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Asymmetric reduction of carbonyl compounds with chiral alkoxyaluminium and alkoxymagnesium halides: an overview

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Abstract. A summary of the work on asymmetric reduction of carbonyl compounds with chiral alkoxyaluminium and alkoxymagnesium halides derived mainly from *exo*- and *endo*-bornan-2-ols done in the present laboratory has been given. The highlights of the contributions are as follows: (i) the development of a new class of extremely enantioselective and diastereoselective reducing reagents which are easily accessible, (ii) practical synthesis of α-deuterated benzyl alcohol, 2,2,2-trifluoro-1-phenylethanol (a chiral NMR solvent) and some aminoalcohols of physiological importance in high chemical and optical yields, (iii) a new chemical method to determine the configuration of chiral ketones and (iv) a highly satisfactory transition state model for these reactions which explains all the literature data so far.

Keywords. Asymmetric reduction; carbonyl compounds; alkoxymagnesium; alkoxyaluminium halides.

1. Introduction

Asymmetric synthesis is usually defined as a reaction in which an achiral unit in a substrate molecule is converted into a chiral one under the influence of some chiral centre or centres present either in the substrate or in the reagent or in both in such a manner that one of the stereoisomers predominates. In a typically asymmetric synthesis, one of the enantiomeric product is formed in excess over the other through a kinetically controlled reaction of prochiral substrate with a chiral reagent. The free energy difference ($\Delta\Delta G^{\ddagger}$) between the two diastereoisomeric transition states arising out of the combination of the chiral reagent and the substrate with developing chiral centre determines the relative amount of the two enantiomers. The difference in free energy ($\Delta\Delta G^{\ddagger}$) is maintained by introducing appropriate steric and electronic interactions in the activated complex which is not often easy since it requires knowledge of the transition state and then the enthalpy and entropy terms of $\Delta\Delta G^{\ddagger}$ function may change drastically with slight change in reaction parameters.

Asymmetric synthesis is the method of choice for preparing chiral molecules of sufficient optical purity to be used subsequently in the synthesis of natural products, flavouring agents, perfumes, foods, drugs and other materials which show their beneficial effects often in one enantiomeric form. In addition to its practical utility (it avoids the tedium of resolution and saves at least half of the material), a well-planned asymmetric synthesis helps to unravel the reaction mechanism and often predicts the

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configuration of the resultant chiral molecule. Work on asymmetric organic reactions started in the beginning of the century (McKenzie 1904) but systematic studies were taken up much later. The area of asymmetric synthesis is now fast expanding and considerable amount of success has been achieved. In a few cases, chemists have engineered almost totally asymmetric synthesis thus emulating nature in her highly stereoselective enzyme reactions.

One major type of asymmetric reactions is the conversion of trigonal carbons into tetrahedral ones and the reduction of prochiral ketones to chiral alcohols falls under this category. A large variety of reagents have been used for this purpose which include modified lithium aluminium hydride, organo-metallics, organo-boranes, alkoxy-aluminium or magnesium derivatives and others all containing chiral components. Since 1966, we have been experimenting with a new class of chiral reagents which reduce different carbonyl compounds by hydride transfer. This paper records a brief account of the results of our investigations.

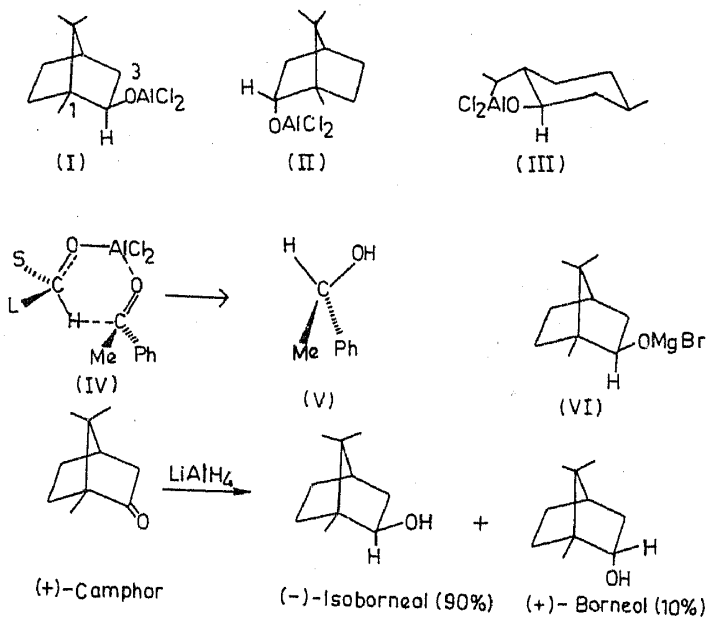
2. Criteria for asymmetric synthesis

Although there is no fixed guide line for asymmetric synthesis, the following criteria should be generally fulfilled for any useful asymmetric reaction: (i) The reagents must be available in high (preferably 100%) optical purity and should be easily accessible or at least recyclisable. (ii) The chirality of the reagents should be such that it will give the desired enantiomer predominantly. In a few syntheses where a series of reactions are involved, it is possible to have either enantiomer by interchange of groups in two appropriate reagents (Meyers and Whitten 1975). (iii) The product must be easily separable from the residual chiral reagents and other side products. (iv) For the reaction to be of any practical utility, the asymmetric induction must be high (over 70%) which means that $\Delta\Delta G^{\ddagger}$ in the reaction should be over 4.2 kJ/mol at ambient temperature. (v) Finally, the step leading to asymmetry should preferably be a reaction of known mechanism with an ordered transition state so that one can predict the configuration of the preponderant enantiomer. Various reactions have been developed which satisfy most of the above criteria and the readers are referred to a comprehensive treatise (Morrison and Mosher 1971), numerous reviews and monographs (ApSimon and Seguin 1979 and references 9–12 cited therein; Izumi and Tai 1977; Kagan and Fiaud 1978; Valentine and Scott 1978) which cover literature on this topic up to 1978.

