemistry.[1] van't Hoff noted that the great majority of optically active organic substances contained asymmetric carbon atoms and he recognised that if the carbon atoms were tetrahedral in character they would produce molecules related to each other as enantiomers. Pasteur mentions the tetrahedron in summarising his researches on molecular dissymmetry and as early as 1808 Wollaston predicted that one day chemists would have to think of atomic arrangements in three dimensions.

Two years before van't Hoff's paper appeared, Hofmann[2] established that a sterically hindered amine such as dimethylmesitylamine did not react with methyl iodide and the concept that steric hindrance of a functional group by a neighbouring non-functional group can retard or prevent a chemical reaction was established. Victor Meyer[3] illustrated this idea particularly well by showing that *ortho*-disubstituted benzoic acids are much more difficult to esterify and their esters are much more difficult to hydrolyse than if *ortho* substituents are absent, whereas phenylacetic acids, even if *ortho*-disubstituted, are easily esterified and their esters are readily hydrolysed. Despite Wollaston's remarkable understanding of three-dimensional atomic arrangements and the clear directive in the title of van't Hoff's paper, most of the experiments performed in the ensuing years provided confirmation of the fundamental theory rather than establishing new lines of approach. Similarly the theory of steric effects remained undeveloped.

A notable exception in this period was the discovery by Kenner[4,5] and Turner[6,7] and their co-workers that 6,6′-dinitrobiphenic acid could be resolved into optically active forms. This observation that rotation about the single bond joining the aromatic nuclei could be restricted because of the effective bulk of the substituents was of great significance because the ideas of van't Hoff had

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[1] J. H. van't Hoff in 'Classics in the Theory of Chemical Combination', ed. O. T. Benfey, Dover Publications, New York, 1963, p. 151.

[2] A. W. Hofmann, *Ber.*, 1872, **5**, 704; 1875, **8**, 61.

[3] V. Meyer, *Ber.*, 1894, **27**, 510.

[4] J. Kenner and W. V. Stubbings, *J. Chem. Soc.*, 1921, 593.

[5] G. H. Christie and J. Kenner, *J. Chem. Soc.*, 1922, 614.

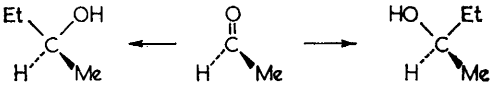
[6] C. V. Ferriss and E. E. Turner, *J. Chem. Soc.*, 1920, 1140.

[7] R. J. W. Le Fèvre and E. E. Turner, *J. Chem. Soc.*, 1926, 2476.

been so successful that chemical thought tended to overlook the fact that these considerations were based on the principles of free rotation about single bonds and of restricted rotation about double bonds. Kenner, and Turner and their co-workers showed that three-dimensional atomic arrangements and rotation about single bonds depend on the size of groups and that steric hindrance as a kinetic phenomenon must depend on mechanism, and it was not until later that mechanisms were sufficiently clearly defined and distinguished. The introduction of the concept of the transition state clearly showed that in order to be able to consider the incidence of steric and electronic effects in any chemical reaction it is essential to know the mechanism at least sufficiently well to be able to define the stereochemistry of the transition state, because it is the difference between the magnitude of the effect in the ground state and in the transition state which is important. These ideas, which are commonly grouped together in conformational analysis, have been used recently to provide a qualitative understanding of asymmetric synthesis.

In 1874 le Bel[8] defined the concept of symmetric synthesis. Any synthesis of dissymmetric molecules, starting from either symmetrical molecules or a racemic modification, and using no optically active reagents or catalysts and no asymmetric physical influence, always produces an equal number of the two enantiomerically related product molecules.

The addition of ethylmagnesium iodide to acetaldehyde produces a dissymmetric molecule. There is no reason for the Grignard reagents to have anything but an equal probability of approaching from either side of the acetaldehyde



molecule, thus producing equal amounts of (+)- and (−)-butan-2-ol. The transition states leading to (+)- and (−)-butan-2-ol are said to be enantiomeric and since acetaldehyde is a single non-dissymmetric molecule the free-energy difference between the transition states is zero. It follows that the two reactions occur at exactly the same rate and the products are formed in exactly equal amounts. le Bel continued '. . . this is not necessarily true of asymmetric bodies formed in the presence of other active bodies, or transversed by circularly polarised light or, in short, when submitted to any cause whatever which favours the formation of one of the asymmetric isomers. Such conditions are exceptional; and generally in the case of bodies prepared synthetically those which are active will escape the observation of the chemist unless he endeavours to separate the mixed isomer product, the combined action of which upon polarised light is neutral.'[8]

When a dissymmetric grouping is already present in the molecule and a second grouping (*e.g.*, an asymmetric carbon atom) is created, an exactly 1:1 mixture

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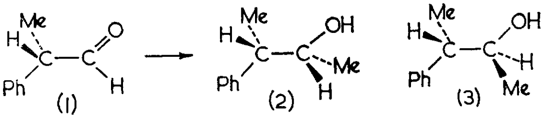
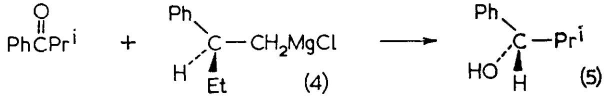
[8] J. A. le Bel, see ref. 1, p. 161.

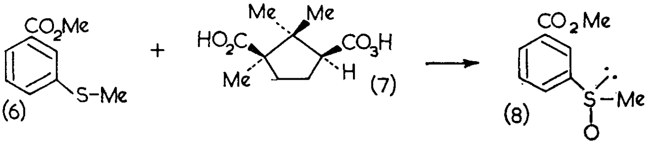
of the two possible stereoisomers (which are now diastereoisomers) is not expected. This follows from the fact that diastereoisomerically related transition states, like diastereoisomerically related ground states, differ in free energy and therefore in stability. This difference shows in the rates of formation and in the rates of reaction of stereoisomers and generally a reaction in which new dissymmetric groupings are produced in unequal amounts is called an asymmetric synthesis.

The addition of methylmagnesium iodide to the optically active aldehyde (1) provides an example.[9] This reaction can yield two diastereoisomerically related alcohols (2) and (3); indeed both are formed but alcohol (3) predominates over (2) by about 2 to 1.



The formation of products related as diastereoisomers is not the only route for asymmetric synthesis. Many examples are known in which enantiomerically related products are formed in unequal amounts. Such a case is the





reduction of isopropyl phenyl ketone with the Grignard (4) reagent from (+)-1-chloro-2-phenylbutane. Isopropylphenylmethanol (5) was obtained in 82% optical yield.[10] The magnitude of the asymmetric synthesis can be expressed as the percentage optical yield:

$$\frac{[\alpha]\text{ (product)}}{[\alpha]\text{ (pure enantiomer)}} \times 100 = \%\text{ optical yield}$$

where [α] (product) is the optical rotation of the product of the asymmetric synthesis and [α] (pure enantiomer) is the maximum optical rotation obtained (usually) by resolution. The oxidation of sulphide (6) with (+)-peroxycamphoric acid (7) to give the sulphoxide (8) in 4·3% optical yield is an example in which the new dissymmetric grouping is not an asymmetric carbon atom.[11] In these

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[9] D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, 1952, **74**, 5828.

[10] J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.* 1964, **29**, 37.

[11] A. Maccioni, F. Montanari, M. Secci, and M. Tramontini, *Tetrahedron Letters*, 1961, 607.

two and in related examples the essential feature of the asymmetric synthesis is the diastereoisomeric nature of the transition states leading to enantiomeric products in unequal amounts. The alcoholysis of various anhydrides has been used by Mislow[12] to illustrate the types of free-energy relationships found in the formation and reactions of stereoisomers. Three basic types of reaction which are under kinetic control are envisaged: In type 1, $\triangle G^\circ = 0$ and $\triangle\triangle G^\ddagger = 0$; in type 2, $\triangle G^\circ = 0$ and $\triangle\triangle G^\ddagger \neq 0$; and in type 3, $\triangle G^\circ \neq 0$ and $\triangle\triangle G^\ddagger \neq 0$, where G° and $G^\ddagger$ represent the free energies of the ground and transition states, respectively. (This passage omits much of the detailed analysis and the reader is urged to consult Mislow's book for amplification of the discussion merely summarised here. Mislow's analysis is of further importance in that it identifies the concept of asymmetric synthesis within the framework of the general phenomenon of stereoselectivity.) Of the preceding examples, the addition of methylmagnesium iodide to acetaldehyde belongs to type 1; the others belong to type 2. The earliest explanation for asymmetric synthesis postulated the dissymmetric polarisation of a symmetrical centre in a molecule under the influence of a nearby pre-existing dissymmetric grouping. Such polarisation was assumed to produce unequal amounts of two diastereoisomeric 'activated species' which react to give unequal amounts of stereoisomers.[13,14] A more recent rationalisation of asymmetric synthesis is one in which the ideas described in the beginning of this Review are used to define topological differences between diastereoisomeric transition states. These differences are ascribed to non-bonded and dipole interactions between the reactants leading to a stereochemically favoured reaction path.

Certain idealised rules and transition state models have been devised to rationalise topological difference between transition states and in the subsequent sections of this Review they will be applied to asymmetric synthesis in a few general reaction types. Morrison[15] has emphasised the limitations of many of the models: 'It is important that one realise the empirical nature of all such models, and appreciate their possible fallibility and theoretical naïvete. It is the opinion of the author that these transition-state models can be useful conceptual devices for correlating experimental results, but they should not be given great credence as predictive tools unless a large number of examples have been successfully accommodated. The utility of the model for correlative and predictive purposes does not necessarily confirm it as an accurate representation of the product-controlling transition state.'

