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# Chiral organometallic NADH mimics: Stereoselective reduction of ethyl benzoylformate utilising the homochiral auxiliary [($\eta^5$-$C_5H_5$)Fe(CO)(PPh3)].

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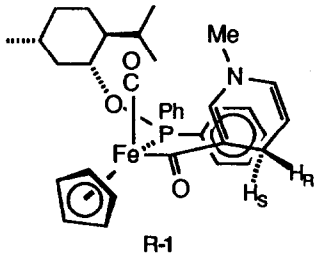
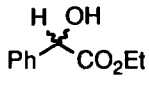
**Abstract**: The homochiral complex (RR)-(-)-[($\eta^5$-$C_5H_5$)Fe(CO)(PPh3)]-1-methyl-5-(N-α-methylbenzylcarbamoyl)-1,4-dihydronicotinoyl reduces ethyl benzoylformate to (R)-(-)-ethyl mandelate in 89% enantiomeric excess.

In designing NADH mimics the prerequisites for high stereocontrol during the hydride transfer step to a reactive ketone are that only one of the prochiral hydrogens at C-4 is available for reaction and that the orientation of the substrate is well defined. This can be achieved through chelation of the substrate with $Mg^{2+}$ coordinated to a suitable 3-substituent on the 1,4-dihydropyridine.[1,2,3] Recently we reported the preparation of the first organometallic NADH mimic **1**,[4] which possesses a sterically demanding chiral auxiliary at C-3 thereby preventing access of the substrate to one of the prochiral hydrogens. However, in the asymmetric reduction of ethyl benzoylformate the enantiomeric excess obtained for the corresponding mandelate **2** was moderate (52%). It was assumed that the steric bulk of the iron auxiliary was preventing efficient chelation of both the substrate and the iron acyl carbonyl at C-3 to the magnesium ion. Hence it was envisaged that incorporation of a polar functional group at C-5 of our model compound could well provide the strong chelation necessary for the orientation of the substrate, particularly in view of the numerous examples of such chelation control existing in the literature,[1,2,3] and thus complement the steric control exerted by the chiral auxiliary at C-3.

Herein we describe the synthesis of homochiral organometallic 1,4-dihydronicotinoyls bearing the chiral auxiliary [($\eta^5$-$C_5H_5$)Fe(CO)($PPh_3$)] at C-3 and a chiral N-substituted carboxamide at C-5 and their utility in the asymmetric reduction of ethyl benzoylformate.



