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NADH MIMICS FOR THE STEREOSELECTIVE REDUCTION OF BENZOYLFORMATES TO THE CORRESPONDING MANDELATES.

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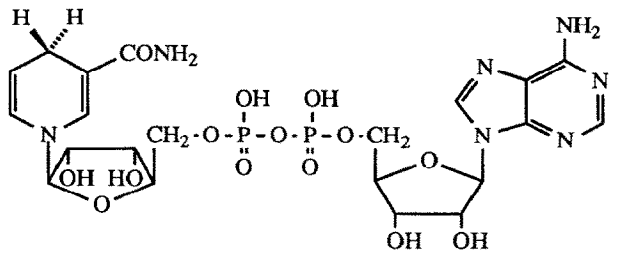
1. INTRODUCTION

Redox processes play an important role in organic synthesis and as a result a vast number of oxidizing and reducing agents have been developed. As new situations arise there is frequently the need for either more reactive or more selective reagents. In particular the demands of asymmetric synthesis require that these reactions be conducted stereoselectively. To this purpose homochiral boranes and homochiral metal hydrides and catalysts have been synthesised and are now in wide general use.[1] There will, however, always be situations where currently available reagents are not successful in achieving a highly stereoselective reaction and therefore there is always a need to develop new types of stereoselective reagents. Furthermore, inherent with the design of these new systems comes the potential to develop reducing agents which may be used in catalytic rather than stoicheiometic amounts.

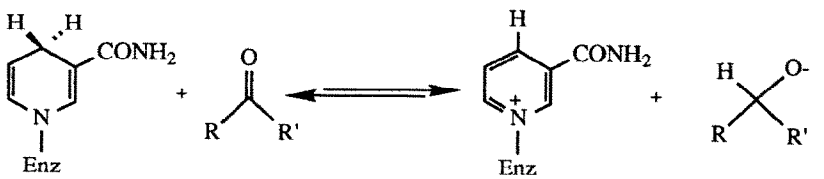
In nature many redox transformations are carried out rapidly and stereoselectively in the presence of enzymes. The selective nature of these enzyme mediated reactions provides an exciting possibility for the development of biomimetic stereoselective reducing agents useful to organic chemists. As a consequence these enzymes have been extensively studied in the hope of determining those features of the enzyme responsible for this selectivity and to then impart similar properties to redox reagents used in modern organic chemistry.

It is certainly a challenge for organic chemists to develop artificial systems which mimic enzymic reactions in biological systems.[2] In order to model the specific action of an enzyme the key features responsible for this action must be identified. Rather than reproduce the complete enzyme, which is usually a large, complex molecule, only those features of the enzyme which are essential for its specific activity need be incorporated into a mimic. Enzymes which carry out biological redox processes require coenzymes such as nicotinamide adenine dinucleotide (NADH/NAD^+) to act as reagents in the active site of the enzyme.[3,4] Attempts to model these oxidoreductases usually rely on identifying the redox portion of the coenzyme and building onto that moiety those features of the enzymes which impart specific activity.



NADH

As an example, the coenzyme NADH acts as a redox reagent by interconverting between a 1,4-dihydropyridine and a pyridinium cation.[5] In the reduction of a ketone the reduced form of the coenzyme NADH donates two electrons and one proton to the substrate and as a consequence the coenzyme is oxidized to the pyridinium cation. The oxidized form of the coenzyme can now catalyze the reverse reaction. The stoicheiometry of the redox reactions is illustrated in Scheme 1. While a consensus as to the details of the mechanism of hydride transfer has not yet been achieved, proposals for this mechanism being a concerted process or proceeding *via* a three step sequence involving two single electron transfers have been made.[6]



Scheme 1:

Reduction of a ketone using NADH as the reducing agent. Enz represents the dinucleotide moiety of NADH.

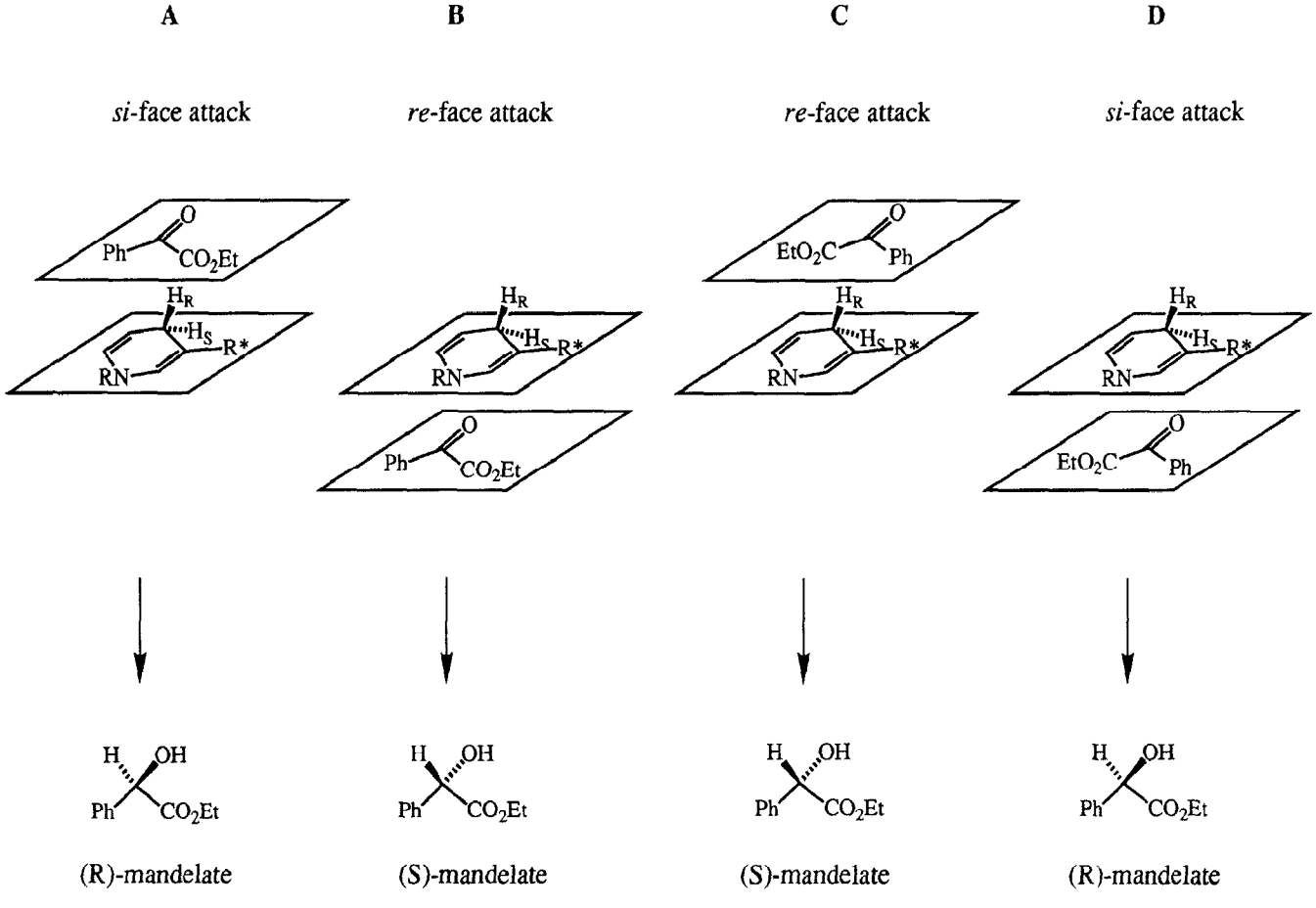
Even though it is clear that the nicotinamide portion of the coenzyme transfers the hydrogen to the substrate, the high stereoselectivity of reaction arises from restrictions created by the homochiral environment within the enzyme.[7] As NADH binds to the enzyme distinct conformational changes occur at the active site. As a result either the 4-*pro*-(R) or 4-*pro*-(S) hydrogen of the dihydronicotinamide ring is aligned for hydride transfer to the substrate. For example, the hydrogen is transferred from the 4-*pro*-(R) position of the coenzyme in the presence of dogfish lactate dehydrogenase[8] while the 4-*pro*-(S) hydrogen is transferred in the presence of lobster muscle glyceraldehyde-3-phosphate dehydrogenase. The restricted access of the substrate to the 4-*pro*-(S) hydrogen of NADH bound to dogfish lactate dehydrogenase has been attributed to the positioning of that face of the dihydronicotinoyl ring containing the 4-*pro*-(S) hydrogen in a hydrophobic environment.[9] Furthermore, the orientation of the substrate with respect to the transferring hydrogen is determined by the enzyme as a result of electrostatic and steric interactions created by the substrate binding site.[7]

To achieve high stereoselectivity in mimetic systems an alternative means for providing the restrictions imposed by the enzyme must be realized. In the simplest type of system involving the interaction of a chiral dihydronicotinoyl derivative and the substrate (e.g. ethyl benzoylformate), each of the two enantiotopic faces of the α-ketoester can interact with either of the two diastereotopic faces of the dihydropyridine ring, so that there are four possible approach pathways (Figure 1, A-D). For example, pathway A shows the *si*-face of ethyl benzoylformate approaching the *pro*-(R) hydrogen with the ester portion lying over the R* substituent. Presentation of the *si*-face of the ethyl benzoylformate results in formation of the (R)-mandelate whereas the (S)-mandelate is formed as a result of *re*-face delivery to the dihydropyridine.