2 Asymmetric Synthesis in Carbonyl—addition Reactions

One of the first applications of the concept of steric control of asymmetric synthesis was to the reduction of carbonyl compounds by certain Grignard reagents containing β-hydrogen atoms. Whitmore suggested a transition state

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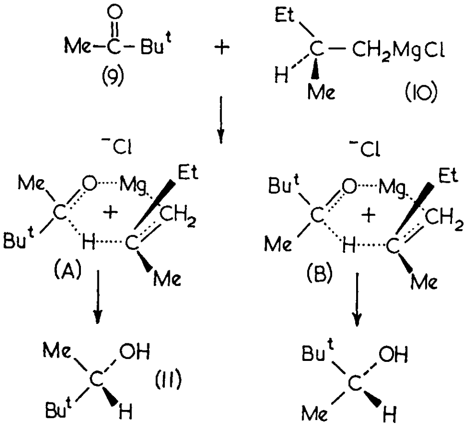
[12] K. Mislow, 'Introduction to Stereochemistry', W. A. Benjamin, New York, 1965, p. 122.

[13] T. M. Lowry and E. E. Walker, *Nature*, 1924, 113, 565.

[14] An attempt to disprove this theory has been described by M. J. Kubitscheck and W. A. Bonner, *J. Org. Chem.*, 1961, **26**, 2194; W. A. Bonner, *J. Amer. Chem. Soc.*, 1963, **85**, 439.

[15] J. D. Morrison, in 'Survey of Progress in Chemistry', ed. A. F. Scott, Academic Press, New York, 1966, vol. 3, p. 147.

in which reduction proceeds *via* an essentially planar six-membered ring structure. On the basis of this model it was predicted that the alcohol resulting from the reduction of t-butyl methyl ketone (9) with (+)-2-methylbutylmagnesium chloride (10) would contain a preponderance of the (*S*)-(+)-enantiomer (11).[16]



This was based on the idea that there would be less non-bonded interaction in the suggested transition state (A) in which the t-butyl group (larger than methyl) of the ketone was *trans* to the ethyl group (larger than methyl) attached to the asymmetric β-carbon atom of the Grignard reagent. The tendency for the transition state to form with the t-butyl and ethyl groups *cis* should be less because of the apparently greater non-bonded interaction in transition state (B). When the reaction was carried out at 20° the enantiomer of the product resulting from transition state (A) was found to predominate.[17,18] Thus

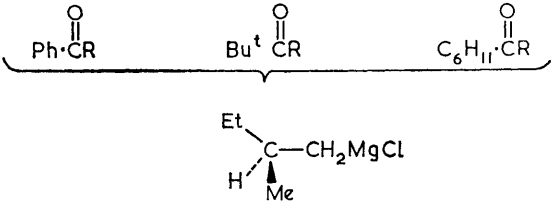


Table 1 *Optical yields* (%)

R	Me	Et	Pr^n	Bu^n	Pr^i	Bu^i	C_6H_{11}	Bu^t	Ph
Ph	3·9	5·7	5·9	7·2	24	9·9	25	16	
Bu^t	13	11	11	11	5	6	2·5		16
C_6H_{11}	3·6	8·8	8·9	11	2·1	16		2·5	25

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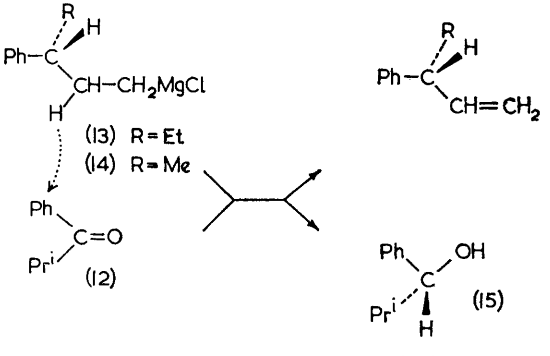
[16] The use of *R* and *S* to specify absolute configuration is described by R. S. Cahn, C. K. Ingold, and V. Prelog, *Experentia*, 1956, **12**, 81; R. S. Cahn, *J. Chem. Educ.*, 1964, **41**, 116, 508.

[17] H. S. Mosher and E. La Combe, *J. Amer. Chem. Soc.*, 1950, **72**, 3994, 4991.

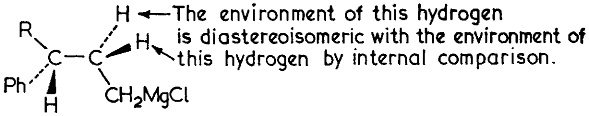
[18] E. P. Burrows, F. J. Welch, and H. S. Mosher, *J. Amer. Chem. Soc.*, 1960, **82**, 880; see also ref. 10.

the direction of the asymmetric synthesis appears to be governed by differences in the free energies of the diastereoisomeric transition states which arise from differences in non-bonded interactions between the groups attached to the β-carbon atom of the Grignard reagent and to the carbonyl group of the ketone. Amongst the possible difficulties which arise in deciding whether this interpretation is consistent with an experimental result is that of arranging the groups involved in order of effective size. The optical yields obtained for the reduction of three series of ketones with the Grignard reagent (10) are summarised in Table 1.[17,18] If the assumption is made that the order of effective size for the three largest groups in the ketone series is phenyl > t-butyl > cyclohexyl and that the ethyl group is larger than the methyl group in the dissymmetric Grignard reagent, then the predominant enantiomer of the product is that which arises from the transition state in which the larger group of the ketone is *trans* to the ethyl group of the Grignard reagent. On the surface this conclusion appears highly plausible in that it correlates the absolute configuration of the predominant enantiomer of the product in each case and that of (+)-1-chloro-2-methylbutane. However, an examination of the percentages in Table 1 appear to diminish its credibility. When R is methyl, ethyl, and n-propyl the percentages are highest for the t-butyl ketones; when R is isopropyl the percentage is highest for the phenyl ketone, and when R is isobutyl the percentage is highest for the cyclohexyl ketone. The difference between the free energies of the two transition states would be expected to decrease as R increases in effective size yet the percentage for cyclohexyl phenyl ketone is much larger than that for methyl phenyl ketone and the percentage for cyclohexyl isobutyl ketone is much larger than that for cyclohexyl methyl ketone. Morrison[15] suggests that since the energy difference between the two transition states is extremely sensitive to subtle changes in the nature of the groups being compressed in these transition states, the phenyl and cyclohexyl groups may have effective sizes that are a function of their rotational conformations in the transition state. If by compression of the groups in the transition state is meant van der Waals compression it should be emphasised that since van der Waals interactions have the steepest potential-energy gradient with respect to distance of all the causes of strain, all other parameters (torsional and angle deformations) will tend to change before van der Waals compression becomes important. Although restricted rotation of the phenyl and cyclohexyl groups may be important in any detailed analysis of the reaction the interpretative difficulties may be due to the limitations imposed by approximately planar transition-state models. For example, one can draw non-planar transition-state models having topological characteristics in which the non-bonded interactions are of quite a different order. Recent results of Mosher and his co-workers emphasise that the difference in effective size of the two substituents attached to the carbonyl group is not the only factor responsible for determining the stereoselectivity of these asymmetric reductions. Reduction of [α-$^2H_1$]benzaldehyde with the optically active Grignard reagent from (+)-1-chloro-2-methylbutane gave [α-$^2H_1$](*S*)-(+)-benzyl alcohol in 19% optical yield; reduction of t-butyl phenyl ketone with the same reagent gave approximately the same optical yield.[19] Several other types of asymmetric reduction have been rationalised in terms of non-bonded interactions in six-membered cyclic transition states; these have been reviewed by Morrison.[15]

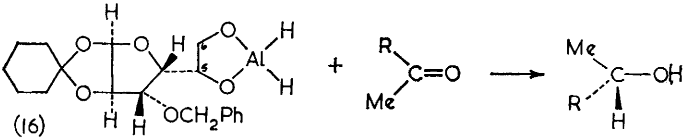
In the examples of asymmetric reduction summarised in Table 1 the hydrogen transfer occurs from the asymmetric β-carbon atom of the Grignard reagent. Morrison[20] has established that asymmetric reduction is possible even when the carbon atom from which hydrogen transfer occurs is not formally asymmetric.



Predominant enantiomer



Thus reduction of isopropyl phenyl ketone (12) with the Grignard reagents prepared from (*R*)-(−)-1-chloro-3-phenylpentane (13) and (*R*)-(−)-1-chloro-3-phenylbutane (14) gives (*R*)-(+)-isopropylphenylmethanol (15) in 29 and 23% optical yields, respectively. The essential feature of this type of asymmetric reduction is the diastereoisomeric environments of the two hydrogen atoms available for transfer to the ketone. Other examples of this phenomenon may be found in the asymmetric reduction of a series of methyl ketones with the lithium aluminium hydride–3-*O*-benzyl-1,2-cyclohexylidene-α-D-glucofuranose com-



Predominant enantiomer(s)

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[19] V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, 1966, **88**, 3595; W. A. Sanderson and H. S. Mosher, *ibid.*, 1961, **83**, 5033.

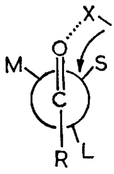
[20] J. D. Morrison, D. Black, and R. Ridgeway, *Chem. Eng. News*, 1967, **45**, 48.