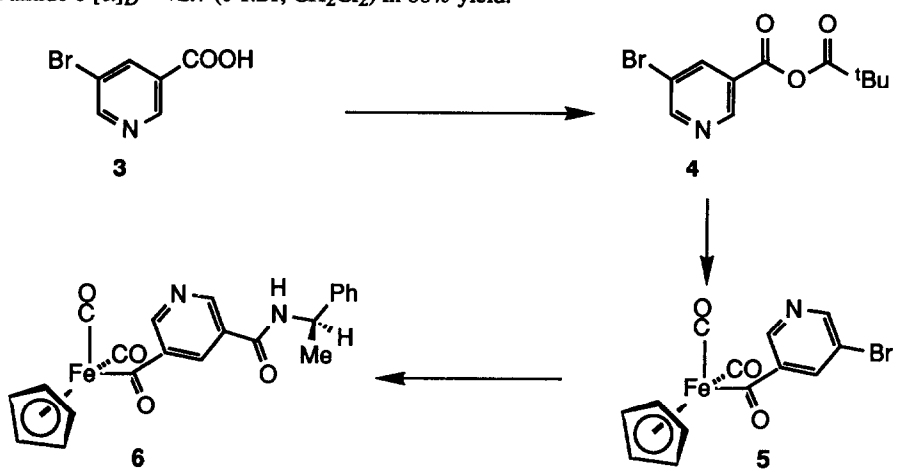

R-1



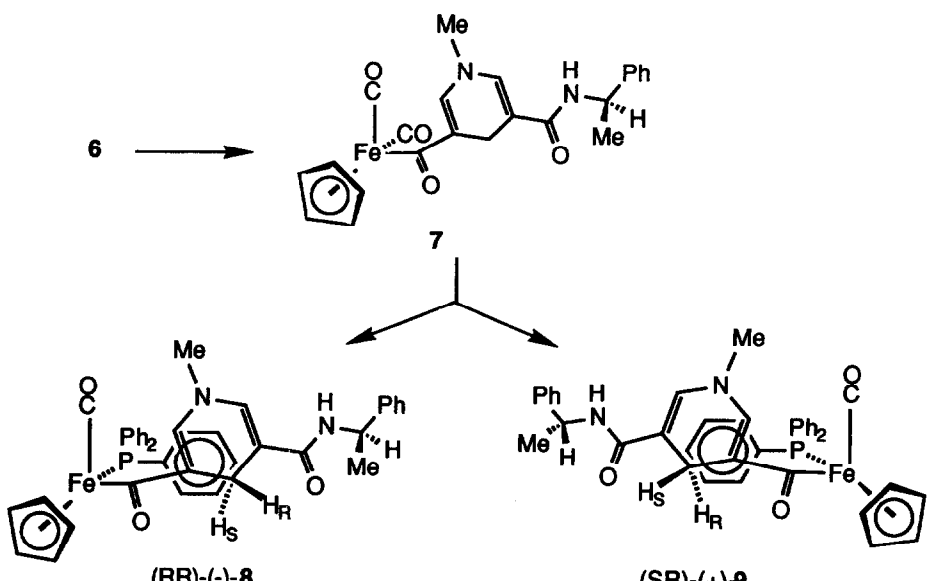

**2**

Treatment of nicotinic acid according to a literature procedure[5] afforded methyl 5-bromonicotinoate, which under base hydrolysis gave 5-bromonicotinic acid (**3**) in 80% overall yield. When a solution of the acid **3** in benzene and triethylamine was treated with pivaloyl chloride the corresponding anhydride **4** was obtained in 95% yield. Addition of a solution of **4** in tetrahydrofuran to cyclopentadienylirondicarbonyl anion[6] at -78°C, followed by warming to room temperature, afforded the iron nicotinoyl complex **5** in 89% yield. Procurement of complex **5** allowed us ready access to a variety of functionalised amides (and esters) by utilising the palladium(0)-catalysed carbonylation reaction.[7] Thus, treatment of a solution of **5** in tetrahydrofuran with palladium(II) chloride (0.04 equiv.), triphenylphosphine (0.08 equiv.) and R-(+)-α-methylbenzylamine[8] under

an atmosphere of carbon monoxide in a Fisher-Porter bottle for six hours at 100°C afforded the corresponding homochiral amide **6** $[\alpha]_D^{22}$ +2.7 (c 1.21, $CH_2Cl_2$) in 88% yield.




Treatment of compound **6** with iodomethane in dichloromethane afforded, in quantitative yield, the corresponding pyridinium salt which was reduced with sodium dithionite under standard conditions[2] to give the corresponding substituted 1,4-dihydronicotinoyl complex **7** $[\alpha]_D^{22}$ +2.1 (c 1.57, $CH_2Cl_2$) in 96% overall yield. Photolytic ligand exchange of carbon monoxide for triphenylphosphine in **7** as a solution in cyclohexane/tetrahydrofuran (1:3) afforded a 1:1 mixture of diastereoisomers **8** and **9** which were readily distinguishable by $^1H$ nmr spectroscopy. It should be noted that the absence of any stereoselectivity in the photolytic step indicates that the chirality present at the amide side chain is too far removed from the iron centre to have any effect. Separation of the two diastereoisomers was achieved by careful chromatography on basic



alumina to afford homochiral (RR)-(-)-**8** $[\alpha]_D^{22}$ -515 (c 0.077, $CH_2Cl_2$) and (SR)-(+)-**9** $[\alpha]_D^{22}$ +198 (c 0.039, $CH_2Cl_2$) in 16% and 12% overall yield, respectively.