3. Reagents and their preparation

Reagents used for asymmetric reduction of ketones in the present investigations, (I)–(III) are derived from chiral alcohols such as *exo*-, *endo*-bornan-2-ols (isoborneol and borneol) and *p*-menthan-3-ol (menthol), all available plentifully as cheap natural products in 100% optical purity. Eliel and Nasipuri (1965) have shown that *sec*-alkoxyaluminium dichlorides, $RR'CHOAlCl_2$ are good reducing agents for ketones, the reduction taking place by a reversible hydride transfer similar to Meerwein-Ponndorf-Oppenauer reaction. The reduction with $RR'CHOAlCl_2$ is much faster and can be carried out in ethereal solution at ambient temperature within 10–30 min. Moreover, the reagents (I) and (II) react irreversibly, camphor that is formed being completely unreactive to further H-exchange due to steric and electronic reasons. Other

CHART 1



alkoxyaluminium dichlorides (as III) when used in slight excess and for a short period also reduce ketones irreversibly and the reactions are thus all kinetically controlled, a necessary condition for enantioselectivity. Of the various alkoxyaluminium dichlorides, the one (I) derived from *exo*-bornan-2-ol is most efficient and has been used extensively in the present research while the others are milder and used only for specific substrates. The hydride to be transferred is attached to a chiral centre and is heavily crowded in all the reagents. This and the conformational rigidity of the ring systems ensure that the H-transfer would be highly stereoselective as indeed it is in the reduction of cyclohexanones in which predominant formation (over 90%) of the axial (the less stable) alcohols is observed (Eliel and Nasipuri 1965; Nasipuri *et al* 1976). A high degree of enantioselectivity in the reduction of proper substrates is also expected. The configurations of borneol, isoborneol and menthol are well established and the enantiomers depicted in chart 1 have (R)-configuration at α-carbon. Assuming a six-centred cyclic transition state, the predominant enantiomer is predictable from a consideration of steric interaction in the two diastereoisomeric activated complexes, the one (IV) with the two larger groups of the carbinol and of the ketone (C-1 in bornane and Ph in acetophenone) oppositely placed being preferred giving (+)-(R)-PhCHOHMe (V) from PhCOMe. Most of the criteria for a good asymmetric synthesis outlined in §2 are thus fulfilled. Along with (I)–(III), bornan-2-*exo*-yloxy-magnesium bromide (VI) (Streitweiser *et al* 1959) and a few related reagents have also been studied. Reagents (I) and (VI) have a further advantage that they are available in α-deuterated form (by reducing camphor with $LiAlD_4$) and may be used for D-transfer as well.

A mixture of (−)-isoborneol (90%) and (+)-borneol (10%) obtained by reduction of (+)-camphor with $LiAlH_4$ was used for the preparation of the reagent (I); the borneol complex being very much less reactive, its presence is ignored. No difference in stereochemical results was observed when pure isoborneol (Gerlach 1966) was used in place of the above mixture. (−)-Borneol and (−)-menthol are available commercially

and were supplied to us by Aldrich Chemical Company. The reduction was carried out either by first preparing a 'mixed hydride' solution by reacting 1 mole of $LiAlH_4$ with 3 moles of anhydrous $AlCl_3$ (Eliel 1961) and adding to it an equimolecular quantity of the chiral alcohol followed by the ketone (method A) or by preparing a solution of lithium aluminium tetra-alkoxide from $LiAlH_4$ and the alcohol, adding the ketone to it and finally introducing an ethereal solution of anhydrous $AlCl_3$ dropwise (method B). The two methods give identical results but method B is more convenient; it also allows the direct reduction product of camphor with $LiAlH_4$ to be used for the preparation of the reagent (I). The precise structures of the reagents are not known but they are usually formulated as alkoxyaluminium dichlorides in monomeric form. The alcohols were purified by removal of the camphoraceous impurities by steam distillation and subsequently converting them into acid phthalates without crystallising at any stage. In a few cases, preparative GC was used.

4. Results and Discussions

4.1 *Asymmetric reduction of alkyl methyl ketones*

A series of alkyl methyl ketones, RCOMe (R = Et, *i*-Bu, *i*-Pr, *t*-Bu and cyclohexyl) was reduced with the reagent (I). The alcohols were purified by the usual combination of steam distillation, distillation, conversion into acid phthalate and regeneration. The reduction was complete but the yield of recovery seldom exceeded 50%. The results are not particularly encouraging (Nasipuri and Sarkar 1967a) but compare favourably with those reported for other reagents in this series, namely, (+)-(S)-2-methylbutylmagnesium chloride (Morrison and Mosher 1971, p. 183) and (+)-*tris* [(S)-2-methylbutyl] aluminium (Giacomelli *et al* 1974b). The data for all the reagents are compiled in table 1. The alcohols from reagent (I) were rich in (−)-enantiomers having (R)-configuration as expected from the transition state (IV). The extent of enantioselectivity depended on the difference in steric bulk between Me and R. Addition of anhydrous $MgBr_2$ in the reaction media enhanced the asymmetric induction by 40–100% (entry 2), the implication of which will be discussed later.