Table 2

R	Ph	Bu^t	Pr^n	$CH_3(CH_2)_5$	Bu^t	$CH_2=C(CH_3)\cdot CH_2$
Optical yield (%)	34·1	2·1	13·4	12·2	25·3	31·0

plex.[21] Optically active alcohols having the *S*-configuration were obtained in up to 34% optical yield (Table 2).[21] The fact that maximum stereoselectivities were always obtained with a 1:1 hydride–sugar complex was rationalised by the suggestion that the ion (16) is a reaction intermediate. In a continuation of these studies, Landor and his co-workers[22] investigated the effect of added ethanol on the reducing properties of complex (16). For all the ketones studied the configuration of the secondary alcohol changed from (*S*) to (*R*) as the quantities of ethanol added to the complex were increased. In addition, the stereoselectivity increased to a maximum and then decreased with further addition of ethanol. Reduction of acetophenone with the ethanol-modified complex gave *R*-(+)-1-phenylethanol in up to 70·9% optical yield. Reduction of acetophenone with complex hydrides prepared *in situ* by reaction of lithium aluminium hydride with optically active amino-alcohols gave active alcohol in up to 48% optical yield.[23]

The carbonyl addition reactions discussed so far all involve the transfer of hydrogen from an optically active reducing agent to the carbonyl group of a non-dissymmetric ketone. Several years ago, Cram and Elhafez suggested[9] an empirical rule which can be used to predict the major product diastereoisomer resulting from hydride and Grignard additions to carbonyl groups directly bonded to asymmetric carbon atoms. Cram's rule states that when the asymmetric carbon atom of a molecule (17), in which the sizes of the groups are



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designated small (S), medium (M), and large (L), is so orientated that the diastereoisomeric faces of the carbonyl function are flanked by the groups S and M, the reagent R^1X in an addition reaction approaches the carbonyl group from the side of the group S, provided that the reaction is non-catalytic and that the products are formed in a kinetically controlled process, and not in a subsequent equilibration. Cram successfully correlated the configurations of a large number of compounds using six different reactions of this type, the stereo-

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[21] S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.* (*C*), 1966, 1822, 2280; for the use of other sugar derivatives see O. Cervinka and A. Fabryova, *Tetrahedron Letters*, 1967, 1179.

[22] S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.*, (*C*), 1967, 197.

[23] O. Cervinka, *Coll. Czech. Chem. Comm.*, 1965, **30**, 1684.

chemical relationships between the asymmetric centres having been independently determined in each case. The addition of methylmagnesium iodide to the aldehyde (18) provides an example. The model predicts that the *erythro*-isomer will predominate in the product if the assumption is made that the order of decreasing effective size on the asymmetric carbon atom is Ph > R > H. When R is methyl,[9,24] ethyl,[25] and isopropyl[26] this is the experimental result.

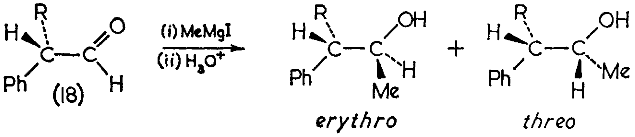

Table 3

	erythro/threo ratio
R = Me	2—4/1[9,24]
R = Et	2·5/1[25]
R = Pr^i	1·0—1·9/1[26]

The decrease in the diastereoisomeric product ratio as R varies from methyl to isopropyl illustrates one of the interpretative difficulties: namely, that of arranging the groups on the asymmetric carbon atom in order of effective size. The above results tend to indicate that the isopropyl group has a smaller effective size than that of methyl. While the actual size of a group is obviously constant, its effect on conformational equilibria or on a nearby reaction site depends very much on its immediate environment and on the reaction mechanism. For example, the isopropyl group when a substituent on a cyclohexane ring appears almost as 'large' as a t-butyl group in certain experiments and nearly the same size as a methyl group in others.[27,28] It is important to the study of asymmetric synthesis in acyclic molecules that the order of effective size of groups established by n.m.r. methods shows significant differences from that of their preference for the equatorial position of a cyclohexane ring.[29] Increasing the steric requirement of the approaching reagent results in an increase in the diastereoisomeric ratio. Thus, reaction of 3-phenylbutan-2-one with the methyl, ethyl, and phenyl Grignard reagent gives the expected *erythro* product predominating by a ratio of 2:1, 3:1, and 5:1, respectively, in the three cases.[30]

The proven utility of Cram's model does not necessarily mean that it is an accurate representation of the diastereoisomeric transition states. It was em-

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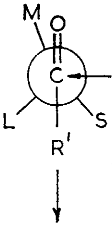
[24] Y. Gault and H. Felkin, *Bull. Soc. chim. France*, 1960, 1342.
[25] D. J. Cram, F. A. Abd Elhafez, and H. Weingartner, *J. Amer. Chem. Soc.*, 1953, **75**, 2293.
[26] D. J. Cram, F. A. Abd Elhafez, and H. LeRoy Nyquist, *J. Amer. Chem. Soc.*, 1954, **76**, 22.
[27] N. L. Allinger, L. A. Freiberg, and Shih-En Hu, *J. Amer. Chem. Soc.*, 1962, **84**, 2836.
[28] R. D. Stolow, *J. Amer. Chem. Soc.*, 1964, **86**, 2170.
[29] G. M. Whitesides, J. P. Sevenair, and R. W. Goetz, *J. Amer. Chem. Soc.*, 1967, **89**, 1135.
[30] Unpublished results of B. P. Thill quoted by E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison in 'Conformational Analysis', Interscience, New York, 1966, p. 34.

phasised earlier that in order to consider the incidence of steric effects in a chemical reaction it is essential to know its mechanism sufficiently well to be able to define the stereochemistry of the transition state. In the first place, several investigations have established that the stable ground state conformation of a carbonyl compound is one in which the carbonyl function is eclipsed and the R group staggered,[31,32,33] and therefore is not that implied in (17). However, this is not a serious objection provided that the activation energy of the reaction is large compared with the energy barrier to rotation about the relevant sp^3—sp^2 carbon–carbon single bond.[34] If this condition obtains, the diastereoisomeric product ratio should depend entirely on the free-energy differences between the two transition states.

Karabatsos[35] has developed the Cram model to a point where semiquantitative predictions of product stereospecificity are possible. The following assumptions are required. (*a*) The two transition states resemble the reactants, *i.e.*, little bond-breaking and -making has occurred at the transition states. Therefore the arrangement of the three groups on the asymmetric carbon atom with respect to the carbonyl group is similar to that in the ground state of the aldehyde or ketone. (*b*) The two product-controlling transition-state models (19) and (20) (though these were not the only models considered[35]) have the incoming group R^2 closest to the smallest group S. (*c*) The diastereoisomeric product ratio A/B reflects the relative magnitude of the carbonyl-eclipsed group interactions M ⟷ O in (19) and L ⟷ O in (20). Karabatsos[35] has calculated the free-energy differences ($G_A^{\ddagger} - G_B^{\ddagger}$) using only M ⟷ O and L ⟷ O interactions for a large number of reactions for which the experimental free-energy differences are available. The experimental $G_A^{\ddagger} - G_B^{\ddagger}$ values are obtained from the experimental product ratios A/B by use of the equation:



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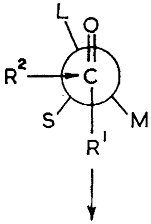
(A)



(20)

(B)

$$G_A^{\ddagger} - G_B^{\ddagger} = -RT \ln A/B$$

The results are summarised in Table 4.[35] Although the generally good agreement between the experimental and calculated free-energy differences must be fortui-

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[31] G. J. Karabatsos and N. Hsi, *J. Amer. Chem. Soc.*, 1965, **87**, 2864.
[32] G. J. Karabatsos and N. Hsi, *Tetrahedron*, 1967, **23**, 1079.
[33] G. J. Karabatsos and K. L. Krumel, *Tetrahedron*, 1967, **23**, 1097.
[34] E. L. Eliel 'Stereochemistry of Carbon Compounds', McGraw-Hill, New York, 1962, p. 151.
[35] G. J. Karabatsos, *J. Amer. Chem. Soc.*, 1967, **89**, 1367.

tous to some extent, it does lend credence to the validity of the general approach. Karabatsos stresses the following factors which may impose serious limitations. (*a*) The model does not include solvation of the transition states. (*b*) All non-bonded interactions except M ⟷ O and L ⟷ O are neglected; the experimental free-energy difference could depend on the effective size of R^2. (*c*) The extent of bond-breaking and -making at the transition state could vary with each reaction. (*d*) Differences in the entropies of the two transition states could affect the experimental $G_A^{\ddagger} - G_B^{\ddagger}$ values.

Table 4 *Experimental and calculated free-energy differences between the two diastereoisomeric transition states*

		$G_A^{\ddagger} - G_B^{\ddagger}$ (cal./mole)		
No.	*Reaction*	*Found*	*Ref.*	*Calc.*[35]
1	PhMeHC-CHO + MeMgI	−410	9	−600
2	PhMeHC-COMe + LiAlH$_4$	−550	9	−600
3	PhMeHC-COEt + LiAlH$_4$	−410	9	−600
4	PhMeHC-CHO + EtMgI	−650	9	−600
5	PhMeHC-COPh + LiAlH$_4$	−830	9	−600
6	PhMeHC-CHO + PhMgBr	−830	9	−600
7	PhMeHC-CHO + MeMgBr	−460	24	−600
8	PhMeHC-COMe + LiAlH$_4$	−660, −700 (0°) (−70°)	24	−600
9	PhMeHC-C(Me) = $\overline{N}$Mg$^+$X + LiAlH$_4$	−400	*a*	−700
10	PhMeHC-C(Me) = $\overline{N}$Mg$^+$X + NH$_4^+$HCO$_2^-$	−420	*a*	−700
11	PhEtHC-CHO + MeMgI	−550	9	−500
12	PhEtHC-COMe + LiAlH$_4$	−650	9	−500
13	PhEtHC-CHO + EtMgBr	−650	25	−500
14	PhEtHC-COEt + LiAlH$_4$	−650	25	−500
15	PhEtMeC-COMe + EtLi	−530	*b*	−500
16	PhEtMeC-COEt + MeLi	−830	*b*	−500
17	PhEtMeC-CHO + PhMgBr	−410	*c*	−500
18	PhEtMeC-COPh + LiAlH$_4$	−470	*c*	−500
19	PhPr^{i}HC-CHO + Pr^{i}MgBr	−380	26	−200
20	PhPr^{i}HC-CHO + Pr^{i}MgBr + 6MgBr$_2$	−160	26	−200
21	PhPr^{i}HC-CHO + Pr^{i}Li (pentane)	0	26	−200
22	C$_6$H$_{11}$MeHC-CHO + MeMgI	−380	*d*	−300
23	C$_6$H$_{11}$MeHC-CHO + MeLi (pentane)	−220	*d*	−300
24	C$_6$H$_{11}$MeHC-CHO + MeLi (ether)	−110	*d*	−300