In essence the selective formation of one enantiomer requires the preferential approach of the substrate toward the dihydropyridine ring along only one pathway i.e. A, B, C or D. In order to achieve this the other three possible pathways must be precluded. A preference must be built into the model system whereby the substrate is constrained to approach the dihydropyridine with a fixed orientation. For example the approach pathway may be such that the ester portion of the substrate approaches directly over a particular substituent (R*) on the dihydropyridine ring, (Figure 1, A and B). While this restriction limits the possible approach pathways to two it does not necessarily result in the selective formation of (R) or (S)-mandelates, i.e. pathway A generates the (R)-mandelate whereas pathway B generates the (S)-mandelate. Pathways A and B differ in the face of the dihydropyridine ring which is approached by the substrate. As a result, a further restriction must be built into the model to control the direction of substrate approach, e.g. to generate the (R)-mandelate pathway A must be followed and as such attack of the substrate from below the plane of the dihydropyridine ring (pathway B), i.e. towards the *pro*-(S) hydrogen, must be avoided.

The purpose of this review is to discuss the different approaches that have been taken in order to control the orientation and direction of approach of the substrate by sufficiently restricting the geometry of the transition state.[10] The emphasis will be on those systems which impart high stereoselectivity in the reduction of prochiral substrates with these stereoselectivities being interpreted in terms of those factors which influence the geometry of substrate attack with respect to the model compound (ethyl or methyl benzoylformate).

Figure 1

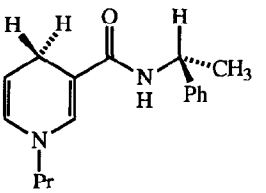

A
B
C
D
si-face attack
re-face attack
re-face attack
si-face attack
Ph
O
CO2Et
EtO2C
HR
HS
R*
RN
H
OH
(R)-mandelate
(S)-mandelate
(S)-mandelate
(R)-mandelate

2. STRATEGIES FOR ACHIEVING DIRECTIONAL AND ORIENTATIONAL CONTROL

A. DIHYDRONICOTINOYL DERIVATIVES AS NADH MIMICS

a. Chelation Control

In 1975 Ohno[11] reported the first stereoselective reduction of a prochiral substrate by a 1,4-dihydropyridine derivative **1** possessing a chiral carboxamide at C-3. In the asymmetric reduction of ethyl benzoylformate by **1** the corresponding (R)-mandelate was obtained in an enantiomeric excess of 20%. Ohno found that in order to facilitate the reduction of ethyl benzoylformate it was essential to conduct the reaction in the presence of magnesium ions; in the absence of magnesium ions the reaction failed to proceed.[11] Furthermore it was observed that the reduction of the more activated ketone α,α,α-trifluoroacetophenone with **1** afforded, in the presence of magnesium ions, the corresponding alcohol in 16% enantiomeric excess, whilst in the absence of magnesium ion reduction of the substrate gave racemic ethyl mandelate. It was deduced therefore that the stereoselectivity of these reductions was dependent upon the presence of Mg^{2+} in the reaction medium.



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Experimental evidence[12,13] implied that the role of the metal ion in this system was not just to act as a Lewis acid by polarizing the carbonyl group of the substrate. The observed stereoselectivity was attributed to the formation of a ternary complex of the type; [substrate - metal ion - dihydronicotinoyl] where the metal ion is located between the dihydronicotinoyl and the substrate in the transition state of the reduction (Figure 2).[12] Furthermore, the ketonic carbonyl of the substrate was assumed to lie over the dihydronicotinoyl ring with the oxygen pointing towards the ring nitrogen. This latter assumption was based on early investigations by Prelog[14] in which a similar orientation was proposed in the 'diamond lattice' model[15] for reasons relating to nonbonded interactions and maximum orbital overlap. Thus in the ternary complex proposed by Ohno the role of the magnesium ion is to specifically orientate the substrate over the reaction centre. This corresponds to the restriction of the four possible pathways for reduction (Figure 1) to two. However, each of these two pathways gives a different product enantiomer so that even though the orientation of the substrate with respect to the dihydropyridine may be fixed, a low enantiomeric excess could result from both of the diastereotopic hydrogens at C-4 being accessible to the substrate.

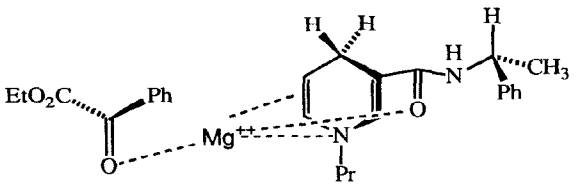
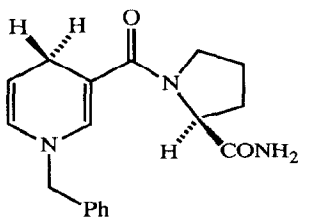


Figure 2:
Ternary structure proposed by Ohno[12] for the reduction of ethyl benzoylformate by **1** in the presence of Mg^{2+}.

Since the initial report by Ohno[11] a large number of attempts have been made to improve the stereoselectivity of the process by modifying both the homochiral carboxamide at C-3 and the substituent at N-1.[16] However the stereoselectivities obtained in the majority of these cases were only moderate. Of the modifications made at the chiral carboxamide the most successful example was mimic **2** developed by Inouye[17] in which a (S)-prolinamide derived moiety was substituted at C-3. The model compound **2** reduced ethyl benzoylformate to afford the (R)-mandelate with an enantiomeric excess of 83%. In this example it was presumed that the rigidity of the ternary complex is enhanced by additonal chelation of magnesium ion to the carbonyl of the primary amide. It should be noted however that in this case Inouye observed that the stereoselectivity depended on the molar ratio of magnesium to the dihydronicotinoyl, with a maximum enantiomeric excess being reached with a half mole ratio of magnesium ions.[18]



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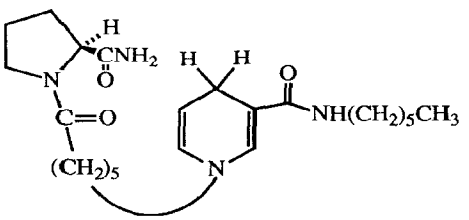

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When Inouye[19] incorporated an (S)-prolinamide derived moiety at N-1 as in compound **3**, an improvement in stereoselectivity was observed, but as in the previous example the stereochemical outcome was found to depend on the molar ratio of the magnesium ion. For example, in the asymmetric reduction of ethyl benzoylformate by **3** the (R)-mandelate was obtained with an enantiomeric excess of 90% only when a 0.5 molar ratio of magnesium was used. Inouye proposed that the metal ion chelates with the homochiral N-substituent in the transition state resulting in stereoselective blockage of one face of the dihydronicotinoyl ring (Figure 3). As a consequence the substrate approaches the unshielded face of the dihydronicotinoyl ring in the orientation shown, but Inouye gives no indication as to how this orientation is controlled. Furthermore, when a one molar ratio of magnesium was used the enantiomeric excess dropped to 71%. This seems to imply that under the optimal conditions the dihydronicotinoyl derivative actually exists as a dimer held together by the magnesium ion. Although the exact nature of the ternary complex is open to speculation it is clear that the model proposed by Inouye is inconsistent with his own experimental evidence.

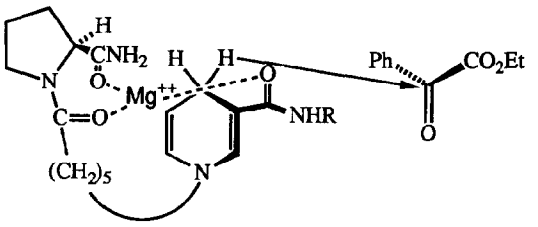
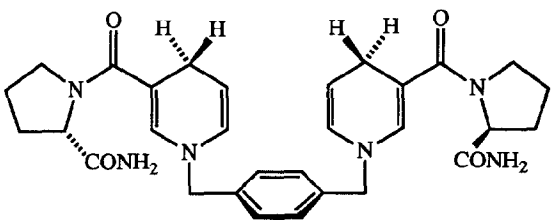


Figure 3:
The ternary structure proposed by Inouye[19] for the reduction of ethyl benzoylformate by **3** in the presence of magnesium ion (R = $(CH_2)_5CH_3$).