4.2 *Asymmetric reduction of alkyl phenyl ketones*

Next, a number of alkyl phenyl ketones, PhCOR (R = D, Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, and cyclohexyl) were reduced by the reagent (I) (Nasipuri and Sarkar 1967b; Nasipuri and

Table 1. Asymmetric reduction of alkyl methyl ketones, RCOMe.

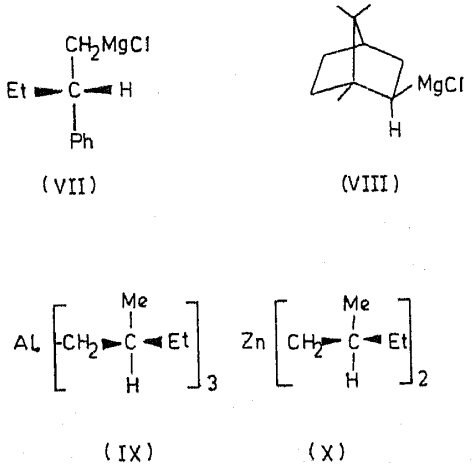
Entry	Reagents	Percent asymmetric reduction[a] with R = Et	*i*-Bu	*i*-Pr	*t*-Bu	cyclohexyl	Abs. confgn.
1.	Bornan-*exo*-2-yloxy-aluminium dichloride (I)	2·8	5·7	16·4	18·0	10·0	(−)-(R)
2.	Reagent (I) + $MgBr_2$ (1·5 mol)	—	10·5	22·0	—	—	(−)-(R)
3.	(S)-2-Methylbutylmagnesium chloride	—	—	—	13·0	9·0	(+)-(S)
4.	Tris[(S)-2-methylbutyl]aluminium	5·3	—	16·7	19·8	—	(+)-(S)

[a] Calculated as $100 \times \alpha_D$ (obsd.)/α_D (max.).

Mukherjee 1974). In this series, the extent of asymmetric induction (10–84 %) depended very much on the size of the alkyl group rising steeply in the order D < Me < Et < *n*-Pr < *i*-Bu < *i*-Pr but decreasing again for R = *t*-Bu and C_6H_{11}. A very similar trend has been observed when these ketones were reduced with other chiral reagents, such as (+)-(S)-2-phenylbutylmagnesium chloride (VII) (Morrison and Mosher 1971, p. 188), bornan-*exo*-2-ylmagnesium chloride (VIII) (Vavon and Angelo 1947), (+)-*tris*[(S)-2-methylbutyl]aluminium (IX) (Giacomelli *et al* 1973) and (+)-*bis*[(S)-2-methylbutyl]zinc (X) (Giacomelli *et al* 1974b) (chart 2). The results of these reductions are shown in table 2.

It may be noted that steric consideration based on cyclic transition state (IV) permits correct prediction of the absolute configuration of the predominant enantiomer in each case, but the higher asymmetric induction with increasing bulk of the alkyl groups, with phenyl still behaving as the bulkiest of all, is hard to reconcile by steric factor alone. Secondly, although phenyl, *t*-butyl and cyclohexyl groups are of comparable size, there is no parity in the extent of asymmetry induced in the three series of ketones. To cite an example, *i*-PrCOR (R = Ph, *t*-Bu and cyclohexyl), when reduced with (+)-(S)-2-methylbutylmagnesium chloride gave alcohols with enantiomeric excess of 24, 5 and 2 % respectively (Morrison 1966). Evidently, as pointed out by Birtwistle *et al* (1964) and Cherest *et al* (1968), the origin of this discrepancy lies in some subtle electronic

CHART 2



(VII) (VIII)

(IX) (X)

Table 2. Asymmetric reduction of alkyl phenyl ketones, PhCOR.

Entry	Reagents	Enantiomeric excess for R=								Abs. confgn.
		D	Me	Et	*n*-Pr	*i*-Bu	*i*-Pr	*t*-Bu	C_6H_{11}	
1.	(I)	10	25	38	44	66	84	35	40	(+)-(R)
2.	(VII)	—	47	52	—	53	82	16	—	(−)-(S)
3.	(VIII)	—	36	19	46	—	55	72	—	(+)-(R)
4.	(IX)	—	6	13	—	—	44	32	—	(−)-(S)
5.	(X)	—	2·5	4·4	—	—	15·2	10·6	—	(−)-(S)

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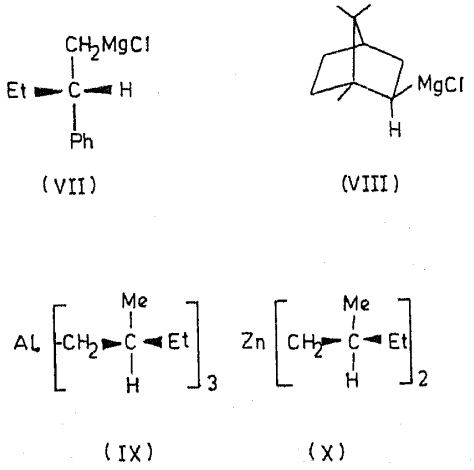

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4.	(IX)	—	6	13	—	—	44	32	—	(−)-(S)
5.	(X)	—	2·5	4·4	—	—	15·2	10·6	—	(−)-(S)

effect of the phenyl group. From practical point of view, however, the asymmetric reduction of aromatic ketones is quite satisfactory.