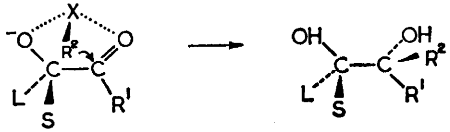
Table 4—*continued*

No.	*Reaction*	$G_A^{\#} - G_B^{\#}$ (cal./mole) *Found*	*Ref.*	*Calc.*[35]
25	C_6H_{11}MeHC-COMe + $NaBH_4$	−320	*d*	−300
26	C_6H_{11}MeHC-COMe + $LiAlH_4$	−200	*d*	−300
27	EtMeHC-CHO + MeMgBr	−220	24	−100
28	EtMeHC-COMe + $LiAlH_4$	−16, +32, +36 (−70°) (0°) (35°)	24	−100
29	PhPr^{i}HC-COPr^i + $LiAlH_4$	−1380	26	−200
30*	C_6H_{11}MeHC-COMe + Al(Pr^{i}O)$_3$	+380	*d*	−300

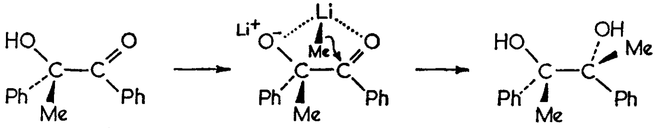
* The model does not predict the stereochemical result.
[a] D. J. Cram and J. E. McCarty, *J. Amer. Chem. Soc.*, 1954, **76**, 5740; [b] D. J. Cram and J. D. Knight, *J. Amer. Chem. Soc.*, 1952, **74**, 5835; [c] D. J. Cram and J. Allinger, *J. Amer. Chem. Soc.*, 1954, **76**, 4516; [d] D. J. Cram and F. D. Greene, *J. Amer. Chem. Soc.*, 1953, **75**, 6005.

Cram and Kopecky[36] have considered a second model for systems in which one of the groups (*e.g.*, OH) attached to the asymmetric carbon atom is capable of chelating with a metal atom in the reagent. This model involves a relatively rigid, five-membered ring structure which fixes the conformation of the reacting species. For systems in which an amino- or hydroxyl group on the asymmetric carbon atom is the medium-sized group, the open-chain and cyclic models predict the same stereochemical result. However, when the chelating group is the small group, only the rigid model (21) predicts the correct result. For example

(21)



the open-chain model (17) predicts that the addition of methyl-lithium to 2-hydroxy-1,2-diphenylpropan-1-one (22) will give a *meso*/(±) product ratio of less than unity; the cyclic model (23) predicts a ratio greater than unity. When the reaction solvent was ether the experimental ratio was 8:11. The stereoselectivity of reactions of this type is strongly dependent on the solvent[37] and on



(22) (23)

meso

Predominant isomer

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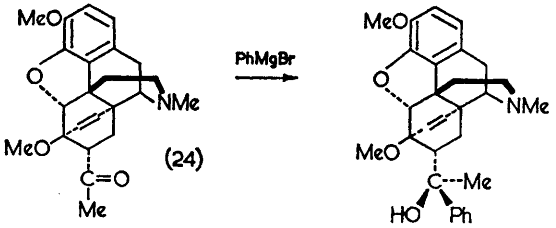
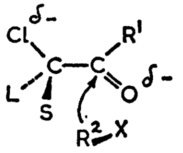
[36] D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, 1959, **81**, 2748.
[37] D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.*, 1963, **85**, 1245.

even slight variation of the reagent. In the addition of Grignard reagents to phenylacetoin, HO·CMePh·COMe, for example, use of phenylmagnesium chloride or bromide gives a preponderance of the *meso*-glycol, whereas with phenylmagnesium iodide the (±)-product predominates (ratios *meso*:(±) = 3·1:1, 2·1:1, and 1:2, respectively).[38] A six-membered cyclic transition state has been suggested to account for the very high stereoselectivity observed in the reaction of phenylmagnesium bromide with the ketone (24).[39] The dipolar model (25) has been used to account for the stereochemistry of additions of Grignard reagents and lithium alkyls to α-chloro-carbonyl compounds.[40]



(24)



(25)

What has been said already about the diastereoisomeric faces of the carbonyl group in compounds of type (17) applies equally well to situations in which the carbonyl group is further removed from the asymmetric centre. Such a case is the asymmetric atrolactic acid synthesis, described originally by McKenzie and Thompson,[41] and submitted to conformational analysis by Prelog.[42] When (−)-menthol is esterified with phenylglyoxalyl chloride and the resulting (−)-menthyl phenylglyoxylate (26) is treated with methylmagnesium iodide, addition of the methyl group to the two diastereoisomeric faces of the ketonic carbonyl group will result in the esters (27) and (28); these are diastereoisomers, which will usually be produced in unequal amounts. Quantitative hydrolysis of the ester mixture will result in unequal amounts of (*R*)-and (*S*)-atrolactic acid plus the original (−)-menthol. (Three cases in which McKenzie's work was in disagreement with Prelog's model were reinvestigated, and the discrepancy proved to result from differential hydrolysis during isolation of the α-hydroxy-acid;

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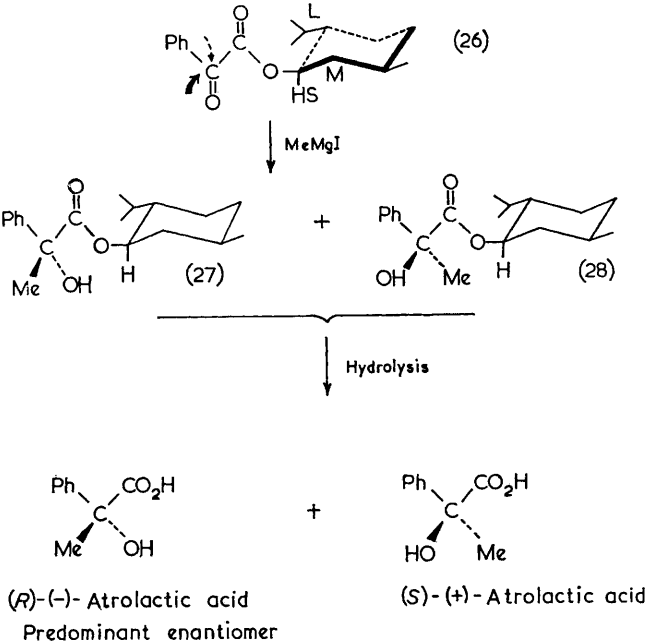
[38] J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *J. Amer. Chem. Soc.*, 1960, **82**, 3913.
[39] K. W. Bentley, D. G. Hardy, and B. Meek, *J. Amer. Chem. Soc.*, 1967, **89**, 3273; see also S. Yamada and K. Koga, *Tetrahedron Letters*, 1967, 1711.
[40] J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 1959, 112.
[41] A. McKenzie and H. B. Thompson, *J. Chem. Soc.*, 1905, 1004; and many later papers.
[42] V. Prelog, *Helv. Chim. Acta*, 1953, **36**, 308.



quantitative hydrolysis is essential, since one diastereoisomer may hydrolyse faster than the other.) Prelog has suggested a model which satisfactorily explains this result and many others. The keto-ester grouping is assumed to lie essentially in a plane in which the two carbonyl groups have the *transoid* conformation and in which the smallest group (hydrogen) is eclipsed with the ketone carbonyl. Addition of methylmagnesium iodide will then be more rapid from the less hindered side of the carbonyl group [*i.e.*, the side of the methylene at C(2)] leading to a preponderance of (*R*)-(—)-atrolactic acid. In cases where a reducing agent is used rather than a Grignard reagent, unequal amounts of (+)- and (—)-mandelic acid or unequal amounts of (+)- and (—)-phenylethane-1,2-diol are obtained, depending on the reducing agent used. In the above example of Prelog's rule (—)-menthol functions as an optical activating agent; and in general, when the configuration of the activating alcohol is known, that of the α-hydroxy-acid obtained in excess can be deduced and *vice versa*. The configuration of (—)-t-butyl ethanol and that of the hydroxyl-bearing carbon atom in a series of triterpenes and steroids have been determined by this method.[43,44,45] A judgment of the relative sizes S, M, and L, of the groups attached to the asymmetric centre is necessary in each case.

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[43] V. Prelog, E. Philbin, E. Watanabe, and M. Wilhelm, *Helv. Chim. Acta*, 1956, **39**, 1086.
[44] W. G. Dauben, D. F. Dickel, O. Jeger, and V. Prelog, *Helv. Chim. Acta*, 1953, **36**, 325.
[45] V. Prelog and H. Meier, Helv, Chim. Acta., 1953, **36**, 320.