Inouye extended this work by incorporating two dihydronicotinoyl moieties within the same compound through a carbon bridge at N-1, describing these compounds as bis(NAH) derivatives.[20] Reductions using these bis(NAH) derivatives with a variety of bridging groups were studied, but the most efficient was found to be **4** which incorporated a *p*-xylenediyl bridge.[20a] As in the previous examples the molar ratio of magnesium was an important feature in determining the stereochemical outcome. Thus, in the asymmetric reduction of ethyl benzoylformate by **4**, in the presence of one equivalent of magnesium ion (i.e. 0.5 equivalents of magnesium ion for each dihydronicotinoyl), an enantiomeric excess of 98% was obtained.



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Inouye proposed that upon addition of magnesium the conformation adopted by the bis(NAH) model possessed a C_2 axis due to chelation of the magnesium to the carbonyls of the primary carboxamides (Figure 4). As a result of this conformation the outer faces of each of the dihydronicotinoyl rings in the bis(NAH) model are equivalent and only one of the diastereotopic hydrogens is available for transfer to the substrate. Although the conformation proposed by Inouye explains the stereoselective transfer of one of the diastereotopic C-4 hydrogens it fails to account for the high stereoselectivity observed in these reactions. In particular the question of substrate orientation has not been addressed. Presumably, based on the conformation proposed (Figure 4), magnesium is not available for orientation of the substrate through chelation. Hence it would appear that the concept of "specific blockage", proposed by Inouye,[21] explains only in part the stereochemical outcome of these reductions. Although the geometry of the transition state is not apparent it would seem likely that the role of magnesium is to coordinate both to the substrate and to the model compound thus controlling the orientation of the substrate.

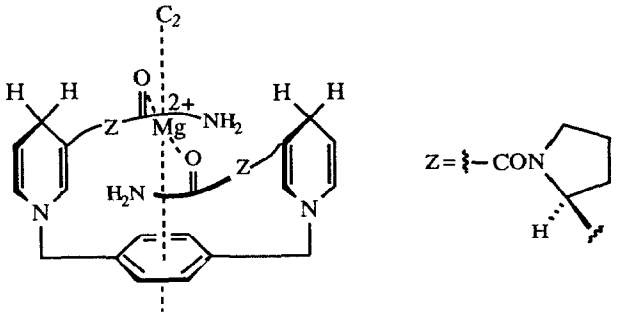
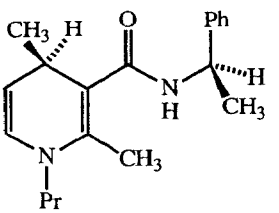


Figure 4:
The conformation proposed by Inouye for the magnesium-chelated bis(NAH) model **4**.

b. C-4 Substitution

In the biological system NADH binds to the enzyme such that only one face of the dihydronicotinoyl ring of NADH is exposed to the substrate for reduction; as a result selective transfer of only one of the C-4 hydrogens can occur.[3,22] In order to achieve asymmetric reduction using mimic systems the model compound must also achieve selective transfer of only one of the diastereotopic C-4 hydrogens. Any feature of the dihydronicotinoyl model compound e.g. puckering of the ring, which enhances the differences between the two C-4 hydrogens, such that one hydrogen is significantly more available for hydride transfer than the other, will influence the direction of substrate attack.[23]

Extending this concept, with a view to enhancing further any asymmetric bias, Ohno[24] stereoselectively replaced one of the two hydrogen atoms at C-4 with a methyl group, thus obviating the need for discrimination at the reaction centre. The dihydronicotinoyl compounds prepared by Ohno possessed methyl groups both at C-2 and C-4 and a chiral carboxamide derived from α-methylbenzylamine at C-3. In the reduction of methyl benzoylformate with compound (R,R)-**5** the (R)-mandelate was obtained with an enantiomeric excess of 98%.



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Ohno attributed the high stereoselectivity of this reduction to the formation of a well-defined transition state where both the orientation and direction of substrate approach to the dihydronicotinoyl ring is fixed. The direction of approach is controlled by the specific blocking of one of the faces of the dihydronicotinoyl ring due to the C-4 substituent and the relative orientation of the substrate is controlled by the Mg^{2+} located between the substrate and the 1,4-dihydronicotinoyl ring at the transition state of the reduction (Figure 5). Ohno[25]

assumed, as in his earlier example, that the carbonyl lies over the dihydronicotinoyl ring with the oxygen of the carbonyl directed towards the ring nitrogen. Selective formation of the (R)-mandelate can be rationalized by preferential delivery of the hydrogen to the *si*-face of the prochiral substrate. It should be noted that reductions with the (S,R) diastereoisomer of **5** gave the (S)-mandelate in a 97% enantiomeric excess which illustrates that although there is a chiral substituent at C-3 it is the chirality inherent at the reaction centre which is transferred to the substrate. Furthermore, in this instance the configuration of the α-methylbenzylamine derived side chain does not appear to influence the stereoselectivity of these reductions; this is in contrast with the reductions carried out using compound **1** where a 16% ee is attributed to the homochiral α-methylbenzylamine derived side chain.

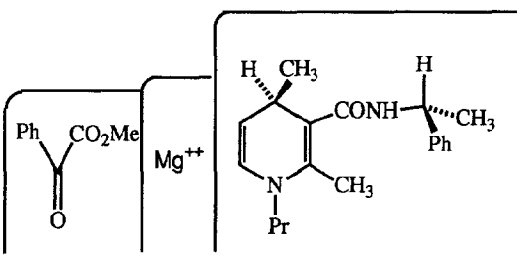
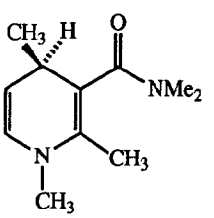


Figure 5:
Ternary complex proposed by Ohno[24] for *si*-face attack of methyl benzoylformate by (R,R)-**5**.

The asymmetric reduction utilising a C-4 methyl-substituted dihydronicotinoyl derivative **6** has also recently been investigated by Vekemans,[26] however in contrast to the mimic developed by Ohno[24,25] the carboxamide substituted at C-3 was achiral. Although these reactions can proceed with high stereoselectivity the stereochemical outcome was found to be temperature-dependent. For example, the reduction of methyl benzoylformate with (R)-3-(N,N-dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine (**6**) afforded the (R)-mandelate in a 95% optical yield when the reaction was conducted at -25°C, whereas at room temperature utilising (R)-**6** the optical yield of the (R)-mandelate dropped to 66%. Moreover the reaction was very rapid, essentially complete after one hour at -25°C and within 5 minutes at room temperature. The optical yield for the reduction carried out at -25°C was based on (R)-**6** having an optical purity of 96%, in real terms the observed enantiomeric excess was 92%. It should be noted that in this instance the pyridinium salt formed from **6** is achiral and hence may not be recycled.



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Vekemans proposed the formation of a ternary complex in the transition state involving chelation of both carbonyl oxygen atoms of the substrate and the oxygen of the carboxamide of the dihydronicotinoyl to a magnesium ion (Figure 6). Furthermore, the carboxamide carbonyl is *syn*-orientated with respect to the migrating hydrogen such that the dihedral angle between C-4 - H-4 and C=O is approximately 0° thus facilitating hydride migration.[27] Evidence for the cation interacting with the carboxamide oxygen of **6**, as first suggested by Ohno for **5**,[24] was provided by shifts in the signals observed in the ^{13}C nmr spectra of **6** in the presence of Mg^{2+}, in particular that of the carboxamide carbon. That the amide carbonyl is *syn*-orientated with respect to the transferring hydrogen in this system is further supported by some recent X-ray data obtained for stable ternary enzymic complexes.[28,29] Vekemans rationalizes the orientation of the ketonic carbonyl relative to the dihydronicotinoyl ring system by combining that illustrated in Figure 2 (first proposed by Ohno) with the necessary steric considerations.