4.3 *Asymmetric synthesis of chiral benzyl-α-d alcohol*

Optically active α-deuterated primary alcohols, *e.g.*, PhCHDOH of known configuration are important for mechanistic and biochemical studies. Several asymmetric reductions involving H- and D-transfer from chiral reagents to aldehydes are known (Streitweiser *et al* 1959; Streitweiser and Granger 1967; Althouse *et al* 1966). Six such reactions were carried out in the present laboratory (Nasipuri *et al* 1970) with reagents derived from *exo*- and *endo*-bornan-2-ols. The results are summarised in table 3 with an additional data (entry 7) from literature (Althouse *et al* 1966). α-D-benzyl alcohol, isolated in nearly 90% yield was purified by preparative GC. The interesting features in the reductions are as follows. (i) Except for reduction with the reagent (II) (entry 3), the absolute configuration of the predominant enantiomer is as expected from the cyclic transition state assuming that C-1 is effectively bulkier than C-3 in both *exo*- and *endo*-bornane derivatives. (ii) The asymmetric induction in D-transfer is appreciably higher than that in H-transfer from analogous reagents (entries 1 & 2 and 4 & 5). (iii) Bromomagnesio-derivatives of bornan-2-ols are the best enantioselective reagents (entries 4–6) bringing the highest ever asymmetric induction by chemical means. The reagents are easy to prepare and by proper combination of substrates (PhCHO and PhCDO) and reagents, either enantiomeric form may be available. The anomaly encountered with the reagent (II) regarding the configuration of the predominant enantiomer will be dealt with in a later Section. The higher asymmetric induction in D-transfer was previously ascribed to a slower rate of reaction with deuterated reagents (Althouse *et al* 1961) but it is now known that the rate factor does not significantly affect the stereochemistry of these reactions (see §4.4). The average C–H bond distance is 0·0008 Å longer than C–D and H has a larger De Broglie wavelength; hence H is able to transfer from reagent to substrate at a greater distance. The closer proximity of the two reacting centres in D-transfer produces more steric compression and more stereoselectivity (ApSimon and Seguin 1979) than in H-transfer.

Table 3. Asymmetric synthesis of PhCHDOH by alkoxymetal halides.

Entry	Reagents	Aldehyde	Enantiomeric excess (%)	Abs. confgn.
1.	(−)-Bornan-*exo*-2-yloxyaluminium dichloride (I)	PhCDO	10·4	(−)-(R)
2.	(−)-α-d-Bornan-*exo*-2-yloxyaluminium dichloride	PhCHO	17·8	(+)-(S)
3.	(−)-Bornan-*endo*-2-yloxyaluminium dichloride (II)	PhCDO	32·7	(+)-(S)
4.	(−)-Bornan-*endo*-2-yloxymagnesium bromide (VI)	PhCDO	52·2	(−)-(R)
			62·5*	(−)-(R)
5.	(−)-α-d-Bornan-*exo*-2-yloxymagnesium bromide	PhCHO	64·1	(+)-(S)
6.	(−)-Bornan-*endo*-2-yloxymagnesium bromide	PhCDO	64·5	(−)-(R)
7.	(+)-2-Methyl-1-butylmagnesium chloride	PhCDO	18·1	(+)-(S)

* Reported by Gerlach (1966).

4.4 *Asymmetric reduction of some substituted phenyl ketones*

To ascertain whether the rate has any influence on the stereochemistry of reduction, a number of acetophenones and phenylglyoxylic acid derivatives substituted at the para position with both electron-donating and electron-withdrawing groups were reduced by reagents (I) and (II) (Nasipuri and Ghosh 1967; Nasipuri and Mukherjee 1974). The results are summarised in table 4. The following observations are made. (i) All the acetophenones underwent reduction with remarkable consistency in asymmetric induction (25–30%) (entries 1–5) although they must have different reactivities. *p*-Methoxyacetophenone could not be reduced but ethyl phenylglyoxylate and *p*-methoxyphenylglyoxylate were reduced both by reagents (I) and (II) with almost identical asymmetric induction (entries 6 & 7 and 8 & 9). The rate of the reaction, therefore, does not have any appreciable effect on stereoselectivity—a conclusion reached by other workers also, working with Grignard reagents (Morrison and Mosher 1971, p. 202). (ii) The configuration of the predominant enantiomer in all cases except two (entries 11 and 13) was predictable from the cyclic transition state assuming that Ph behaves as a bulkier group than CO_2Et. (iii) The extent of asymmetric induction is in general low with one exception—the reduction of $PhCOCO_2H$ with borneol-complex (II) (entry 11) in which the stereochemistry is in contravention to the normally accepted transition state. We suggest that for this slow-reacting reagent, CO_2H and possibly CN (entry 13) form some sort of complex with the reagent before the ketonic function gets reduced and thus become effectively bigger than Ph group. (iv) *p*-Nitroacetophenone was reduced smoothly and quantitatively with the reagent (I). It may be superior to sodium borohydride for the reduction of aromatic nitro-ketones which often give coloured by-products with borohydrides. (v) Finally, *p*-methoxyacetophenone remained completely inert to the reagents, possibly due to complexation with $AlCl_3$; conversely, the dichloroalumino-derivative of *p*-methoxyphenylcarbinol may be an

Table 4. Asymmetric reduction of substituted acetophenones and phenylglyoxylates.