3 Asymmetric Synthesis in Additions to Carbon–Carbon and Carbon–Nitrogen Double Bonds

The most striking examples of asymmetric synthesis in olefin-addition reactions have been discovered by Brown and his co-workers using the hydroboronation reaction.[46] Dialkylboranes, prepared by hydroboronation of hindered olefins, exhibit very high stereoselectivity towards olefins with different structural features. Brown has shown that (—)-*sym*-tetraisopinocampheyldiborane gives alcohols of very high optical purity when used as a reagent for the hydration of 1,2-disubstituted *cis* olefins.[47] The hydroboronation of (+)-α-pinene (29) proceeds readily to give (—)-*sym*-tetraisopinocampheyldiborane (30) by stereo specific *cis* addition of the boron–hydrogen bond to the double bond of (+)-α-pinene from the less hindered side of the molecule. Reaction of *cis* but-2-ene with (30) followed by oxidation of the resulting diisopinocampheyl-2-butylborane (31) with alkaline hydrogen peroxide gives (*R*)-(—)-butan-2-ol of 87% optical purity.[47] The hydroboronation of a number of 1,2-disubstituted *cis* olefins proceeds similarly to give alcohols of high optical yield (Table 5).[47] These exceptionally high values have been ascribed to an unusually good steric fit of the olefin and a particular conformation of the borane in a model in which the

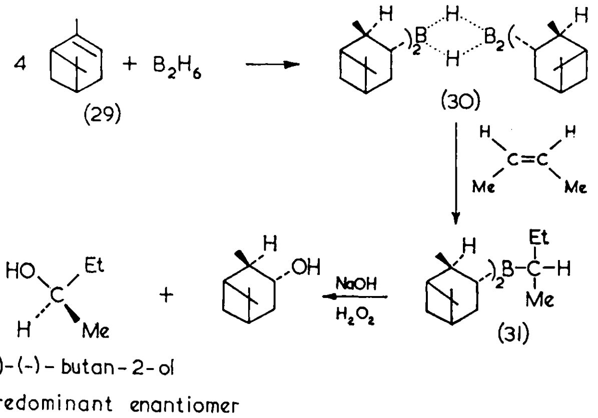

Table 5

α-Pinene used	*Olefin*	*Alcohol*	*Optical purity* (%)
+	*cis*-But-2-ene	(—)-Butan-2-ol	87
—	*cis*-Pent-2-ene	(+)-Pentan-2-ol	82
+	*cis*-Hex-3-ene	(—)-Hexan-3-ol	91
—	*cis*-4-Methyl -pent-2-ene	(+)-4-Methyl -pentan-2-ol	76
+	Norbornene	(—)-*exo*-Norborneol	67—70
+	Bicycloheptadiene	(+)-*exo*-Dehydro -norborneol	48—51

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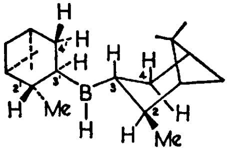
[46] H. C. Brown, 'Hydroboration', W. A. Benjamin, New York, 1962.
[47] H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, 1964, **86**, 397.

cis-addition of the boron–hydrogen bond on to the olefin proceeds *via* a four-centre transition state. Although (−)-*sym*-tetraisopinocampheyldiborane exists as the dimer, the monomeric form (32) is used (for simplicity) in representations of the product-controlling transition states.[48] The absolute configuration of (+)-α-pinene is known and (32) is considered to represent the most stable conformation of (−)-di-isopinocampheylborane.[47] The significant non-bonded interactions in the transition-state models (33) and (34) are thought to be those between the methyl and hydrogen groups of the olefin and the hydrogen atom at C(3′) and the larger methylene group at C(4) of the borane. Model (33) has the methyl group and C(4) positioned away from each other, whereas model (34) has these two groups in close proximity. On this basis, (33) is preferred and it will lead to (*R*)-(−)-butan-2-ol after oxidation of the organoborane. Similar transition-state models may be used to predict the absolute configurations of alcohols resulting from the hydroboronation of 2-methylalk-1-enes with di-isopinocampheylborane. The significant non-bonded interactions are different and the optical yields are much lower than those obtained with 1,2-disubstituted *cis* olefins.[49] Brown has also established that the models devised for *cis* and terminal olefins do not apply to *trans* and hindered olefins. For example, application of the hydroboronation–oxidation sequence to *trans*-but-2-ene gives butan-2-ol of 13% optical purity and of configuration opposite to that predicted by model (33).[50] This discrepancy between the behaviour of *cis* and *trans* olefins was traced to a difference in mechanism for it was observed that the reaction of di-isopinocampheylborane with *trans*-but-2-ene was much slower than that with *cis*-but-2-ene and it was accompanied by the dissociation of the reagent into α-pinene and tri-isopinocampheyldiborane. Displacement of α-pinene from di-isopinocampheylborane was also observed in the hydroboronation of highly



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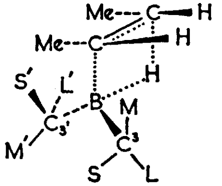
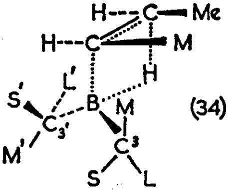
(33)





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[48] For a recent publication describing the use of the dimer in representations of the transition state for these asymmetric hydroboration reactions see D. R. Brown, S. F. A. Kettle, J. McKenna, and J. M. McKenna, *Chem. Comm.*, 1967, 667.

[49] G. Zweifel, N. R. Ayyangar, T. Munekata, and H. C. Brown, *J. Amer. Chem. Soc.*, 1964, **86**, 1076.

[50] H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, 1964, **86**, 1071.

hindered olefins. Although a model utilising tri-isopinocampheyldiborane has not been formulated, Brown has suggested the following generalisation to account for the behaviour of *trans* and hindered olefins. 'Whenever displacement of α-pinene occurs in stoicheiometric amounts in the hydroboronation of olefins with di-isopinocampheylborane, the alcohol (or the olefin; this refers to the kinetic resolution of a racemic olefin with di-isopinocampheylborane[47]) obtained will possess the configuration opposite from that predicted on the basis of the simple addition model. For such olefins the use of tri-isopinocampheyldiborane will yield the same result.'[50] Streitwieser and his co-workers have suggested a model which accounts for the formation of [1-$^2H_1$] (*R*)-(−)-butan-1-ol in the hydroboronation of [1-$^2H_1$]*cis*-but-1-ene with (−)-di-isopinocampheyldiborane.[51]

The composition of transition-state models for asymmetric synthesis in terms of reactants only should not be taken as evidence that solvation is unimportant. Solvent effects have been observed in the reactions of olefins with peroxy-acids. Some olefins give optically active epoxides when dissymmetric peroxy-acids are used as oxidants. For example, epoxidation of styrene (35) with (+)-peroxycamphoric acid (36) in chloroform gives (*S*)-(−)-styrene oxide (37) of 4·4% optical purity.[52,53] Additional results that have been obtained with (+)-peroxycamphoric acid are summarised in Table 6.[52,53] The optical yields of these asymmetric epoxidations are extremely low; 4·4% being taken as the upper limit for the optical purity of the epoxides produced, the free-energy difference between the diastereoisomeric transition states is about 45 cal./mole at the temperature of the epoxidation. Although a simple transition-state model

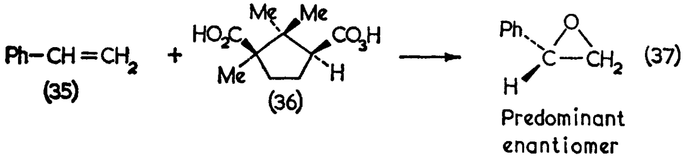

Table 6

	Epoxide	
R *in* R-CH=CH_2	*Optical purity* (%)	*Configuration*
Methyl	2·0	*S*
n-Butyl	2·5	*S*
n-Pentyl	1·8	*S*
n-Hexyl	2·5	*S*
t-Butyl	1·7	*S*
Phenyl	4·4	*S*
Cyclohexyl	3·7	*S*
2-Phenylethyl	2·1	*S*

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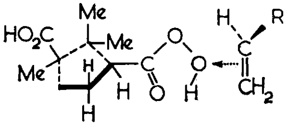
[51] A. Streitwieser, jun., L. Verbit, and R. Bittman, *J. Org. Chem.*, 1967, **32**, 1530.

[52] R. C. Ewins, H. B. Henbest, and M. A. McKervey, *Chem. Comm.*, 1967, 1085.

[53] H. B. Henbest, in 'Organic Reaction Mechanisms', *Chem. Soc. Special Publ.*, No. 19, 1965, p. 83.

of the type (38) can be used to interpret the absolute configurations of the epoxides listed in Table 6, it does not take into account the effect of solvent on the reaction. The suggestion has been made that the non-bonded interactions at the transition state can be transmitted partly through interposing solvent molecules; if this is so, then a transition state which is not well solvated could lead to a low optical yield, whereas a transition state with which there is associated a definite solvent structure could lead to a higher optical yield. The results with the reaction of styrene with (+)-peroxycamphoric acid show that optical yields and reaction rates are highest in dichloromethane and chloroform. On the other hand, ether and carbon tetrachloride produce a much slower reaction and smaller optical yields. For the range of solvents studied, there is a correlation between (*a*) the optical yield in the epoxidation of styrene, (*b*) the rate of this reaction, and (*c*) the axial–equatorial product ratio in the epoxidation of (39a) and (39b) (Table 7).[52,53] For a more detailed discussion of solvent effects in the reaction of olefins with peroxy-acids, see refs. 54 and 55.