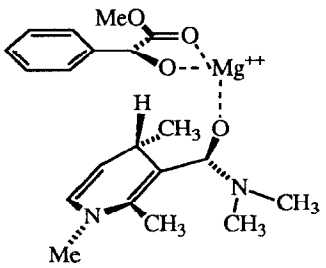
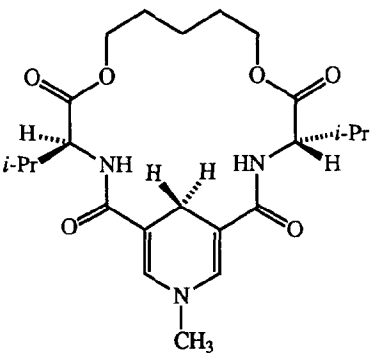


Figure 6:
Ternary complex proposed by Vekemans[26] for the interaction of **6** with methyl benzoylformate in the presence of magnesium ion.

It should be noted that although the systems developed by Ohno[24] and Vekemans[26] are similar in that they both have a C-4 and a C-2 methyl substituent there are some notable differences in reactivity and stereoselectivity. For example, although both reactions were essentially taken to completion at room temperature the reactions of Vekemans took less than five minutes whereas those performed by Ohno required two days. Moreover there was a marked difference in stereoselectivity at room temperature between the two systems, with Ohno achieving an enantiomeric excess of 98% compared to 66% achieved by Vekemans. To account for the dramatic dependence on temperature Vekemans proposed the intermediacy of a competitive mechanism in which free dihydronicotinoyl derivative and Lewis acid-activated methyl benzoylformate lead to racemic reaction products. This was supported by Ohno since the reduction of methyl benzoylformate by **5** to form racemic products can be achieved without magnesium ions.[24] By comparing the two systems of Ohno and Vekemans it is clear that, although the configuration at C-4 determines the configuration of the predominant mandelate, the nature of the carboxamide side chain also plays an important role in determining both the stereochemical course and rate of reaction.

c. C_2-axis of symmetry

An innovative approach which addressed the problem of directional control was that proposed by Kellogg[30,31] in which a series of bridged dihydronicotinoyl compounds with a C_2-axis of symmetry was prepared. As a result of this symmetry the C-4 hydrogen atoms are equivalent and consequently approach of Mg^{2+} to either face of the dihydronicotinoyl ring will result in the formation of the same transition state. The intention of Kellogg was to design a suitable 1,4-dihydronicotinoyl incorporated in a macrocyclic ring such that the ring would hold the metal ion in a fixed and predictable position relative to the 1,4-dihydronicotinoyl. It was anticipated that the incorporation of a "crown ether" segment[32] to form the macrocycle would provide additional sites for chelation and thereby hold the magnesium ion in the desired position. However, of the large number of bridged compounds designed by Kellogg the most efficient was compound **7** which incorporated a $(CH_2)_5$ bridge, rather than a cyclic ether linkage, and a carboxamide derived from *L*-valine. Thus, in the asymmetric reduction of ethyl benzoylformate by **7** the (S)-mandelate was obtained with an enantiomeric excess of 90%.



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To account for this stereochemical outcome Kellogg[31] assumed sequential complexation of Mg^{2+} to the carboxamide oxygen on the least hindered side of one face of the macrocycle **7**, followed then by complexation of the bound Mg^{2+} to the substrate (Figure 7). Evidence for the carboxamide carbonyl group contributing to complexation was provided by observations made in the ^{13}C nmr spectra. The positioning of the ketonic carbonyl of the substrate such that it is directed away from the ring nitrogen, which is in contrast to that proposed by Ohno,[12] was rationalised on the basis of a similar arrangement found in pig lactate dehydrogenase and lobster 3-phosphoglyceraldehyde dehydrogenase.[33] The preferred orientation of the substrate (Figure 7) has been rationalized in terms of steric interference between the aromatic group of the substrate and the isopropyl substituent of the amino acid derived moiety.

d. Remote steric blocking

While the incorporation of a C-4 substituent may increase asymmetric induction, as outlined in section (b), the task of regioselectively synthesizing C-4 substituted dihydronicotinoyls is not trivial. Moreover the C-4 substituted dihydronicotinoyls are one step further removed from the natural system: This is particularly

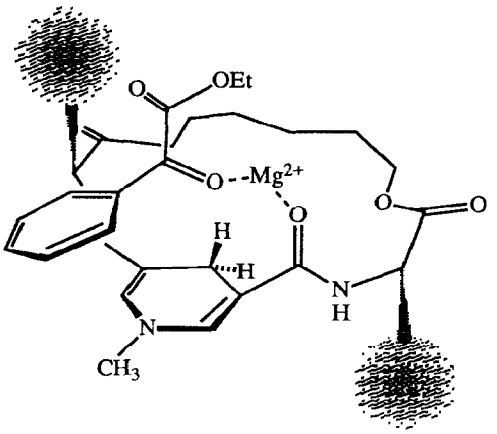
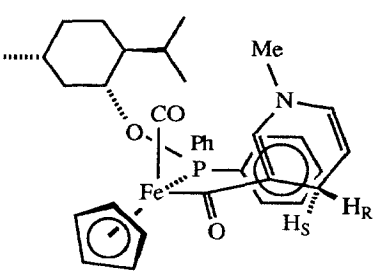


Figure 7:

The ternary structure proposed by Kellogg for the reduction of ethyl benzoylformate by **7**. The large spheres represent the isopropyl moiety.

important when considering the development of catalytic NADH mimic systems since the stereoselective, *in situ* regeneration of a C-4 substituted dihydronicotinoyl derivative would be very difficult to achieve.[34] When a dehydrogenase catalyses the reduction of a substrate with NADH one face of the dihydronicotinoyl ring of the coenzyme appears to be blocked by a wall enzyme protein and as a consequence the direction of substrate attack in these biological systems depends upon a remote feature of the enzyme.[22,35] Davies[36] therefore anticipated that the incorporation of an appropriate bulky chiral substituent on a dihydronicotinoyl ring could prevent access of the substrate to one of the C-4 diastereotopic hydrogens. In an early model **8** reported by Davies[37] the sterically demanding chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_2(O-(*l*)-menthyl))] was incorporated at the C-3 carbonyl of the dihydronicotinoyl moiety and utilised in the asymmetric reduction of ethyl benzoylformate.



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Although the enantiomeric excess obtained in the reduction of ethyl benzoylformate was moderate (52%), this did serve to demonstrate that a sterically demanding chiral auxiliary could be incorporated into a model as a face-blocking moiety. It was assumed that the large phosphine rotor forced substrate attack toward the *pro*-(R) hydrogen at C-4 and that the moderate enantiomeric excess arose from a poorly controlled

orientation of the ketone. A suitable conformation was proposed in which it was anticipated that chelation of the magnesium ion to the C-3 carbonyl oxygen of the dihydronicotinoyl derivative **8** and the ketonic and ester carbonyl oxygens of ethyl benzoylformate would present the *si*-face of the ketone to the C-4 *pro*-(R) hydrogen of **8** thus producing the (R)-mandelate as the major enantiomer (Figure 8). The alternative approach, which would deliver the *re*-face of ethyl benzoylformate to the *pro*-R hydrogen of the dihydronicotinoyl, was shown by molecular modelling studies to introduce steric interactions between the bulky iron auxiliary and the phenyl ring of the substrate. This preference for *si*-face attack did not however achieve a high enantiomeric excess of the mandelate and it was concluded that the low level of stereoselectivity was due to inefficient chelation of the substrate as a result of the steric bulk of the chiral auxiliary.

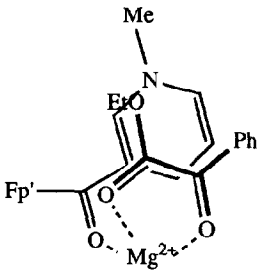
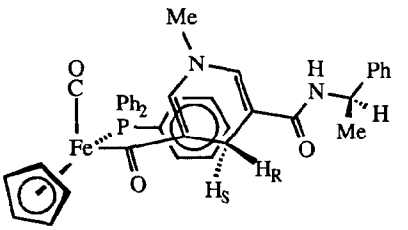


Figure 8:

The ternary structure proposed by Davies for the delivery of the *si*-face of ethyl benzoylformate to the *pro*-(R) hydrogen of **8** in the presence of magnesium ions. Fp' = [(η^5-C_5H_5)Fe(CO)(PPh_2(O-(*l*)-menthyl))].

