Chiral Organometallic NADH Mimics: Stereoselective Reduction of Ethyl Benzoylformate Utilising the Homochiral Auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)] at C-3 and a Chiral β-Hydroxy-carboxamide Derived from Valinol at C-5

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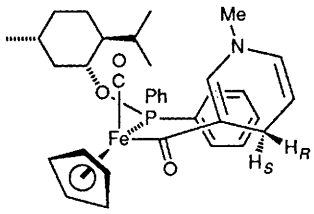
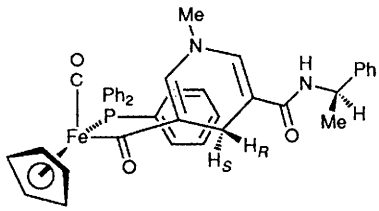
Homochiral complexes incorporating the chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)] at C-3 and a chiral β-hydroxy-carboxamide, derived from valinol, at C-5 reduce ethyl benzoylformate to ethyl mandelate in greater than 97% enantiomeric excess.

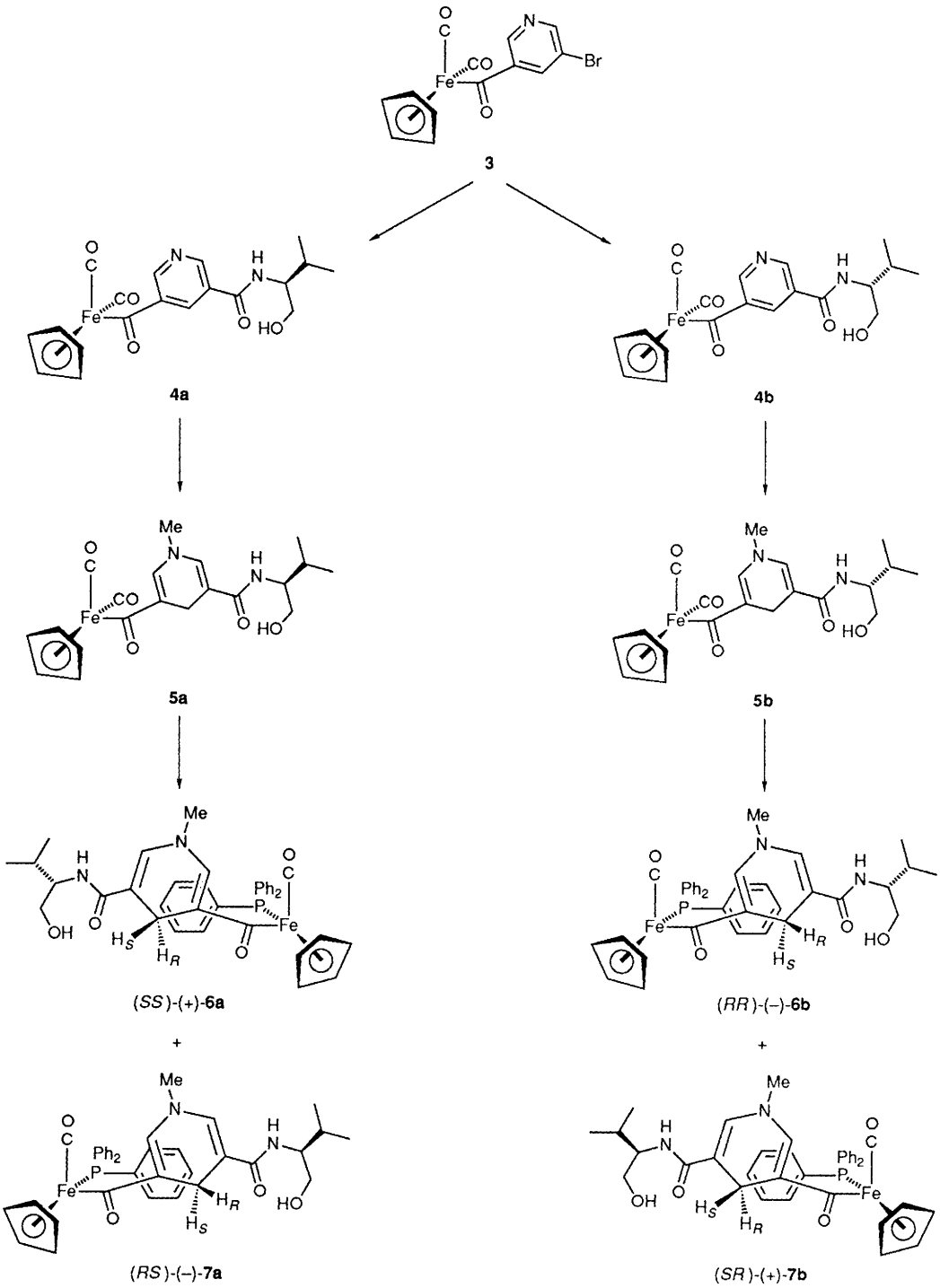
For a chiral NADH mimic to stereoselectively transfer a hydride to a prochiral ketone two conditions need to be fulfilled. Only one of the diastereotopic hydrogens at C-4 must be available for reaction and the orientation of the substrate must be well defined. These requirements can be achieved through chelation of magnesium to both the substrate and a suitable polar substituent at the 3-position of the 1,4-dihydropyridine.[1–4] Recently we reported[5] the preparation of the first organometallic NADH mimic (*R*)-**1** in which one face of the dihydronicotinoyl is effectively shielded by the sterically demanding chiral auxiliary (*R*)-[(η^5-C_5H_5)Fe(CO){PPh_2(*O*-(−)-menthyl)}] such that only one of the diastereotopic hydrogens at C-4 is available for reaction. However, the enantiomeric excess (e.e.) obtained in the asymmetric reduction of ethyl benzoylformate by (*R*)-**1** was moderate (52%), since presumably 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. More recently we reported[6] a modified mimic compound (*RR*)-**2** possessing the chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)] at C-3 and a chiral *N*-substituted carboxamide at C-5. Complex **2**, when