The products **8** and **9** were diastereomerically pure within the detection limits of $^1H$, $^{13}C$ and $^{31}P$ nmr spectroscopy, and hence homochiral. Furthermore, each diastereoisomer exhibited distinct and discernible $R_f$ values by t.l.c. analysis. The absolute configuration at the iron centre was assigned by analogy to the sign of rotation of the iron complex **1**.[4]

The results of the asymmetric reduction of ethyl benzoylformate to ethyl mandelate (**2**) by complexes **8** and **9** are summarised in the Table. A number of general comments can be made. As predicted, both diastereoisomers **8** and **9** enhance the enantiomeric excess of **2** compared with the earlier mimic compound **1**, presumably because of the stronger chelation afforded by the oxygen carbonyl of the amide, e.g. using (RR)-(-)-**8** gave (R)-(-)-**2** in 89% ee. Unless a stoicheiometric amount of magnesium perchlorate is used in the reaction the stereoselectivity of the reaction falls (78 *vs* 89%), consistent with chelation being necessary to ensure high stereoselection. Of note is that, in contrast to most other model NADH systems[1,2,3] where reaction times are in the range of 7-14 days, our reactions are essentially complete after 24 hours. The significance of the steric control afforded by the chiral iron auxiliary is illustrated by comparison with the reaction of an early NADH mimic compound,[9] similar to **8**, but lacking the iron auxiliary, in which (R)-(-)-ethyl mandelate was obtained in only 20% ee. Given that both **8** and **9** show higher stereoselectivities than **1** in the reduction of ethyl benzoyl formate it may be concluded that the carboxamide group is having a significant effect, presumably *via* chelation, while the α-methylbenzyl side chain exerts a relatively minor influence (± 6% ee).

**Table.** Asymmetric reduction of ethyl benzoylformate to ethyl mandelate (**2**).[a]

| Reagent | Time(h) | Configuration of **2** | Chemical Yield[b] (%) | Optical Yield[c] (%) |
|---|---|---|---|---|
| (RR)-**8** | 24 | R | 68 | 89 (88) |
| (SR)-**9** | 24 | S | 66 | 77 (78) |
| (RR)-**8**[d] | 168 | R | 66 | 78 (78) |

[a]General Procedure: To a flame-dried Schlenk tube containing ethyl benzoylformate (0.20 mmol) was added the dihydronicotinoyl complex (0.205 mmol), magnesium perchlorate (0.205 mmol) and 0.6 ml of dry acetonitrile. The reaction mixture was stirred under nitrogen in the dark at 20°C and then quenched with one drop of water and the solvent removed *in vacuo* . The crude solid was taken up in dichloromethane, loaded on a silica gel column (elution with petrol:diethyl ether; 10:1) and distilled to afford pure ethyl mandelate (**2**). [b]Isolated yield. [c]Based on the $^{19}F$ and $^1H$ nmr spectra of the corresponding (R)-α-methoxy-α-(trifluoromethyl)phenylacetate.[10] Figures in brackets are based on the specific rotation of pure **2**, $[\alpha]_D^{20}$ -104 (EtOH) for (R)-(-)-**2**.[11] [d]Ratio of reagent to magnesium perchlorate was 1:0.75 in 3 ml of dry acetonitrile.

In line with our previous model[4] we anticipate that chelation of the magnesium to the C-5 carbonyl oxygen and the ketonic carbonyl oxygen of ethyl benzoylformate will present the *si*-face of the ketone to the C-4 *pro*-R hydrogen of (RR)-**8** thus producing the mandelate (R)-(-)-**2** 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 iron chiral auxiliary.[4]

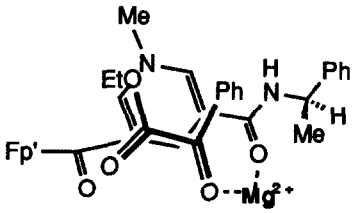



**Figure:** Delivery of the *si*-face of ethyl benzoylformate to the *pro*-R hydrogen of (RR)-(-)-[($\eta^5$-$C_5H_5$)Fe(CO)(PPh3)]-1-methyl-5-(N-α-methylbenzylcarbamoyl)-1,4-dihydronicotinoyl by chelation. Fp' = [($\eta^5$-$C_5H_5$)Fe(CO)(PPh3)].

Compared to our earlier mimic, compound **1**, the incorporation of an additional carbonyl at C-5 has improved the enantiomeric excess for the reduction of ethyl benzoylformate by *ca.* 31%, presumably through better chelation with magnesium. It should be noted however that the higher enantiomeric excess of 89% is achieved when the (R)-α-methylbenzyl side chain is matched with the (R)-configuration at iron. In the light of these results efforts are currently being undertaken to further modify these NADH mimics.

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