Having demonstrated that a sterically demanding chiral auxiliary at C-3 gives rise to a stereoselective reaction, Davies[38,39,40] prepared a series of analogous homochiral dihydronicotinoyl complexes possessing a chiral carboxamide at C-5, with the intention of controlling substrate orientation and thus complement the steric control exerted by the chiral auxiliary at C-3. An initial model **9** possessing the sterically demanding chiral auxiliary (R)-[(η^5-C_5H_5)Fe(CO)(PPh_3)] at C-3 and a N-α-(R)-methylbenzylcarbamoyl moiety at C-5, reduced ethyl benzoylformate to (R)-ethyl mandelate in 89% enantiomeric excess.[38]



9

It was assumed that the carboxamide side chain, through chelation to the Mg^{2+}, assists the stereocontrol exerted by the iron auxiliary. ^{13}C Nmr experiments indicated that magnesium ion chelates to the carbonyl oxygen of the C-5 carboxamido substituent rather than that of the auxiliary at C-3. Although in this instance the Mg^{2+} is chelated to the oxygen of the carboxamide at C-5, as illustrated in Figure 9, the orientation of the substrate is assumed to be the same as that shown in Figure 8. It should be noted that analogous with the ternary structures proposed by Kellogg,[31] the ternary structures of Davies also show the ketonic carbonyl of the substrate directed away from the ring nitrogen. The rationale for this orientation was based on aligning the transferring C-4 hydrogen of the dihydronicotinoyl ring along the best Burgi-Dunitz-Lehn[41] approach line toward the ketonic carbonyl of the substrate.

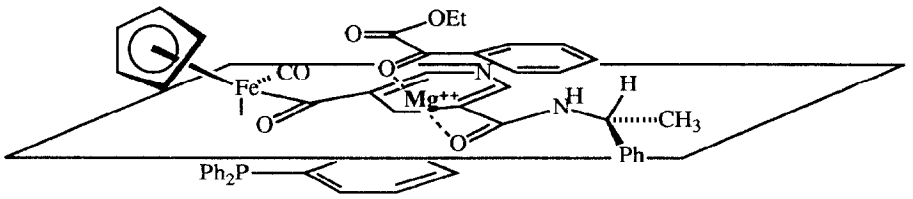
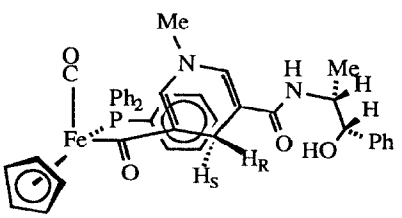


Figure 9:

Ternary structure proposed by Davies[40] for the interaction between **9** and ethyl benzoylformate.

Davies[39,40] found that by incorporating a chiral hydroxycarboxamide moiety at C-5 a further improvement in the enantiomeric excess was observed. Two model complexes, **10** and **11**, which were found to be most efficient were those which incoroporated a carboxamide side chain derived from norephedrine and valinol respectively.



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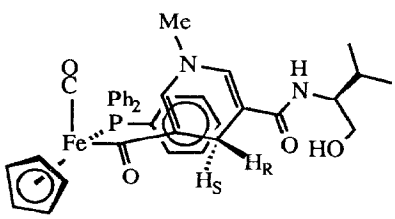


11

In both cases, when the configuration of the carboxamide side chain was matched with the appropriate configuration at the iron centre, the enantiomeric excess for the reduction of ethyl benzoylformate was greater than 97%. The high stereoselectivity in these reactions was attributed to a tightly bound transition state resulting from the additional chelation provided by the alcohol function. As illustrated in Figure 10 both the carbonyl and hydroxy functions of the carboxamide of **11** chelate to Mg^{2+} such that the substrate is held in a fixed orientation. For the diastereoisomer of **11** where the configuration of the carboxamide side chain was mismatched with that of the iron centre the enantiomeric excess of the product mandelate was only 16%.

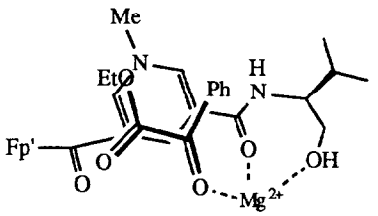


Figure 10:
Delivery of the *si*-face of ethyl benzoylformate to the *pro*-(R) hydrogen of **11** by chelation to magnesium ion (Fp'=[(η^5-C_5H_5)Fe(CO)(PPh_3)]).

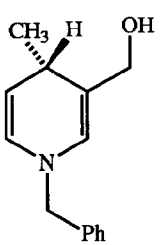
These compounds provide an excellent example of how high stereoselectivities can be achieved by providing a means of independently introducing both direction and orientation control within a NADH mimic. In these examples direction control is achieved by the incorporation of a sterically demanding chiral auxiliary at C-3 while orientation control is achieved by incorporating a hydroxy carboxamide at C-5.

B. NON-DIHYDRONICOTINOYL DERIVATIVES AS NADH MIMICS

While the predominant emphasis in the study of NADH mimics has been to investigate the reductions of those dihydropyridine derivatives with a carbonyl function at C-3 the incorporation of alternative polar substituents at this position has recently been studied.

a. Achiral hydroxymethyl function at C-3

The first example of a highly stereoselective NADH mimic possessing a non-carbonyl moiety at C-3 was reported by Meyers[42] in 1986. The approach taken by Meyers was similar to that of Ohno[24] in that the reductions of C-4 methyl substituted dihydropyridines were studied although in this case achiral rather than chiral substituents were incorporated at C-3. For example, in what Meyers describes as a "self-immolative process", the reduction of methyl benzoylformate by N-benzyl-3-(hydroxymethyl)-4(S)-methyl-1,4-dihydropyridine **12** afforded the (S)-mandelate in an optical yield of 94%. It should be noted that the optical yield was calculated by accounting for the lack of enantiomeric purity in **12**; in fact as **12** was only available 88% enantiomerically pure the actual observed enantiomeric excess was 83%.



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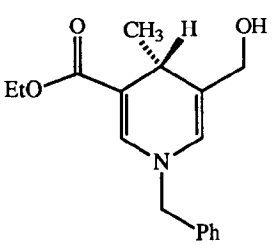

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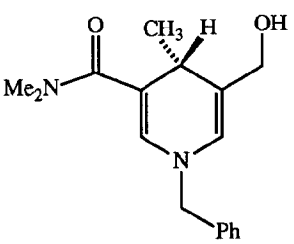

14

The stereoselectivity of the reduction was rationalized by assuming the formation of a rigid magnesium ion-containing ternary complex (Figure 11). As in the example of Ohno,[12] but contrary to those of Kellogg[31] and Davies,[40] the ketonic carbonyl of the substrate was assumed to lie over the dihydropyridine ring with the oxygen facing the ring nitrogen. The orientation of the substrate is controlled by interactions between the hydroxyl group at C-3 and the carbomethoxy group of the substrate as a result of non-bonding electron pair donation or hydrogen bonding or both, as shown in Figure 11. The importance of hydrogen bonding was illustrated by the deleterious effect on the stereoselectivity (94 *vs* 62% optical yield) as a result of converting the hydroxy function to a methyl ether.

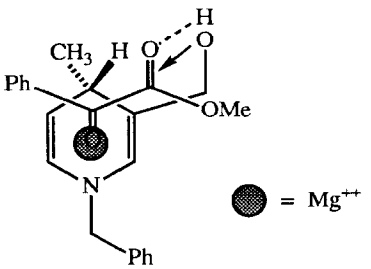

Figure 11:

The ternary structure proposed by Meyers[42] showing *re*-face attack of methyl benzoylformate by **12**.

An interesting observation made by Meyers was that, although incorporation of a carboethoxy group at C-5, as in **13**, did not appreciably lower the optical yield of the (S)-mandelate (91%), when a carboxamide was substituted at C-5, as in **14**, a reversal in the absolute configuration of the mandelate was observed. Thus when compound **14** was utilised in the asymmetric reduction of methyl benzoylformate the (R)-mandelate was obtained in 62% enantiomeric excess. In the reaction of the carboethoxy derivative **13** the stereochemical outcome can be rationalised as in Figure 11. On the other hand, for the carboxamide derivative **14**, the assumed conformation of the ternary complex is such that the orientation of the substrate is reversed as a result of the amido substituent successfully competing with the hydroxy function for the ester carbonyl (Figure 12).

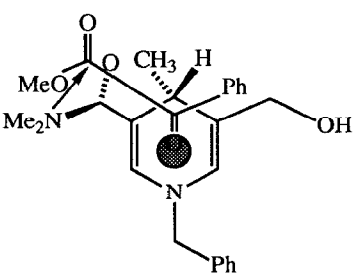

Figure 12:

The ternary structure proposed by Meyers[42] showing *si*-face attack on methyl benzoylformate by **14**.