Entry	Ketones	Reagents	e.e. (%)	Abs. confgn.
1.	PhCOMe	(I)	25–27	(+)-(R)
2.	*p*-$O_2NC_6H_4COMe$	(I)	25[a]	(+)-(R)
3.	*p*-ClC_6H_4COMe	(I)	28[b]	(+)-(R)
4.	*p*-BrC_6H_4COMe	(I)	25[b]	(+)-(R)
5.	*m*-BrC_6H_4COMe	(I)	30	(+)-(R)
6.	$PhCOCO_2Et$	(I)	14	(+)-(S)[c]
7.	*p*-$MeOC_6H_4COCO_2Et$	(I)	17	(+)-(S)
8.	$PhCOCO_2Et$	(II)	10	(+)-(S)
9.	*p*-$MeOC_6H_4COCO_2Et$	(II)	12	(+)-(S)
10.	$PhCOCO_2H$	(I)	8	(+)-(S)
11.	$PhCOCO_2H$	(II)	57	(−)-(R)
12.	PhCOCN	(I)	4	(+)-(S)
13.	PhCOCN	(II)	9	(−)-(R)

[a] The alcohol was resolved through brucine salt of its acid phthalate and had α_D (max) 73·6°. [b] The optical purity of the halogenated alcohols was determined by converting them into phenylmethylcarbinol on catalytic reduction ($Pd + NEt_3$). [c] (+)-(S)-Mandelic acid is configurationally related to (+)-(R)-phenylmethylcarbinol.

excellent reducing agent. Some encouraging results have already been obtained (Nasipuri and Datta Gupta unpublished).

4.5 *Asymmetric reduction of phenyl trifluoromethyl ketone*

The dichloroalumino- and bromomagnesio-derivatives of *exo*-, *endo*-bornan-2-ols and *p*-menthan-3-ol vary considerably in their reducing property and could not be extended to include a complete series of reductions. Recently, Morrison and Ridgway (1974) have shown that phenyl trifluoromethyl ketone ($PhCOCF_3$) undergoes a ready and virtually irreversible Meerwein-Ponndorf-Verley-type of reduction and is thus an ideal substrate for a comparative study of stereoselectivity by this group of reagents. It was therefore reduced with dichloroalumino- and bromomagnesio-derivatives of four optically active alcohols, *e.g.*, (−)-bornan-2-*exo*-ol, (−)-bornan-2-*endo*-ol, (−)-*p*-menthan-3-ol and (+)-l-phenylethanol all having (R)-configuration at the carbinol carbon and designated for the sake of brevity as B^iOAlCl_2 (I), B^iOMgBr (VI), $BOAlCl_2$ (II), BOMgBr, $MenOAlCl_2$ (III), MenOMgBr, $PeOAlCl_2$ (XI) and PeOMgBr (XII) (chart 3). The results are summarised in table 5 (entries 1–10), along with some additional data from the literature. Other abbreviations in table 5 are 2MbMgCl for

CHART 3

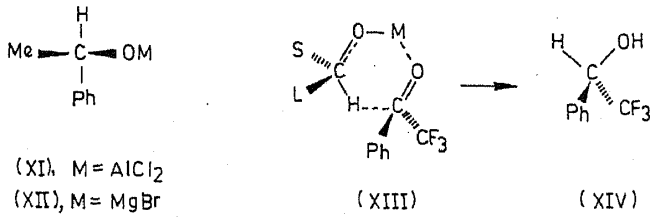


Table 5. Asymmetric reduction of $PhCOCF_3$ with alkoxy- and alkyl-metal halides.

Entry	Reagents	Yield (%)	e.e. (%)	Abs. confgn.*
1.	(R)-B^iOAlCl_2	85	8·4	(+)-(S)
2.	(R)-B^iOAlCl_2,$MgBr_2$	65	16·1	(+)-(S)
3.	(R)-B^iOMgBr	60	2·0	(−)-(R)
4.	(R)-$BOAlCl_2$	85	68·0	(+)-(S)
5.	(R)-$BOAlCl_2$, $MgBr_2$	40	62·0	(+)-(S)
6.	(R)-BOMgBr	50	23·3	(+)-(S)
7.	(R)-$MenOAlCl_2$	50	77·0	(+)-(S)
8.	(R)-MenOMgBr	50	10·0	(−)-(R)
9.	(R)-$PeOAlCl_2$	80	4·0	(−)-(R)
10.	(R)-PeOMgBr	80	15·8	(−)-(R)
11.	(S)-2MbMgCl	—	22·0	(+)-(S)
12.	(S)-2PpMgCl	—	47·0	(+)-(S)
13.	(S)-Al2Mb, OEt_2	—	11·6	(+)-(S)
14.	(S)-Zn2Mb	—	5·2	(+)-(S)

* (+)-(S)-2,2,2-Trifluoro-1-phenylethanol is configurationally related to (+)-(R)-1-phenylethanol due to priority sequence.