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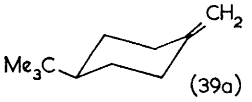
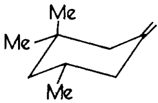


(39a)



(39b)

Table 7

Solvent	*Optical yield* (%)	10^4k(l. mole^{-1} sec.$^{-1}$)	*Axial attack* (%) (39a)	 (39b)
Et_2O	2·0	(0·3)	85	35
CCl_4	2·0	3·7	85	25
C_6H_6	2·5	6·4	82	20
CH_2Cl_2	3·5	8·6	79	17
$CHCl_3$	4·4	13·3	79	17

Asymmetric synthesis has been observed in the epoxidation of linaloöl (40). The epoxide (41) obtained after removal of the original asymmetric centre was found to be optically active.[56] Grundon and co-workers have used (+)-peroxy-

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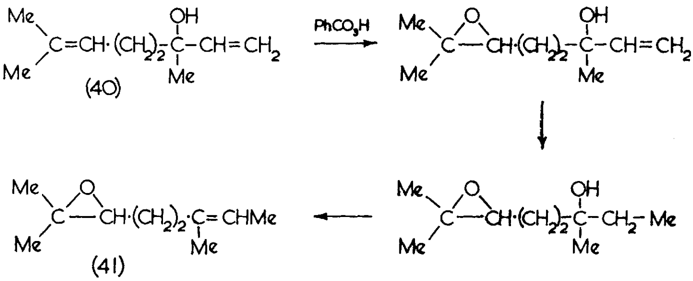
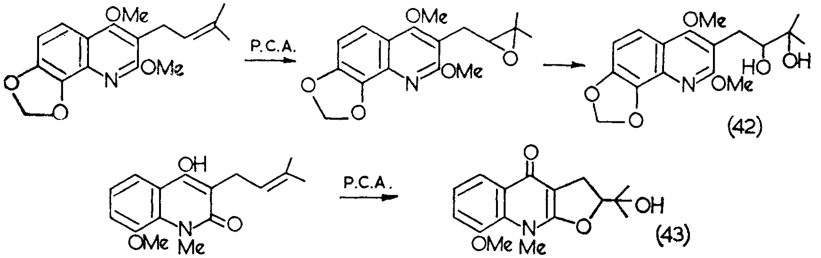
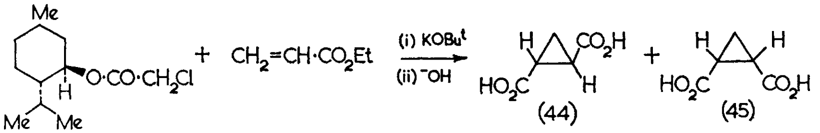
[54] P. Renolen and J. Ugelstad, *J. Chim. phys.*, 1960, **57**, 634.
[55] R. G. Carlson and N. S. Behn, *J. Org. Chem.*, 1967, **32**, 1363.
[56] G. V. Pigulevskii and G. V. Markina, *Doklady Akad. Nauk S.S.S.R.*, 1948, **63**, 6277. (*Chem. Abs.*, 1949, **43**, 4628).



camphoric acid (P.C.A.) in the asymmetric synthesis of the optically active quinoline alkaloids (42) and (43).[57]



Although the optical yield in the asymmetric epoxidation of styrene is solvent-dependent, the configuration of the predominant enantiomer of the product remains the same throughout the range of liquids studied. There is at least one example of an olefin addition in which both the stereochemical outcome and the optical yield are solvent-dependent. The base-catalysed condensation of (—)-menthylchloroacetate with ethyl acrylate gives optically active *trans*-cyclopropane-1,2-dicarboxylic acid (44) plus a trace of the *cis* diacid (45) after removal of the optical activating menthyl group by hydrolysis.[58,59] The stereochemistry of this reaction depends markedly on the solvent; in toluene, the *trans* diacid



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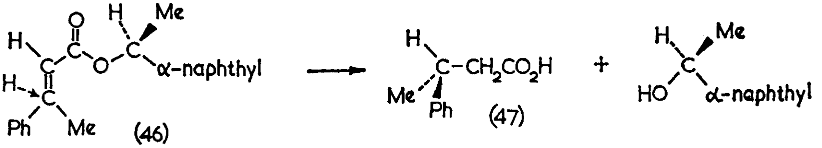
[57] R. M. Bowman and M. F. Grundon, *J. Chem. Soc.* (*C*), 1967, 2368; R. M. Bowman, J. F' Collins, and M. F. Grundon, *Chem. Comm.*, 1967, 1131.

[58] Y. Inouye, S. Inamasu, M. Ohno, T. Sugita, and H. M. Walborsky, *J. Amer. Chem. Soc.*, 1961, **83**, 2962.

[59] H. M. Walborsky and C. G. Pitt, *J. Amer. Chem., Soc.* 1962, **84**, 4831.

obtained is lævorotatory (optical yield 1·8—3·1 %) whereas in dimethylformamide, this acid has the opposite configuration and the optical yield is higher (10·2—10·9 %).[58,59] It has been suggested[60] that the actual asymmetric synthesis of the *trans* diacid is unaffected by a change of solvent but that the *cis–trans* isomer ratio is solvent-dependent; and that the change in configuration of the *trans* diacid is due to an asymmetric *cis* to *trans* isomerisation during the alkaline hydrolysis of the *cis* diester which is formed in the initial kinetically controlled process. Recent results of Inouye and his co-workers cast doubt on this interpretation. These authors report that the *cis–trans* and the (+)-(−) stereoselectivities are both solvent-dependent in the sodium hydride-catalysed condensation of (−)-menthylchloropropionate and methyl methacrylate (a system in which isomerisation of the diesters is excluded).[61] Condensation of (−)-menthyl or (+)-bornyl 2-arylacrylates with dimethyloxosulphonium methoxide or dimethylsulphonium methoxide followed by alkaline hydrolysis gives optically active 2-arylcyclopropanecarboxylic acids.[62]



(46) (47)

Partial asymmetric synthesis has been realised in the Diels–Alder reaction of butadiene with (−)-dimenthyl fumarate, both thermally and at lower temperatures with catalysis by Lewis acids.[63] The predominant enantiomer of the product obtained in the presence of the Lewis acids was of opposite configuration from that produced in the thermal reaction.[63] A more recent study has revealed that the stereoselectivity of this reaction is subject to temperature and pressure effects.[64,65]

Prelog's interpretation of asymmetric synthesis in the catalytic hydrogenation of olefins is based on the generalisation that the stereochemical course can often be explained by assuming that the least hindered face of the molecule is preferentially adsorbed on the catalyst surface and that addition of hydrogen occurs from the same side.[66] For example, the optically active β-methylcinnamate (46) on hydrogenation and hydrolysis yields preferentially (*R*)-(−)-β-phenylbutyric acid (47).[66] The ester is represented as reacting in the preferred conformation (46) in which all the groups except those on the asymmetric carbon atom lie in a plane parallel to the catalyst surface. Addition of hydrogen then

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[60] L. L. McCoy, *J. Org. Chem.*, 1964, **29**, 240.

[61] Y. Inouye, S. Inamasu, and M. Horiike, *Chem. and Ind.*, 1967, 1293.

[62] H. Nozaki, H. Ito, D. Tunemoto, and K. Kondo, *Tetrahedron*, 1966, **22**, 441.

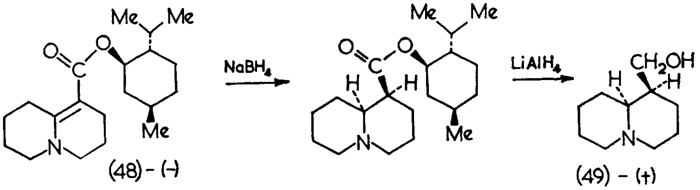
[63] H. M. Walborsky, L. Barash, and T. C. Davis, *Tetrahedron*, 1963, **19**, 2333.

[64] B. S. Elyanov, E. I. Klabunovskii, M. G. Gonikberg, G. M. Parfenova, and L. F. Godunova, *Izvest. Akad. Nauk. S.S.S.R., Ser. khim.*, 1966, **9**, 1678. (*Chem. Abs.*, 1967, **66**, 6088).

[65] J. Saver pnd J. Kredel, *Tetrahedron Letters*, 1966, 6359.

[66] V. Prelog and H. Scherrer, *Helv. Chim. Acta*, 1959, **42**, 2227.

occurs predominantly from the side of the small group (in this case hydrogen). In this example the incipient asymmetric centre is four bond lengths removed from the optical activating group. Arcus[67] has studied a number of examples in which these two centres are adjacent to each other. Thus, by catalytic hydrogenation of the enantiomers of 3-ethylhept-3-en-2-ol to 3-ethylheptan-2-ol followed by oxidation to optically active 3-ethylheptan-2-one it was shown that asymmetric hydrogenation had occurred to the extent of 70%.[67] The partial asymmetric synthesis of optically active lupinine has been achieved by sodium borohydride reduction of the carbon–carbon double bond in the menthyl ester (48). Removal of the menthyl group by reductive cleavage with lithium aluminium hydride gave (+)-lupinine (49) in *ca.* 10% optical yield.[68] The asymmetric reduction of carbon–nitrogen double bonds has been examined as a possible route for the preparation of optically active amines and amino-acids. A recent case involves the use of optically active organoborane derivatives in



(48)-(−) (49)-(+)

(50) (S) (R)

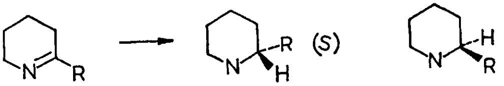


Table 8

			Amine	
	(50)-R	*Reagent*	*Configuration*	*Optical purity* (%)
(1)	CH_3	DIPCB	*S*	2·0— 3·3
(2)	CH_3	TIPCB	*S*	2·2— 3·2
(3)	$CH_2{\cdot}CH_2{\cdot}CH_3$	TIPCB	*S*	2·9—10·7
(4)	CH_3	LHBIB	*R*	19·5—24·0
(5)	$CH_2{\cdot}CH_2{\cdot}CH_3$	LHBIB	*R*	4·0— 4·3

the reduction of 2-methyl- and 2-propyl-Δ^1-piperideine (50).[69] Reactions (1)—(3) (Table 8), in which the Δ^1-piperideines were treated with di-isopinocampheylborane (DIPCB) or tri-isopinocampheyldiborane (TIPCB), gave preferentially the (*S*)-amine in low optical yield. On the other hand, lithium hydro-(1-butyl)-bis(isopinocampheyl) borate (LHBIB), prepared from di-isopinocampheyl-

