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Chiral organometallic NADH mimics: Preparation of homochiral (R)-(-)-[(η^5-C_5H_5)Fe(CO)(PPh$_2$(O-(*l*)-menthyl^1))]-1-methyl-1,4-dihydronicotinoyl and asymmetric reduction of ethyl benzoylformate.

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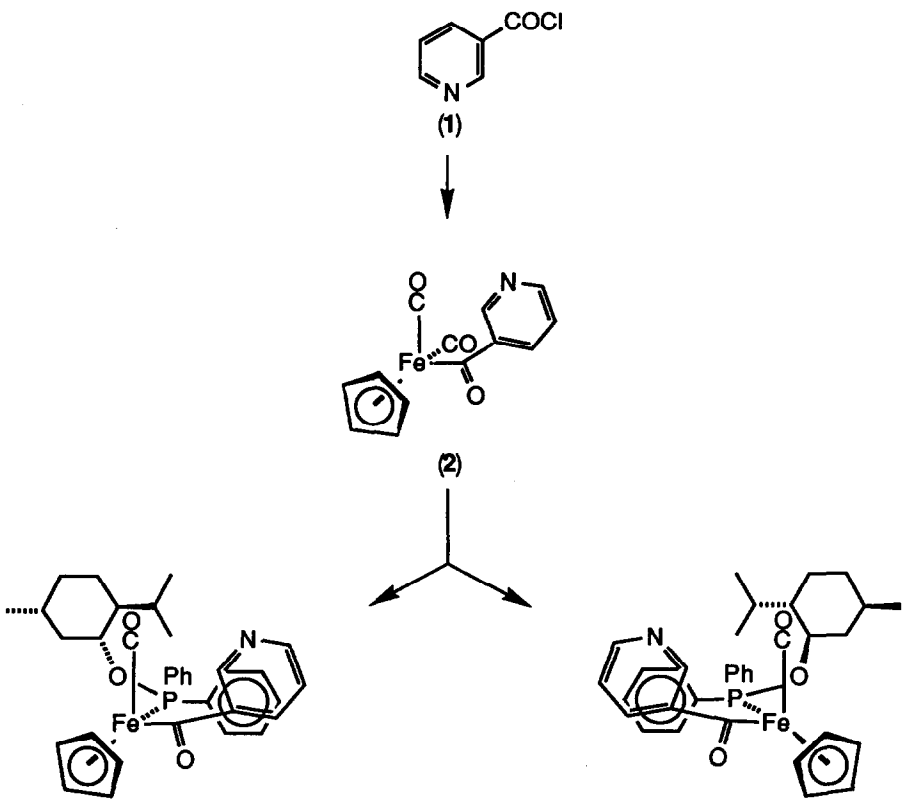
Summary: The homochiral complex (R)-(-)-[(η^5-C_5H_5)Fe(CO)(PPh$_2$(O-(*l*)-menthyl))]-1-methyl-1,4-dihydronicotinoyl reduces ethyl benzoylformate to ethyl mandelate in 52% enantiomeric excess.

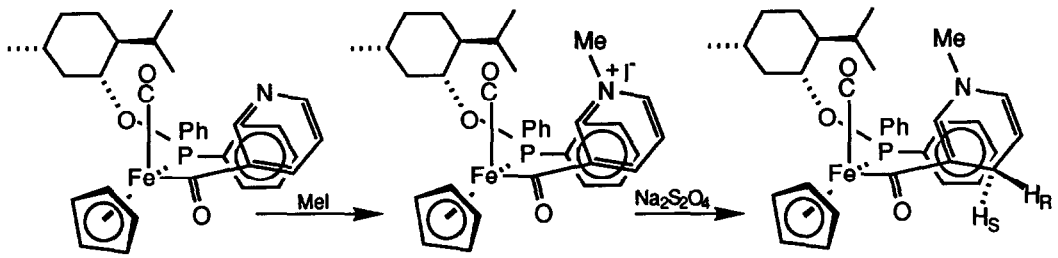
During the past decade considerable interest has been expended on creating model compounds mimicking the activity of the NAD$^+$-NADH redox couple.[2,3] In contrast to the natural system it is essential in the model systems that a metal ion (Mg^{2+}) is employed in order to facilitate reaction and stereocontrol during the hydride transfer step to, for example, moderately reactive prochiral ketones. Hence, all model 1,4-dihydropyridine compounds to date possess a polar functionality at C-3, which by chelation, delivers and orientates the substrate over the reaction site. In the majority of early models, the 1,4-dihydropyridines possessed a chiral N-substituted amide[2] at C-3 although recent models have imparted a high degree of chirality transfer by utilising a sulphinyl[4] or hydroxymethyl[5] moiety at this position. In order to achieve high stereocontrol during the hydride transfer step it is essential that only one of the prochiral hydrogens at C-4 is available for reaction and that the orientation of the substrate is well defined by chelation with Mg^{2+} and the 3-substituent of the 1,4-dihydropyridine.[2] In the models developed by Ohno[3] and others[5,6] it was possible to ensure that the mode of hydride transfer was stereospecific by incorporating a chiral centre at C-4, thus obviating the need for discrimination at C-4, as well as maintaining a polar functional group at C-3. It was our opinion that a similar stereospecificity could be achieved by incorporating a sterically demanding chiral auxiliary at C-3 thereby preventing the substrate from access to one of the diastereotopic hydrogens. Herein we describe the first synthesis and resolution of a homochiral organometallic 1,4-dihydronicotinoyl complex possessing the sterically demanding chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh$_2$(O-(*l*)-menthyl))] at C-3 and its utility in the asymmetric reduction of ethyl benzoylformate.