(S)-2-methylbutylmagnesium chloride, 2PpMgCl for (S)-2-phenylpropylmagnesium chloride (Morrison and Mosher 1971, p. 191), Al2Mb for tris-[(S)-2-methylbutyl] aluminium-diethyl ether complex (IX) (Giacomelli *et al* 1975) and Zn2Mb for bis-[(S)-2-methylbutyl]zinc (X) (Giacomelli *et al* 1974a). The following general observations are made. (i) Only two of the reagents, $BOAlCl_2$ (II) and $MenOAlCl_2$ (VI) are of high enantioselectivity, affording 2,2,2-trifluoro-1-phenylethanol (XIV) with 68 and 77% enantiomeric excess respectively (entries 4 and 7) (Nasipuri and Bhattacharya 1975, 1977). This alcohol is a common chiral solvent used in NMR experiments for determining the absolute configuration and optical purity of compounds such as alcohols, amines, sulphoxides etc. (Pirkle and Beare 1969) in which it induces enantiomeric non-equivalence (Raban and Mislow 1967). The present method offers a convenient route to this alcohol of sufficient optical purity to be used directly for this purpose. (ii) Barring one or two cases (entries 3 and 8), the stereochemical results fall under two broad categories: (a) reduction with reagents derived from cyclic (R)-alcohols gives a preponderance of (+)-(S)-trifluorophenylethanol in accord with the preferred transition state (IV); (b) reduction with reagents derived from acyclic chiral components gives opposite stereochemistry, *i.e.*, (R)-alcohol from (R)-reagents and (S)-alcohol from (S)-reagents (entries 8–14). The preferred transition state for cases under (b) appears to be the one (XIII) in which Ph and L are on the same side of the ring, *i.e.*, CF_3 behaves as bulkier than Ph. This will be discussed in §6. (iii) The addition of $MgBr_2$ (Lewis acid) increases the stereoselectivity in one case (entry 2) almost by 100%.

4.6 *Asymmetric reduction of aminoketones*

A few aminoketones (XV)–(XXIII) (chart 4) were reduced with the reagent (I) (Samaddar *et al* 1983). The aminoalcohols were readily separable because of their acid-solubility and obtained in high chemical yields (table 6). Some of them are physiologically active and their availability in optically pure form is desirable. Tomina *et al* (1972) and Andrisano *et al* (1973) reduced a number of these ketones using chiral organomagnesium reagents and $LiAlH_4$ modified by (−)-menthol respectively. The easy accessibility of our reagent, the predictability of the product configuration and high optical yield make the present method a practical one. The three acetylpyridines (XXI)–(XXIII) were reduced to 1-(2-, 3-, and 4-pyridyl)ethanols but the asymmetric induction was low.

Chart 4

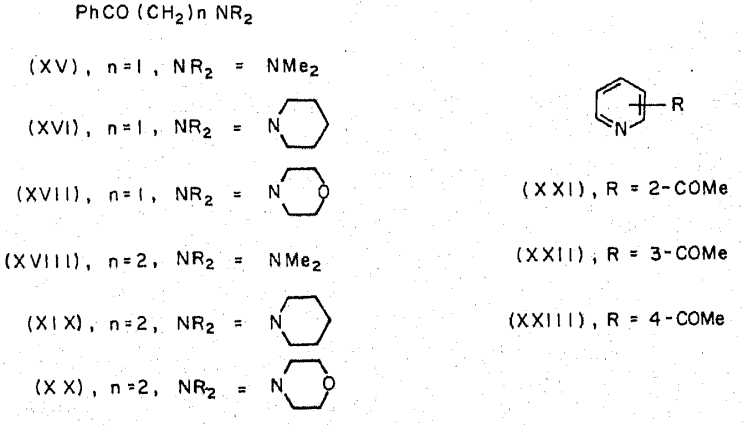


Table 6. Asymmetric reduction of aminoketones (XV)–(XXIII).

Entry	Aminoketone	Yield (%)	e.e. (%)	Abs. confgn[a].
1.	(XV)	78·0	66·7	(+)-(S)
2.	(XVI)	90·5	60·0	(+)-(S)
3.	(XVII)	81·5	71·0	(+)-(S)
4.	(XVIII)	82·0	65·0	(+)-(R)
5.	(XIX)	84·5	58·0	(+)-(R)
6.	(XX)	77·5	92·0	(+)-(R)
7.	(XXI)	75·0	11·5	(+)-(R)
8.	(XXII)	60·0	37·0	(+)-(R)
9.	(XXIII)	70·0	14·7	(+)-(R)

[a] (S)-Configuration of XV–XVII are related to (R)-configuration of XVIII–XXIIII.