It was proposed that this preferential orientation of the ester portion of the substrate with the carboxamide substituent of **14** is due to the greater electron donating properties of the dimethylcarboxamide moiety toward the ester carbonyl of the substrate. As a result the dimethylcarbamoyl group is rotating out of the dihydropyridine plane with the carbonyl lying *anti* to the migrating hydrogen. This proposition has recently been disputed by Buck[27] and Vekemans[26] on the grounds that it conflicts with their calculations predicting the preferential *syn*-orientation of the migrating hydride and the carboxamide carbonyl dipole in the transition state. It should be noted that the conformation of the ternary complex shown in Figures 11 and 12 varies from other previous proposals in that the interaction between the substrate and the carboxamide oxygen does not directly involve chelation to Mg^{2+}. In this instance the magnesium ion is sandwiched between the π-system of the dihydropyridine ring and the ketonic carbonyl to be reduced.

With a view to further enhancing the stereoselectivity of this process by restricting the possible orientations of the substrate Meyers[43] studied the reduction of a carbonyl function covalently bound to the dihydropyridine. When compound **15** was treated with Mg^{2+} the reduction was complete after 4 days, similar to the rate of reduction reported in the intermolecular process. However when compound **15** (90% ee) was formed from the magnesium alkoxide of **12** upon treatment with benzoylformyl chloride, the reaction was complete within minutes. After workup the (R)-mandelate was obtained in an enantiomeric excess of 90%. Meyers concluded that the extent of stereotransfer was >99% based on the enantiomeric purity of **15**. The extraordinary enhancement observed in the rate of reduction was rationalised by assuming that the magnesium salt, by virtue of the esterification reaction, is closely associated in the solvent shell forming the ternary complex. Four ternary structures were proposed with the most favoured of these being illustrated in Figure 13. In this complex it was assumed that both electron-rich carbonyl groups and the lone pair on nitrogen coordinate with the hexa-coordinate magnesium ion. This represents the first example of an intramolecular version of a non-enzymic hydride transfer to a covalently bound carbonyl group.

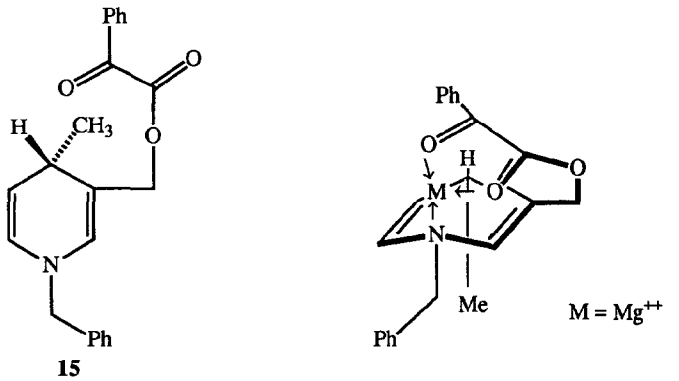

Figure 13:
Proposed ternary structure for the intramolecular reduction of **15**.

Thus, in contrast to the requirements for high stereoselectivity developed by Ohno,[24] Meyers[42,43] has illustrated that the presence of a chiral carboxamide at C-3 is not essential to ensure high stereoselectivity in the reduction of a prochiral ketone.

b. Sulphinyl function at C-3

Recently Iwata[44] prepared a compound in which the chirality on the C-3 side chain was only two bonds removed from the reaction centre. This was accomplished by incorporating a chiral sulphinyl moiety at C-3 as in **16**. In the asymmetric reduction of methyl benzoylformate by **16** the (R)-mandelate was obtained in 96% enantiomeric excess. The high stereoselectivity was attributed to the close proximity of the sulphinyl moiety to the reaction centre, however, a rationale explaining the observed stereochemistry of the reduction was not provided.

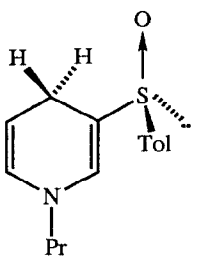

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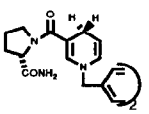
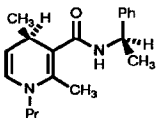
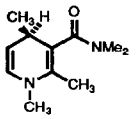
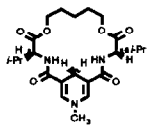
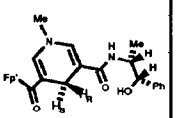
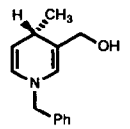
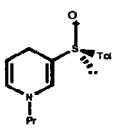
Table 1 summarises the results of the asymmetric reduction of methyl or ethyl benzoylformate by some of the NADH mimics discussed above. The absolute configuration and enantiomeric purity of the mimics is provided so that one can relate the sense of chirality transfer to that of the product mandelates. In addition the enantiomeric excess of the mandelates and reaction time is provided. It should be noted that the stereoselectivities are all high ranging from 90% (Kellogg)[31] to 98% (Inouye,[20] Davies[40] and Ohno[24]).

3. SCOPE AND LIMITATIONS OF NADH MIMICS

One feature which is common to all of the examples discussed so far is that the substrate, an alkyl benzoylformate, possesses an activated electrophilic carbonyl which makes it amenable to reduction by mild reducing agents. None of the structurally related 1,4-dihydropyridines discussed above, apart from that developed by Vekemans,[26] are kinetically potent reducing agents. As such one of the limitations in utilising such compounds for asymmetric reductions is that of choosing substrates which are activated by some electron withdrawing function.

TABLE 1: Asymmetric Reduction of Methyl or Ethyl Benzoylformate by NADH Mimics.

Reagent	Principal Author	%ee of Reagent (configuration)	% ee of Mandelate (configuration)	Time
	Inouye	100 (SS)	98 (R)	1 hour
	Ohno	100 (RR)	98 (R)	2 days
	Vekemans	96 (R)	95 (R)	1 hour (-25°C)
	Kellogg	100 (SS)	90 (S)	4 days
	Davies	100 (RRS)	98 (R)	90 minutes
	Meyers	88 (S)	94 (S)	5 days
	Iwata	100 (S)	96 (R)	7 days

Some of the other activated substrates which have been stereoselectively reduced include 2-acetylpyridine and ketopentolactone. Table 2 and Table 3 summarise the results of the asymmetric reduction of these substrates by some of the NADH mimics discussed above. The enantiomeric excesses in these tables have been rounded to unit accuracy in order to reflect the accuracy of these measurements. In the reduction of 2-acetylpyridine (Table 2) the stereoselectivity ranges from 62% (Ohno)[45] to 99% (Meyers).[46] However the reported 'optical yield' of Meyers accounts for the lack of enantiomeric purity in the reducing agent so that the highest actual observed enantiomeric excess obtained is that of Davies[40] (98%). In the reduction of ketopentolactone (Table 3) the stereoselectivities are more widely spread ranging from 38% (Inouye)[20a] to 91% (Davies).[47] It would appear that with regard to the substrates discussed above the mimic compounds which impart the highest stereoselectivites are those of Meyers and Davies.

Recently Meyers[46] and Ohno[48] have demonstrated that β,γ-unsaturated-α–ketoesters can be reduced regio- and stereo-selectivity to afford the corresponding β,γ-unsaturated-α–hydroxyesters. Meyers[46] has also shown that other prochiral substrates such as imines can be reduced in excellent stereoselectivity to afford the corresponding amines.

While the reduction of activated ketones can be achieved by both mimetic and enzymic systems the latter has the advantage of being catalytic. An important limitation in terms of the applicability of the current mimic systems to organic synthesis is that the reductions must be conducted stoicheiometrically. Attempts to generate an efficient, stereoselective catalytic system using these mimics have to date been unsuccessful.[31,40,49,50] In addressing this problem part of the solution lies in finding a suitable reductant such that the pyridinium salt can be selectively reduced in the presence of the substrate.[51]

Although these reductions must be carried out stoicheiometrically and the models cannot as yet be regenerated *in situ* from their corresponding pyridinium salts, the salts can in some cases be isolated from the reaction mixture and reduced to regenerate the original dihydropyridine. For example, the pyridinium salts obtained from the oxidation of **10** and **11** were recovered from the reaction and reduced to achieve an overall 70-80% recovery of the homochiral dihydronicotinoyl complexes.[40] In a similar way the homochiral bis(NAH) derivative **4**[20a] was recovered from the reduction mixture in up to 60% yield. In the above examples no loss of stereochemical integrity was observed in the regeneration procedure and when these recovered mimics were re-utilized in the reduction of ethyl benzoylformate the same level of asymmetric induction was observed as when fresh. These regenerative properties could not however be extended to those models with C-4 substituents, e.g. **12** (Meyers),[42] **5** (Ohno),[24] and **6** (Vekemans),[26] where reduction of the resulting pyridinium salt would result in either racemic mixtures (**6** and **12**) or a diastereomeric mixture (**5**).