(*R*)-**1**



(*RR*)-**2**



Scheme 1

utilised for the asymmetric reduction of ethyl benzoylformate, afforded the corresponding (*R*)-mandelate in 89% e.e. In this case the α-methylbenzyl side chain exerted minimal stereochemical influence (equivalent to 6% e.e.) and it was concluded that the oxygen of the carboxamide was providing a better site for chelation of the magnesium ion than the iron acyl carbonyl of (*R*)-**1**. We anticipated that a further improvement in stereoselectivity, due to additional chelation and the influence of a second but complementary chiral auxiliary, could be achieved by incorporating a chiral alcohol function[4] within the C-5 substituent. Herein we describe the synthesis of homochiral 1,4-dihydronicotinoyls bearing the chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ at C-3 and a chiral *N*-substituted β-hydroxy-carboxamide, derived from valinol, at C-5 and their utility in the asymmetric reduction of ethyl benzoylformate.

8 9

Table 1 Asymmetric reduction of ethyl benzoylformate **8** to ethyl mandelate **9**[a]

Reagent	Time/h	Configuration of **9**	Chemical yield (%)[b]	Optical yield (%)[c]
(*SS*)-**6a**	8	*S*	64	16(18)
(*RR*)-**6b**	21	*R*	85	15(16)
(*RS*)-**7a**	8	*R*	82	98(99)
(*SR*)-**7b**	12	*S*	84	97(99)

[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 dry acetonitrile (0.6 ml). 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 **9**. [b] Isolated yield. [c] Based on the ^{19}F and ^{1}H NMR spectra of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate.[9] Figures in brackets are based on the specific rotation of pure **9**, $[\alpha]_D^{20}$ −104 (EtOH) for (*R*)-(−)-**9**.[10]