4.7 *Asymmetric reduction of miscellaneous ketones*

Benzyl methyl ketone on reduction with the reagent (I) afforded benzylmethylcarbinol in 50% yield with α_D-3·1° corresponding to 11.5% of enantiomeric excess (Nasipuri and Datta Gupta Unpublished). β-Tetralone although reduced smoothly did not give any optically active alcohol. α-Tetralone, α-hydrindone and fluorenone were not reduced at all. Dichloroaluminoderivative of 9-fluorenol proved to be a very good reducing agent for cyclic ketones (Nasipuri and Datta Gupta Unpublished).

4.8 *Stereoselective reduction of triterpenoid ketones*

A number of 3-oxotriterpenoids and 3-oxosteroids such as α-amyrone, lupenone, arborinone, methyl ursonate, methyl oleanonate, friedelin, cholestan-3-one and 2,2-dimethylcholestan-3-one were reduced by the reagent (I). In all cases, axial alcohols were obtained predominantly (75–100%) (Nasipuri *et al* 1976). In the wider sense of the term, this may also be regarded as asymmetric synthesis or more specifically diastereoselective synthesis. In most cases, a single crystallisation of the epimeric mixture afforded the pure axial alcohol.

5. Kinetic resolution of exo- and endo-bornan-2-ols

Four chiral ketones, namely, (+)-(R)-3-methylcyclohexanone (XXIV), (−)-1(R), 4(S)-*p*-menthan-3-one (XXV), (+)-1(S), 4(R)-fenchone (XXVI) (Chart 5) and 5-α-cholestan-3-one all of known configuration were treated with 2 moles of dichloroaluminocomplexes of (±)-*exo*- and (±)-*endo* bornan-2-ols (Nasipuri and Mukherjee 1974). Camphor formed was uniformly (+)-rotatory isolated as alkali-soluble (−)-rotatory oxime (table 7). Evidently, (−)-*exo*-bornan-2-yloxyaluminium dichloride (I) was consumed faster than its antipode and the transition state (XXVII) must be favoured over its diastereoisomer. The reagent attacks the ketones from the less hindered side (equitorial or β) (see §4.8) as shown in XXVII and steric interactions arise due to substituents which are only on the upper side (β) of the ring. Any substituent below the plane of the ring (α) such as Pr^i in menthone or more than two carbon atoms away from

Chart 5

(XXIV), R=H
(XXV), R=Pr^i (XXVI) (XXVII)

Table 7. Kinetic resolution of camphor by oxidation of bronan-2-ols.

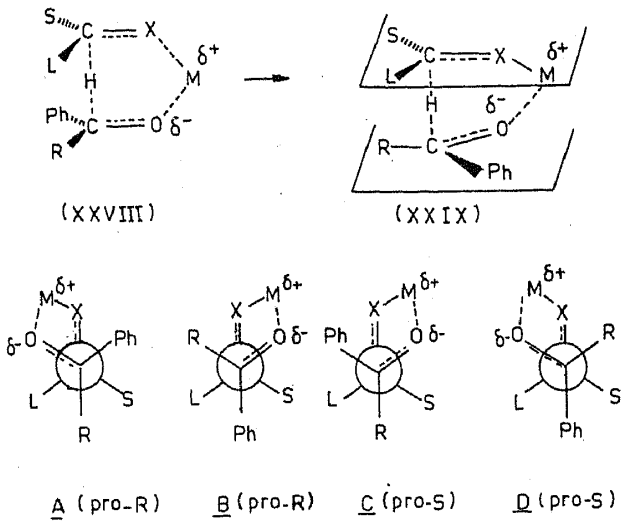
		Camphor-oxime from (±)-exo-isomer		Camphor-oxime from (±)-endo-isomer	
Entry	Ketone	α_D	e.e. (%)	α_D	e.e. (%)
1.	(+)-3-Methylcyclohexanone (XXIV)	−3·1°	7·3	+0·36°	1·0
2.	(−)-Menthone (XXV)	−37·8°	89·0	+6·48°	15·3
3.	(+)-Fenchone (XXVI)	−29·55°	70·0	—	—
4.	3-Cholestanone	−3·8°	9·0	+0·42°	1·1

C=O as 10-Me in 3-cholestanone will have no appreciable steric effect. Thus for 3-methylcyclohexanone (XXIV) and menthone (XXV), it is only the equatorial β-Me that matters and it is better off being on the side away from C-1-Me of bornane moiety. This puts XXIV and XXV on a similar footing both of them consuming (−)-*exo*-bornan-2-ol at a faster rate, menthone more so perhaps due to its rigid molecular frame (see also Morrison *et al* 1969). It thus constitutes a convenient chemical method for the determination of configuration of chiral ketones.