An alternative approach to producing stereoselective reducing agents useful in organic reactions, is to develop methods whereby the enzymes can be used in organic solvents. However, with few exceptions enzymes are active only under strict conditions and although reactions with enzymes in organic solvents are being studied[52] the progress is limited due to the requirements of the enzymes being particularly troublesome in organic systems. Mimetic systems may not be catalytic as yet however they do have an advantage over enzyme mediated reductions in their applicability to a variety of organic reaction conditions.

TABLE 2: Asymmetric Reduction of 2-Acetylpyridine by NADH Mimics.

Principal Author	Configuration of Reagent[a]	% ee of mandelate (configuration)	Yield (%)	Time
Ohno	RR	62 (R)	100	2.5 days
Inouye	SS	90 (R)	67	16 hours
Davies	RRS	98 (R)	63	4 days
Meyers	S (88% ee)	99[b] (S)	72	7 days

a "Reagent" refers to that mimic compound represented in Table 1 which corresponds to the appropriate principal author.
b Enantiomeric excess accounting for the lack of enantiomeric purity of the reagent (optical yield).

TABLE 3: Asymmetric Reduction of Ketopentolactone by NADH Mimics.

Principal Author	Configuration of Reagent[a]	% ee of mandelate (configuration)	Yield (%)	Time
Inouye	SS	38 (R)	100	67 hours
Kellogg	SS	41 (S)	90	several days
Ohno	RR	51 (R)	100	5 days
Meyers	S (88% ee)	82[b] (S)	40	6 days
Davies	RRS	91 (R)	73	4 days

a "Reagent" refers to that mimic compound represented in Table 1 which corresponds to the appropriate principal author.
b Enantiomeric excess accounting for the lack of enantiomeric purity of the reagent (optical yield).

4. ROLE OF THE METAL ION

All the above reductions by NADH model compounds require the presence of a divalent metal ion in order to enhance the rate and stereoselectivity of reaction. In most instances this ion is divalent magnesium which is added to the reaction mixture in the form of magnesium perchlorate. While there is no dispute as to the necessity of these ions in order to achieve a highly stereoselective reaction there exists a difference of opinion concerning the positioning of the magnesium ion in the transition state of the reduction.

Ohno,[12,25] Vekemans,[26] Kellogg[31] and Davies[40] propose that the magnesium ion chelates with the carbonyl of the carboxamide substituent on the dihydronicotinoyl ring as well as to the ketonic carbonyl of the substrate (Figures 2, 6, 7 and 9). Ohno also proposes additional chelation of Mg^{2+} to the dihydronicotinoyl ring π-system (Figure 2). In those examples of Davies where the carboxamide substituent contains a hydroxy function additional chelation to the metal ion is proposed (Figure 10). In a similar vein Inouye[19] postulates that in the reduction of ethyl benzoylformate by **3** the magnesium ion chelates with both the carboxamide carbonyl oxygens of the prolinamide substituent, however chelation to the substrate was not represented (Figure 3). In these examples of Davies and Inouye the proposed positioning of the magnesium ion between the oxygen atoms of the carboxamide side chain is consistent with the optimal magnesum ion locations determined by pair-potential calculations.[53] In the reduction using the bis(NAH) derivative **4**, Inouye[20a] proposes chelation to only the primary carboxamide substituents of the model compound and not to the carbonyl directly attached at C-3 (Figure 4). In contrast to the aforementioned examples Meyers[42] proposes that the magnesium ion is locked between the π-system of the dihydropyridine ring and the substrate and does not chelate with any polar substituents on the ring (Figure 11).

It would appear that in most of these reductions it is generally agreed that the magnesium ion chelates with polar substituents attached to the dihydropyridine ring. Evidence for this type of interaction has been discussed by Ohno,[10b,12a] Kellogg,[31] Davies[40] and others.[54,55,56]. In particular the ^{13}C nmr spectra of these model compounds show a shift in the carboxamide carbonyl peak when magnesium ions were added.

Extensive investigations have also been made into the effect of magnesium ion concentration on both the rate and the stereoselectivity of reduction. The results of these investigations have been discussed in depth previously[10a-b,12,57,58] and as such will only be summarised here. In general for ethyl or methyl benzoylformates, where magnesium ion does not chelate with the substrate except to form the ternary structure,[12a] the maximum stereoselectivites are observed with 0.5-1.0 equivalents of magnesium ion to the dihydronicotinoyl derivative. Below 0.5 equivalents of magnesium the enantiomeric excess is reduced and above 1.0 equivalent the enantiomeric excess either remains constant or is reduced gradually in proportion to the excess of magnesium ion. Variations in this general trend can occur, however, depending on a variety of factors, e.g. the type of dihydronicotinoyl complex used,[42] the concentration of alkyl benzoylformate present in the reaction mixture,[18] the reduction temperature[26] and any contribution made to the transition state by the pyridinium salt formed in the reaction.[16d,18b]

Reductions have also been carried out using metal ions other than magnesium ions. One common choice is Zn^{2+}, a component of many dehydrogenases.[59] In a limited number of instances the replacement of magnesium by zinc ions has equalled or improved the stereoselectivity,[44,60] however in general zinc ions do not achieve the enantiomeric excesses observed with magnesium ions.

A small number of reductions using chiral shift reagents, e.g. lanthanide β-diketonates, have also been investigated. Gelbard[61] observed stereoselective reduction when hydrogen transfer between an achiral substituent and an achiral dihydronicotinoyl derivative was carried out in the presence of one of these chiral shift reagents.

5. REQUIREMENTS FOR HIGH STEREOSELECTIVITY

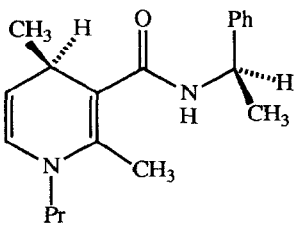
In biological systems the high selectivity and reactivity observed in reductions carried out by the coenzyme NADH is determined by the environment constructed by the enzyme. The direction of substrate approach to one face of the dihydronicotinoyl ring of NADH is controlled in the enzymic system by the combined effect of shielding the unreactive face (negative differentiation) and directing the reactive face toward the substrate (positive differentiation). The orientation of the substrate with respect to the transferring hydrogen is controlled in the enzyme by certain functional groups held in the viscinity of the substrate binding site.

In mimetic systems the direction and orientation of substrate reduction can be controlled by creating a suitable environment about the dihydronicotinoyl ring. It should be noted here that it is not sufficient to just construct, about the dihydronicotinoyl ring, a reaction field which has a number of chiral centres close to the reaction site. For example, dihydronicotinoyl derivatives with covalently bound cyclodextrins,[62] polystyrene beads,[63] bovine serum albumin[64] and a variety of exotic peptide chains[65] have not been successful in stereoselectively reducing ethyl benzoylformate. It is clear that it is vital to design a well-ordered environment about the 1,4-dihydronicotinoyl moiety in order to achieve high asymmetric reductions. Those key features of mimetic systems which facilitate highly stereoselective reductions will be discussed in this section. While each feature will be introduced separately it is ultimately the combined effect of these factors which determine the prefered geometry of the reaction.

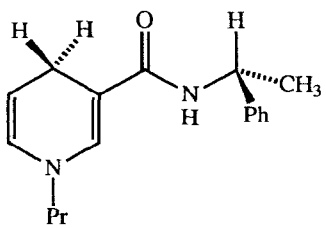
As illustrated by both Davies[40] and Ohno[24] the reactivity of the *pro*-(S) and *pro*-(R) hydrogens can be controlled by designing a model where one face of the dihydronicotinoyl ring is rendered unreactive. High stereoselectivities were achieved by Davies using a remote sterically-demanding side chain and by Ohno by incorporating a methyl substituent at the reaction centre. This later feature was also used by Vekemans[26] and Meyers.[42] It should be noted that the high enantiomeric excesses observed by Davies were only achieved when the sterically-demanding iron chiral auxiliary was matched with an appropriate chiral carboxamide.