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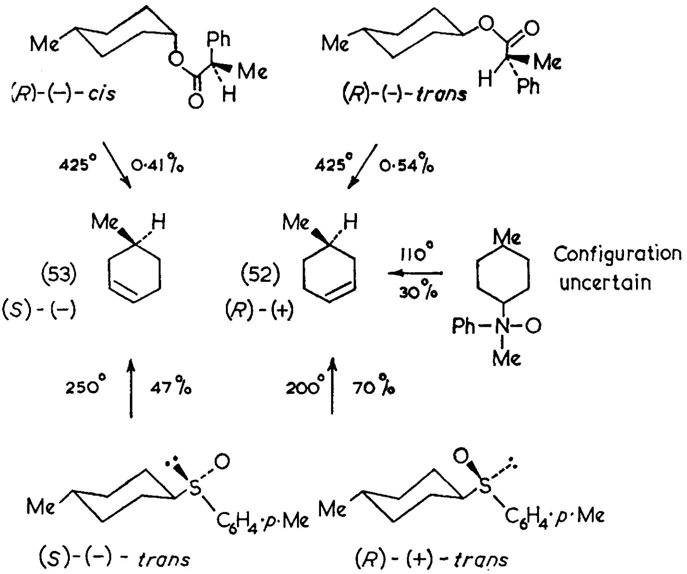
[67] C. L. Arcus, *Proc. Chem. Soc.*, 1964, 135.
[68] S. I. Goldberg and I. Ragade, *J. Org. Chem.*, 1967, **32**, 1046.
[69] D. R. Boyd, M. F. Grundon, and W. R. Jackson, *Tetrahedron Letters*, 1967, 2101.

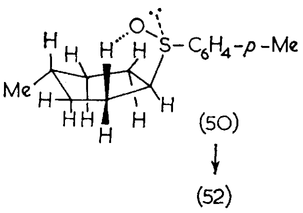
borane and n-butyl-lithium, gave preferentially the (*R*)-amine [reactions (4) and (5)]. The important contributions of Hiskey and Northrop[70] to the asymmetric synthesis of amino-acids have been reviewed by Morrison.[15]

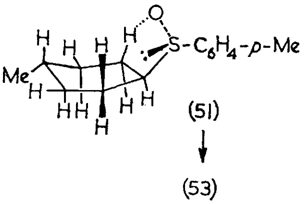
4 Asymmetric Synthesis in Elimination Reactions

Most examples of asymmetric synthesis in elimination reactions involve the formation of optically active olefins. Goldberg and Lam[71] have investigated the pyrolysis of the four possible stereoisomers of optically active 4-methylcyclohexyl hydratropate (two of which are illustrated in the Scheme). In each case, optically active 4-methylcyclohexene of very low optical purity (0·87% maximum) was obtained. Although transition-state models capable of accounting



Scheme. Asymmetric synthesis in ester, sulphoxide, and amine oxide pyrolysis. The arrows indicate the reaction temperature, the optical yield, and the predominant enantiomer of the olefin.





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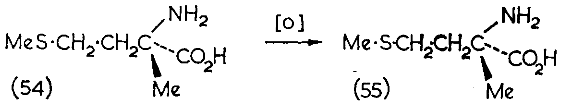
[70] R. G. Hiskey and R. C. Northrop, *J. Amer. Chem. Soc.*, 1961, **83**, 4798; *ibid.*, 1965, **87**, 1753; see also K. Harada, *J. Org. Chem.*, 1967, **32**, 1790, and K. Harada and K. Matsumoto, *ibid.*, p. 1794.

[71] S. I. Goldberg and F-L. Lam, *J. Org. Chem.*, 1966, **31**, 2336.

for these results have been formulated, the authors agree that the very small free-energy difference between the diastereoisomeric transition states makes interpretation difficult. In a conceptually similar study, Goldberg and Sahli[72] obtained optically active 4-methylcyclohexene in up to 70% optical yield from the pyrolysis of (*R*)-(+)-*trans*- and (*S*)-(−)-*trans*-4-methylcyclohexyl *p*-tolyl sulphoxide (Scheme). The two low-energy transition states (50) and (51), which successfully correlate the configuration of the predominant enantiomer of the olefin with that of the sulphoxide, are considered to be those in which the bulky *p*-tolyl group is positioned away from the hydrogen atoms of the cyclohexane ring. Pyrolysis of optically active *N*-methyl-*N*-(4-methylcyclohexyl)-*N*-phenylamine oxide also gives optically active 4-methylcyclohexene.[73] Further aspects of the molecular dissymmetry of *trans*-cyclic olefins have been demonstrated by the preparation of optically active *trans*-cyclo-octene by an asymmetric Hofmann degradation of (−)-*N*-n-butyl-*N*-isobutyl-*N*-methylcyclo-octylammonium hydroxide; the normal Hofmann procedure, *i.e.*, pyrolysis of the hydroxide, gave predominantly the (−)-enantiomer whereas treatment of the corresponding perchlorate with potassium amide in liquid ammonia gave the (+)-enantiomer.[74] The preparation of *cis*, *trans*-1,5-cyclo-octadiene by an asymmetric Hofmann degradation has also been reported.[75]

5 Asmmyetric Synthesis of Sulphoxides

The preceding discussion was illustrated primarily with examples in which the relative and absolute configurations of the molecules were well established by independent methods. Aysmmetric synthesis of sulphoxides differs notably in that much speculative work had been done before the absolute configurations of simple sulphoxides were known. There was ample scope, therefore, for predictions based on empirical rules.



(54) (55)

The asymmetric oxidation of optically active methionine (54) was first described by Lavine.[76] The different methods used to introduce the second asymmetric centre (at sulphur) gave products (55) of different optical purities and Lavine concluded that this was due to the formation of different proportions of the two diastereoisomeric methionine sulphoxides. Cram and Pine[77] applied this technique to the determination of the configurations of the diastereoisomeric sulphoxides produced in the oxidation of (*R*)-(−)-2-octyl phenyl sulphide (56)

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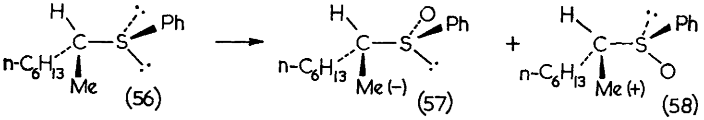
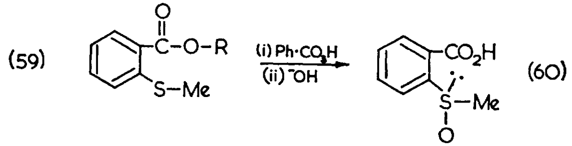
[72] S. I. Goldberg and M. S. Sahli, *J. Org. Chem.*, 1967, **32**, 2059.
[73] G. Berti and G. Bellucci, *Tetrahedron Letters*, 1964, 3853.
[74] A. C. Cope, W. R. Funke, and F. N. Jones, *J. Amer. Chem. Soc.*, 1966, **88**, 4693.
[75] A. C. Cope, C. F. Howell, and A. Knowles, *J. Amer. Chem. Soc.*, 1962, **84**, 3190.
[76] T. F. Lavine, *J. Biol. Chem.*, 1947, **169**, 477.
[77] D. J. Cram and S. H. Pine, *J. Amer. Chem. Soc.*, 1963, **85**, 1096.

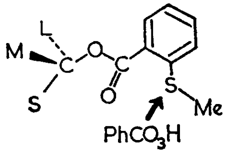


with t-butyl hydroperoxide, using as a basis the argument that oxidation occurs more rapidly on the diastereoisomeric face of sulphur which has the electron pair situated between the hydrogen and n-hexyl groups of the adjacent asymmetric carbon atom (cf. Cram's rule for additions to carbonyl compounds). According to this reasoning, the predominant sulphoxide (57) has the *R*-configuration at sulphur. Montanari and his co-workers[78] oxidised *o*-(methylthio)benzoic acid esters (59) of optically active alcohols and obtained the optically active sulphoxide (60) after removal of the optical activating group by hydrolysis.



	Optical purity (%)	Configuration
R = (−)-menthyl	6·2	(*S*)-(−)
R = (+)-methylmesitylmethyl	20·5	(*S*)-(−)
R = (−)-methyl-α-naphthylmethyl	8·9	(*R*)-(+)

The absolute configuration of the predominant enantiomer of the product was predicted by assuming that the most probable conformation of the sulphide was


(61)

(61) in which the carbonyl oxygen is placed in the least hindered region with respect to the groups S, M, and L, and that peroxy-acid attack occurs preferentially from the side remote from the large group (cf. Prelog's rule for the atrolactic acid synthesis). Montanari and his co-workers[78,79] also suggested a model which may be used to predict the stereochemical result of the oxidation of non-dissymmetric sulphides with dissymmetric peroxy-acids of known absolute configuration. Thus, oxidation of n-alkyl phenyl sulphides with (+)-

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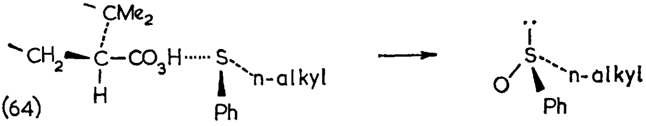
[78] A. Maccioni, F. Montanari, M. Secci, and M. Tramontini, *Tetrahedron Letters*, 1961, 607.
[79] A. Mayr, F. Montanari, and M. Tramontini, *Gazz. Chim. Ital.*, 1960, **90**, 739; see also K. Balenovic, N. Bregant, and D. Francetic, *Tetrahedron Letters*, 1960, 20.