6. A new transition state model

During the discussion of the results, we made certain observations which did not fit in the cyclic transition state (IV). These include (i) high asymmetric induction when a Ph group is attached to C=O or is a part of the reagent or both; (ii) enhanced enantioselectivity in the reduction of PhCOR as the bulk of R increases; (iii) atypical enantiomer formed in reduction of $PhCOCF_3$ with acyclic chiral reagents; and (iv) anomalous behaviour of bornan-*endo*-2-yloxyaluminium dichloride (II) during reduction of PhCDO. We suggested a transition state model for these reductions (Nasipuri *et al* 1967) to explain observation (ii) primarily based on the effect of rate on stereochemistry which subsequently proved to be wrong (see §4.4). Recently, we have advanced a new transition state model (Nasipuri *et al* 1971) which as we shall see in the sequel explains all the discrepancies and has been accepted and used by other workers in this field (Giacomelli *et al* 1973; Cabaret and Welvart 1974; ApSimon and Seguin 1979). The metal in the reagent first coordinates with C=O which is followed by an energetically preferred linear H-transfer. The complex (XXVIII) (chart 6) twists along C . . . H . . . C axis to relieve steric and torsional strain, with the two oppositely developing dipoles, O^- and XM^+ (M stands for Al, Mg and Zn, and X for O and CH_2)

CHART 6

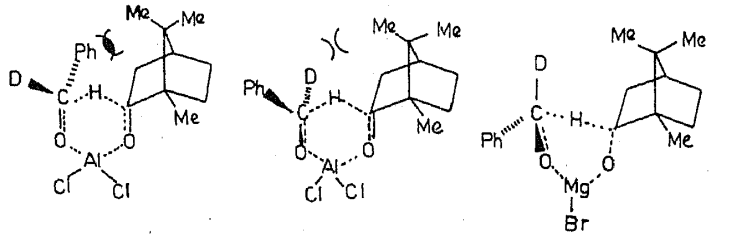


loosely bound in space as shown in structure (XXIX) for (R)-reagents. The steric interactions in the reactive conformations may be appraised in Newman-type formulae viewed along C . . . H . . . C bond, the relatively short C–H bond and the radial distribution of the groups largely compensating for the extra H sandwiched between carbons (Nasipuri and Mukherjee 1974). Four such structures *A*, *B*, *C* and *D* (chart 6) may be envisaged the first two leading to (R)-alcohol and the last two to (S)-alcohol. Between *A* and *B*, *A* is favoured both sterically (L and Ph anti) and electronically (XM^+ flanked by two negative dipoles, O^- and Ph), while between *C* and *D*, *C* is favoured on similar grounds. The product ratio, R/S will, therefore, depend mainly on the relative stability of *A* (pro-R) and *C* (pro-S). Simple steric consideration (Ph ↔ S + L ↔ O^- in *A* and Ph ↔ L + S ↔ O^- in *C*) shows that *A* is more stable and so (R)-alcohol predominates. As R increases in bulk, a buttressing effect operates, rotation to separate L and R in *C* will push Ph against L whereas a similar rotation in *A* is easy. This explains the puzzling fact of increased asymmetric induction with increasing size of R in PhCOR. To put it in a different language, the increased steric hindrance due to bulkier R prevents the conformational mobility of all the groups being compressed but more so in *C* than in *A* (Giacomelli *et al* 1973). Conformational analysis of *B* (pro-R) and *D* (pro-S) shows that *D* is more stable (L ↔ R + S ↔ O^- in *B* and S ↔ R + L ↔ O^- in *D*) and hence their involvement will reduce the stereoselectivity. This is exactly what happens in the reduction of aliphatic ketones which lacks the electronic effect of Ph and the participation of *A* and *C* lessens.

For reduction of $PhCOCF_3$ (R = CF_3 in *A*–*D*), the reactive conformers in which XM^+ lies between $-O^-$ and CF_3 (*i.e.*, *B* and *D*) should determine the steric course since CF_3 is a stronger (−)-dipole than Ph, and *D* being more stable, the enantioselectivity will be reversed. For cyclic reagents (L and S joining to form a ring), conformations *B* and *D* are, however, seriously destabilised by steric interaction between Ph and ring substituents and the stereochemical control is relayed back to *A* and *C*. Three anomalous observations (i)–(iii) are thus explained.

The linearity of C . . . H . . . C bond in XXIX depends on two factors: the strength of the coordinating bond and the size of the groups staggered around the C . . . H . . . C

CHART 7



(XXX)(pro-R) (XXXI)(pro-S) (XXXII)(pro-R)

linkage. Thus $OAlCl_2$ being a stronger electrophile than OMgBr, is drawn nearer to $-O^-$ leading more or less to the classical cyclic transition state shown in figure (XXX) (chart 7) for reaction of PhCDO with (−)-$BOAlCl_2$ (II). In this conformation, one of the overhanging 9-Me interacts strongly with Ph and so the other transition state (XXXI) with Ph on the same side as C-1 is preferred. With (−)-BOMgBr, on the other hand, the preferred conformation is XXXII with Mg loosely bound to $-O^-$. Thus the differential behaviour of $BOAlCl_2$ and BOMgBr is also explained. For $ROAlCl_2$ reagents, it is probable that the transition state (XXIX) leans more towards semi chair conformation with non-linear C . . . H . . . C bond in which the steric interactions are eased out so that asymmetric induction is low (*e.g.*, PhCDO reduction, table 3). But when both the carbinol and ketone bear heavy substituents, the quasi chair conformation changes over to the linear one (XXIX) to avoid 1,3-diaxial interaction and the asymmetric induction goes up. This is borne out by the observation that when anhydrous $MgBr_2$ is added in the reaction media, asymmetric induction increases due to weakening of the coordinating bond (Gould 1964).

7. Conclusion

The present investigation has provided a few highly enantioselective and diastereoselective reducing agents. Because of their easy accessibility, they will prove very useful in organic synthesis. A highly satisfactory and generally accepted transition state model for these reductions has also been postulated.

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