The direction of substrate approach can also be controlled by directing the substrate toward the reactive face of the dihydronicotinamide ring. Theoretical calculations as well as some experimental evidence suggest that when NADH forms a reactive complex with an enzyme the carboxamide group loses the freedom to rotate and becomes fixed in an out-of-plane orientation with respect to the dihydropyridine ring.[3,66,67] As a consequence the oxygen of the carboxamide side chain points roughly parallel to the direction of one C-4 hydrogen and it is this hydrogen that is transferred to the substrate. That the carboxamide carbonyl is *syn* orientated with respect to the transferring hydrogen was supported by some recent X-ray data obtained for stable enzymic complexes, e.g. the ternary complex NAD^+-DMSO-LADH (horse liver alcohol dehydrogenase, A-specific)[28] and the binary complex consisting of NAD^+ and GAPDH (glyceraldehyde-3-phosphate dehydrogenase, B-specific).[29]

It would appear that the fixing of the orientation of the carbonyl of the carboxamide substituent at C-3 in the model compound could result in controlling the direction of reaction in a manner similar to the enzyme. Consistent with this rationale, both the stereoselectivity and the rate of reaction of the dimethyl-substituted dihydronicotinamide **17** are increased compared with the non-methylated equivalent **1**.[10b] Both X-ray analysis and ^1H nmr spectroscopy of the dimethyl-substituted derivative **17** support the out-of-plane orientation of the carbonyl group with the hydrogen at the 4-position being *syn*-oriented toward the carbonyl oxygen.[68] While the electron-donating ability of these methyl substituents must be considered,[69] it could also reasonably be assumed that the presence of the C-4 methyl and C-2 methyl substituents restrict rotation about the C-3 carbonyl bond thereby fixing the orientation of the carboxamide carbonyl and facilitating reaction with the substrate.[70]

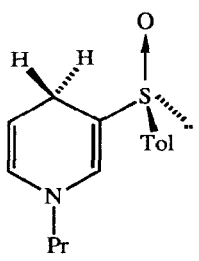


17

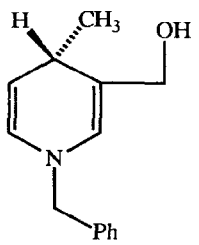


1

Although the presence of a C-3-substituted carbonyl provides a method of guiding the substituent to one face of the dihydropyridine ring it is not an essential requirement for achieving high stereoselectivities. Both



16



12

Iwata[44] and Meyers[42] achieved enantiomeric excesses of 96% and 94% using the non-dihydronicotinoyl derivatives **16** and **12** respectively. These model compounds, while lacking a C-3 carbonyl, still contained polar functions at C-3. The basic requirement for high stereoselectivity in model compounds appears, therefore, to be the presence of a polar function at C-3 and the ability of this polar function to become *syn* orientated with the leaving hydrogen at C-4.

Most model systems require the presence of a suitable bivalent metal ion to achieve highly stereoselective reductions.[10] Chelation between the metal ion and polar functions of both the substrate and those substituted on the dihydropyridine ring results in the formation of a ternary complex such that one of the enantiotopic faces of the substrate preferentially approaches one face of the dihydropyridine ring. As a result of this chelation with magnesium ion it is generally accepted that the more polar portion of the substrate lies *syn* to the polar substituent of the dihydropyridine compound (see section on the Role of the Metal Ion). However the orientation of the substrate may also be influenced by the steric bulk of adjacent groups, e.g. for **9**, where there are two polar substituents attached to the dihydropyridine ring, Davies proposes that the bulky nature of the C-3 iron auxiliary forces chelation between the C-5 carbonyl and the magnesium ion.[40]

Furthermore it should be noted that the approach path of the substrate to the C-4 hydrogen is constrained by stereoelectronic requirements. Although there is no dispute that stereoelectronic requirements must be realized in the formation of a ternary complex between the substrate and the dihydronicotinoyl derivative, the contribution of individual requirements is debated. Both Meyers[42] and Ohno[12] propose that in the ternary structure the ketonic carbonyl of the substrate lies over the dihydronicotinoyl ring with the oxygen of the carbonyl lying towards the ring nitrogen, [Figure 14, (a)]. Their rationale was based on pioneering investigations carried out by Prelog[14] whereby orbital overlap is maximised and nonbonded interactions minimized when this geometry is adopted. In contrast Kellogg[31] and Davies[40] model the ternary structure such that the hydride will approach the prochiral carbonyl of the substrate on the best Burgi-Dunitz-Lehn approach line, i.e. the approach path of the nucleophile lies in a plane bisecting the RCR' angle and is virtually along a straight line inclined at an angle of about 107° to the carbonyl bond [Figure 14, (b)].[41,71] Of those enzyme mediated systems studied, the geometrical arrangement of this carbonyl appears to be close to the *anti*-parallel arrangement illustrated in Figure 14, (b).

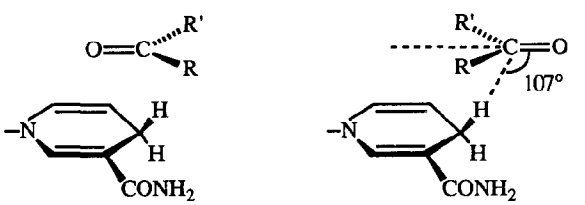
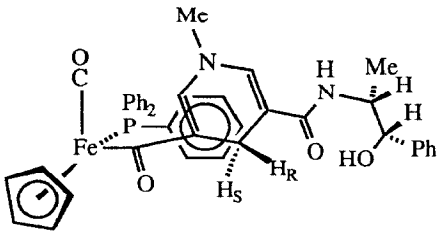


Figure 14:

(a) parallel and (b) *anti*-parallel orientations of the substrate with respect to the dihydronicotinoyl ring.

In summary the features necessary for a reactive NADH model include the incorporation of a polar substituent at C-3 of a dihydropyridine derivative and the presence of a bivalent metal ion in the reaction system to introduce the substrate with a specific orientation while also realizing the stereoelectronic requirements. Furthermore the two faces of the model must be successfully differentiated by (a) the incorporation of a remote or localized chiral substitutent to block one face and/or (b) the specific orientation of the polar function at C-3 to guide the substrate to the reactive face of the dihydropyridine ring. The synergistic nature of all these features, as requirements for high stereoselectivity, is illustrated in the studies carried out by Davies.[40] Highly stereoselective reductions were achieved only when a remote sterically-demanding substituent and a chiral carboxamide were incorporated into the model compound **10**, and the reduction was carried out in the presence of magnesium ions. In the absence of any one of these features the enantiomeric excess was drastically reduced.



10

A general working model which indicates the expected preferred stereochemistry of reduction of an activated prochiral substrate by a NADH mimic is illustrated in Figure 15. The polar portion of the substrate lies over the polar portion of the model compound, presumably as a result of chelation with magnesium. The exact positioning of the magnesium ion is still under discussion and as such has not been illustrated. Face selectivity may be provided by either a face-blocking substituent (negative differentiation) or the guiding of the substrate to the reactive face of the dihyropyridine ring (positive differentiation) or both. Although the proposed orientation of the activated carbonyl varies according to author, in this illustration the substrate carbonyl has been represented as lying in a Burgi-Dunitz-Lehn approach line[41] with the transferring hydrogen.

6. CONCLUSION

It is apparent that a large number of NADH mimics have been developed during the last fifteen years with enantiomeric excess ranging from 0 to >99%. In this review we have sought to briefly discuss the development of these model compounds and in particular those which result in highly stereoselective reductions. Furthermore we hope to have outlined those features of model systems required to achieve these highly stereoselective reductions; it is clear that future attempts to simulate enzymic systems should consider these features.

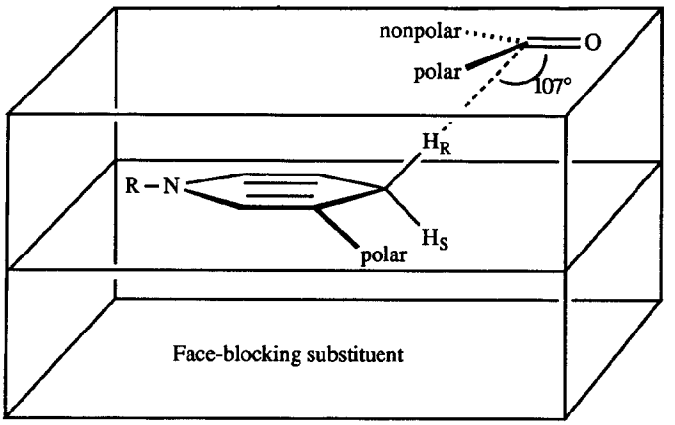


Figure 15:
Ternary structure for the reduction of an activated ketone by an NADH mimic.

Continuing attempts to develop highly stereoselective and catalytic NADH mimics remains a significant and worthwhile goal. In particular, for these model compounds to find general use the reductions must be rendered catalytic. While many model systems are comparable to enzyme mediated systems in that the reductions are essentially completely stereoselective, the multifunctional nature of the enzyme cannot be reproduced completely. Attempts to make stereoselective reductions by model compounds catalytic, by recycling the pyridinium salt back to the dihydropyridine derivative, have to date been unsuccessful. Future attempts to mimic reductions carried out by enzymes should be towards the formation of a single universal system that can achieve high stereoselectivity in the reduction of a variety of substrates under catalytic conditions.

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