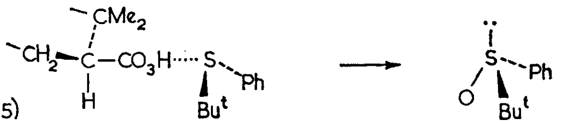
peroxycamphoric acid gave (+)-n-alkyl phenyl sulphoxides (62) of low optical purity: a similar reaction with t-butyl phenyl sulphide gave (−)-t-butyl phenyl sulphoxide (63). According to the authors, the attack of peroxy-acid on sulphur occurs in a direction perpendicular to the C–S–C plane of the sulphide and the two most probable transition-state conformations are the staggered arrangements (64) and (65) in which the order of decreasing effective size of the groups attached to sulphur is t-butyl > phenyl > *n*-alkyl. This interpretation predicts the *R*-configuration for (62) and the *S*-configuration for (63). The question of the absolute configuration of sulphoxides was finally settled by Mislow *et al.*[80] using a combination of *X*-ray analysis and optical rotatory dispersion. It was established that (+)-alkyl aryl sulphoxides have the *R*-configuration. This conclusion was significant because Cram and Pine had assigned the *R*-configuration to the (−)-alkyl aryl sulphoxide (57) whereas Montanari had (correctly) assigned the *R*-configuration to (+)-alkyl aryl sulphoxides. Mislow points out that in using asymmetric synthesis to predict absolute configuration one always has a 50% chance of being correct and even though Montanari's model gives the correct answer, the arguments used in constructing the model are not necessarily correct. Mislow further contends that these models do not provide a qualitative estimate of the non-bonded interactions which indicate the diastereoisomeric transition state with the lower free energy because (*a*) there is no way of knowing the preferred arrangements of the peroxy-acid and the sulphide at the transition state, (*b*) the rôle of the sulphoxide oxygen and of the lone pair on sulphur in conformational analysis is not well understood, (*c*) a correlation between the stereochemical result and the model is by no means unambiguous insofar as different models may lead to the same result, and (*d*) 'Conformational rules empirically derived from one type of system may not be legitimately extrapolated and transferred to another.'[80] Mislow and his co-workers[81] have shown that configurational assignments based on the transition-state models of Montanari fail in the case of n-alkyl benzyl sulphoxide; Montanari[82] claims that these results

(64)



(62)

(65)



(63)

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[80] K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, 1965, **87**, 1958.

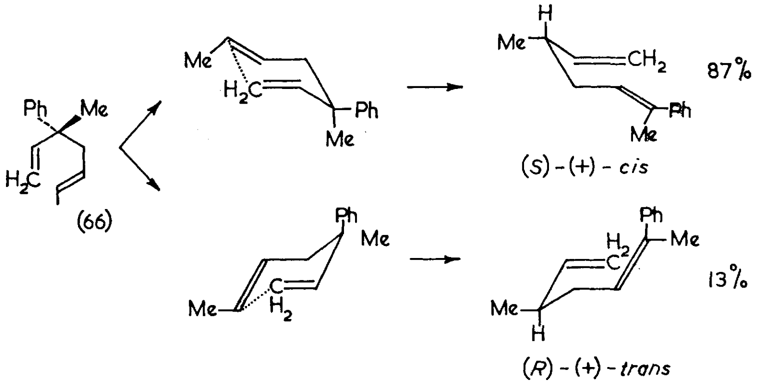
[81] K. Mislow, M. M. Green, and M. Raban, *J. Amer. Chem. Soc.*, 1965, **87**, 2761.

[82] F. Montanari, *Tetrahedron Letters*, 1965, 3367.

are difficult to interpret and that solvent effects may change the sign of rotation and the optical rotatory dispersion curves of these sulphoxides.

6 Other Examples of Asymmetric Synthesis

A. Intramolecular Rearrangements.—The transfer of asymmetry from one asymmetric centre to another *via* the intramolecular route has proved a valuable method for elucidating transition-state topology. This method, developed mainly by Hill, has been applied to the Cope rearrangement (66) (optical yield



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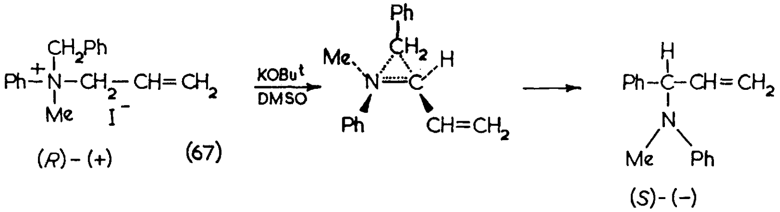

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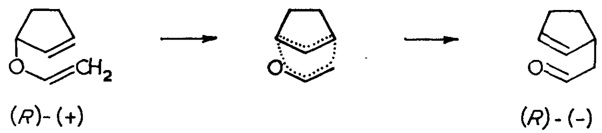
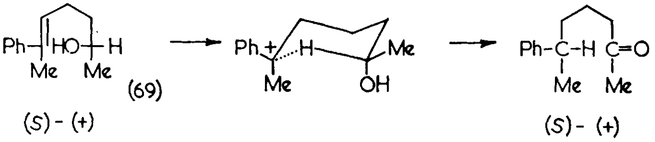
(68)

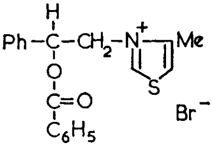




(69)

94—96%),[83a] the Stevens rearrangement (67) (optical yield probably high),[83b] the Claisen rearrangement (68) (optical yield not reported),[83c] and the intramolecular 1,5-hydride transfer (69) (optical yield 15%),[83d] the absolute configurations of the reactants and products having been independently determined in each case. The very high optical yield and the almost exclusive formation of the (*S*)-(+)-*cis*- and the (*R*)-(+)-*trans*-dienes from (66) not only confirm the concerted cyclic mechanism for the rearrangement but also indicate that the transition states have the chair conformations shown (the alternative boat conformations predict the opposite stereochemical results). A transition state with *cis* phenyl and vinyl groups is required to explain the stereochemistry of rearrangement (67) and the conversion of the (*R*)-(+)-vinyl ether=into the (*R*)-(−)-aldehyde is consistent with the cyclic mechanism suggested for the Claisen rearrangement (68). The formation of the (*S*)-(+)-ketone in the acid-catalysed rearrangement (69) is in agreement with the suggestion that the transition state adopts a chair conformation in which the phenyl group at C(6) and the methyl group at C(2) occupy equatorial positions (cf. the reduction of ketones with optically active Grignard reagents).

B. Asymmetric Catalysis.—Several attempts have been made to achieve asymmetric synthesis with use of non-enzymic homogeneous and heterogeneous asymmetric catalysts. The asymmetric hydrogenation of methyl acetoacetate with Raney nickel modified with tartaric acid has been reported.[84] Examples from the field of homogeneous catalysis include the asymmetric oxidation of benzyl methyl sulphide by iodine in the presence of (+)-2-methyl-2-phenylsuccinic acid.[85] The low optical purity (6%) of the sulphoxide produced may be compared with the much higher optical purities (up to 100%) obtained in the oxidation of sulphides in the presence of growing ærobic cultures of *Aspergillus niger*.[86] Sheehan and Hunneman[87] observed asymmetric synthesis using (+)-*N*-[2-phenyl-2-(cyclohexanecarboxy)ethyl]-4-methylthiazolium bromide (70) as a catalyst in the benzoin condensation. Methylphenylketen reacts with methanol or ethanol in the presence of optically active bases such as brucine, acetylquinine, or acetylquinidine to give optically active α-phenylpropionate esters.[88] The



(70)

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[83] (*a*) R. K. Hill and N. W. Gilman, *Chem. Comm.*, 1967, 619; (*b*) R. K. Hill and T-H. Chan, *J. Amer. Chem. Soc.*, 1966, **88**, 866; (*c*) R. K. Hill and A. G. Edwards, *Tetrahedron Letters*, 1964, 3239; (*d*) R. K. Hill and R. M. Carlson, *J. Amer. Chem. Soc.*, 1965, **87**, 2772.

[84] Y. Izumi, S. Tatsumi, and M. Imaida, *Bull. Chem. Soc. Japan*, 1966, **39**, 2223.

[85] T. Higuchi, I. H. Pitman, and K. H. Gensch, *J. Amer. Chem. Soc.*, 1966, **88**, 5676.

[86] B. J. Auret, D. R. Boyd, and H. B. Henbest, *Chem. Comm.*, 1966, 66.

[87] J. C. Sheehan and D. H. Hunneman, *J. Amer. Chem. Soc.*, 1966, **88**, 3666.

[88] H. Pracejus, *Annalen*, 1960, **634**, 9.

stereoselectivity of this reaction was shown to be temperature-dependent. For example, (R)-(−)-methyl α-phenylpropionate was obtained in up to 74% optical yield from methylphenylketen and methanol in the presence of acetylquinine at −110° at −60°, the (*S*)-(+)-ester was the dominant product (optical yield 20%), and at 25° the optical yield approached zero. Pracejus[88] suggests that complex formation between the keten and the amine is rate-determining at low temperatures whereas at higher temperatures the reaction is uncatalysed and therefore non-stereoselective. Grimshaw and co-workers[89] have reported the asymmetric synthesis of 3,4-dihydro-4-methylcoumarin by electro-chemical reduction of 4-methylcoumarin in the presence of certain alkaloids.

(D.R.B.) gratefully acknowledges an S.R.C. Postdoctoral Fellowship.

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[89] R. N. Gourley, J. Grimshaw, and P. G. Millar, *Chem. Comm.*, 1967, 1278.