Cyclopentadienylirondicarbonyl anion[7] was treated with a solution of nicotinoyl chloride (1) in tetrahydrofuran at -78°C, and, upon warming to room temperature, afforded the achiral iron nicotinoyl complex (2) in 72% yield. Photolytic ligand exchange of carbon monoxide for *l*-menthyl diphenylphosphinate[8] in cyclohexane afforded a 1:1 mixture of diastereomeric complexes (3) and (4) which were readily distinguishable by ^{1}H nmr spectroscopy. Isolation of one of the diastereomers was achieved by slow crystallisation from a solution of dichloromethane/heptane (approx. 1:5). Usually a single crystallisation gave a diastereomeric ratio of (3) and (4) greater than 100:1 and in all cases homochiral (3) $[\alpha]_D^{25}$ +155 (c 0.07, C_6H_6) was obtained in 11-15% yield after a second crystallisation. The assignment of the absolute configuration at iron as *R* for complex (3) follows from a single crystal X-ray structure analysis.[9] The configuration at iron being assigned relative to the known absolute configuration within the *l*-menthol fragment.[8] The crystal structure reveals the pseudo-octahedral geometry around iron[10] with the nicotinoyl moiety adopting the expected[6] conformation with C-4 *syn* to the nicotinoyl carbonyl oxygen. One face of the nicotinoyl ligand is, as expected, shielded by the *l*-menthyl diphenylphosphinite ligand. Structure (3) in Scheme 1 illustrates these effects.



Scheme 1

Treatment of complex (3) with iodomethane afforded, in quantitative yield, the pyridinium salt (5), which was reduced with sodium dithionite under standard conditions[3] to give the homochiral 1,4-dihydronicotinoyl complex (6) $[\alpha]_D^{25}$ -170 (c 0.08, ethanol) in 73% yield (Scheme 2).

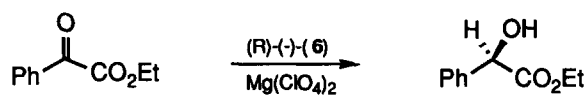


(R)-(3) (R)-(5) (R)-(6)

Scheme 2

The reduced complex (6) is assumed to adopt the conformation shown in Scheme 2 on the basis of an X-ray crystal structure analysis on the related racemic triphenylphosphine analogue (R,S)-[(η^5-C_5H_5)Fe(CO)(PPh_3)]-1-methyl-1,4-dihydronicotinoyl.[11] Consistent with this conformation, the diastereotopic C-4 hydrogens exhibit significantly different chemical shifts (δ 2.98 and 2.65) in the ^1H nmr spectrum ($CDCl_3$).

When a solution of ethyl benzoylformate (7) in anhydrous acetonitrile was reacted with a stoicheiometric amount of magnesium perchlorate and the homochiral complex (R)-(-)-(6) for seven days at 25°C (R)-(-)-ethyl mandelate (8) was isolated in 71% yield after radial chromatography. The enantiomeric excess was determined to be 52% based on the optical rotation of the ethyl mandelate $[\alpha]_D^{20}$ -53.8 (c 0.43, ethanol), lit[12] $[\alpha]_D^{25}$ -104.4 (ethanol). An enantiomeric excess of 54% was indicated by analysis of the ^{19}F nmr spectrum of the corresponding (R)-(+)-α–(trifluoromethyl)phenylacetates.[13]



(7) (R)-(-)-(8)

Although the enantiomeric excess obtained in the reduction of ethyl benzoylformate is moderate, it does serve to demonstrate that face blocking chiral auxiliaries can be used to induce stereoselectivity in this type of reaction. It is most probably the orientation of the ketone which is poorly controlled since one face of the 1,4-dihydronicotinoyl is essentially blocked by the phosphine rotor and thus only the *pro*-R hydrogen at C-4 is free to react (Scheme 2). In line with previous models[3,6] we anticipate that chelation of the magnesium to the C-3 carbonyl oxygen and the keto and ester carbonyl oxygen of ethyl benzoylformate will present the *si*-face of the ketone to the C-4 *pro*-R hydrogen thus producing the mandelate (R)-(-)-(8) as the major enantiomer (Figure). Delivery of the *re*-face has been shown by molecular modelling studies to be energetically disfavoured due to steric interactions between the benzoyl-phenyl and the chiral auxiliary. It appears that although the steric bulk of the iron auxiliary is shielding effectively one face of the 1,4-dihydronicotinoyl as predicted, it is also preventing

sufficient chelation of the substrate. Efforts are currently been directed towards modifying this NADH mimic to take account of this.

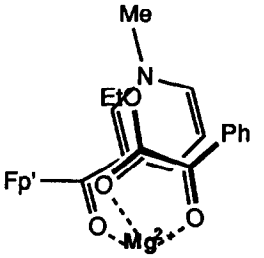


Figure: Delivery of the *si*-face of ethyl benzoylformate to the *pro*-R hydrogen of (R)-(-)-[(η^5-C_5H_5)Fe(CO)(PPh_2(O-(*l*)-menthyl))]-1-methyl-1,4-dihydronicotinoyl by chelation. Fp'=[(η^5-C_5H_5)Fe(CO)(PPh_2(O-(*l*)-menthyl))].

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References and notes

1. For clarity only the absolute configuration of the iron centre is given; (*l*)-menthol is (1R, 2S, 5R)-(-)-2-isopropyl-5-methylcyclohexan-1-ol. Menthyl is the radical formed by loss of the 1-hydroxy group: in (*l*)-menthyl the *l* indicates that solutions of these molecules rotate plane polarised light to the left.

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