Complex **3**, the preparation of which has previously been described,[6] was utilised as the starting material for the synthesis of the homochiral complexes described below. Thus, under palladium(0)-catalysed carbonylation condtions[6,7] compound **3**, in the presence of *S*-valinol,[8] gave the homochiral amide **4a** $[\alpha]_D^{22}$ −18.5 (*c* 0.054, CH_2Cl_2) in 92% yield,† whereas in the presence of *R*-valinol[8] the homochiral amide **4b** $[\alpha]_D^{22}$ +18.0 (*c* 0.083, CH_2Cl_2) was obtained in 64% yield.[9] It should be noted that these reactions could be performed without protection of the alcohol function. Compounds **4a** and **4b** were converted into the corresponding pyridinium salts which, upon reduction with sodium dithionite under standard conditions[2] afforded the corresponding substituted 1,4-dihydronicotinoyls **5a** $[\alpha]_D^{22}$ −7.2 (*c* 0.14, CH_2Cl_2) and **5b** $[\alpha]_D^{22}$ +6.9 (*c* 0.058, CH_2Cl_2) in 93 and 98% overall yield, respectively. Photolytic ligand exchange of carbon monoxide for triphenylphosphine in a solution of **5a** in tetrahydrofuran–cyclohexane (*ca.* 3 : 1) afforded a 1 : 1 mixture of diastereoisomers **6a** and **7a** which were distinguishable by ^{1}H NMR spectroscopy. Similarly, **5b** afforded a 1 : 1 mixture of diastereoisomers **6b** and **7b**. Separation of the diastereoisomeric mixture **6a** and **7a** was achieved by careful chromatographic separation on basic alumina affording homochiral (*SS*)-(+)-**6a** $[\alpha]_D^{22}$ +393 (*c* 0.055, CH_2Cl_2) and (*RS*)-(−)-**7a** $[\alpha]_D^{22}$ −394 (*c* 0.069, CH_2Cl_2) in 11 and 18% yield, respectively. Likewise, chromatographic separation of the diastereoisomeric mixture **6b** and **7b** gave homochiral (*RR*)-(−)-**6b** $[\alpha]_D^{22}$ −391 (*c* 0.026, CH_2Cl_2) and (*SR*)-(+)-**7b** $[\alpha]_D^{22}$ +394 (*c* 0.087, CH_2Cl_2) in 13 and 17% yield, respectively (Scheme 1). It should be noted that the diastereoisomers **6** and **7** were pure within the detection limits of ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The absolute configuration at the iron centre was assigned by analogy with the sign of rotation of an iron complex reported earlier.[5]

† The yield is based on recovered complex **3**. Reactions were typically run for 2–4 hours at 100 °C until consumption of CO ceased; further reaction resulted in decomposition of both product and complex **3**.

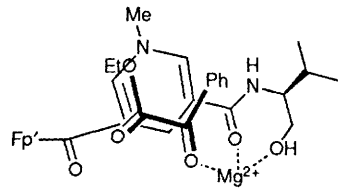


Fig. 1 Delivery of the *si*-face of ethyl benzoylformate to the *pro-R* hydrogen of (*RS*)-(−)-[(η^5-C_5H_5)Fe(CO)(PPh_3)]-1-methyl-5-(1-hydroxymethylisopropylcarbamoyl)-1,4-dihydronicotinoyl by chelation. Fp′ = [(η^5-C_5H_5)Fe(CO)(PPh_3)].

The results of the asymmetric reduction of ethyl benzoylformate **8** to ethyl mandelate **9** by complexes **6a**, **6b**, **7a** and **7b** are summarised in Table 1. A number of general comments can be made. As predicted, the incorporation of a β-hydroxy-carboxamide at C-5 can enhance the enantiomeric excess of **9** compared with the earlier mimic compound **2**, presumably because of the additional chelation afforded by the alcohol function of the amide with the magnesium ion, *e.g.* utilising (*SR*)-(+)-**7b** afforded (*S*)-(+)-**9** in 98% e.e. The configuration of the predominant mandelate is governed by the configuration at the iron centre even though it is three bonds removed from the reaction site. As such, since the complex **7** is available in each enantiomeric form, both the corresponding (*R*)- and (*S*)-mandelates are available in high enantiomeric purity. In contrast to most other model NADH systems, in which reaction times are in the range of 2–14 days, our reactions are essentially complete after 12 h.

In line with our previous model[6] we anticipate that magnesium chelates to both the carbonyl oxygen and the alcohol function of the amide and to the ketonic oxygen of ethyl benzoylformate. This will, for example, present the *si*-face of the ketone to the C-4 *pro-R* hydrogen of (*RS*)-**7a** thus producing the mandelate (**R**)-(−)-**9** as the major enantiomer (Fig. 1). 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.[5]

Of interest (Table 1) is the dramatic effect on the stereoselectivity of the reduction exerted by the valinol substituted carboxamide in the diastereoisomeric complexes **6** and **7**, *e.g.* complex (*RR*)-**6b** affords (*R*)-**9** in 15% e.e. whereas complex (*SR*)-**7b** affords (*S*)-**9** in 97% e.e. Thus, it appears that in compound **7b** the high e.e. of 97% is achieved through a complementary matching of the effects of the (*R*)-valinol derived carboxamide with the (*S*)-iron auxiliary. However, in compound **6b** the two chiral auxiliaries are mismatched with the complex being forced to adopt a conformation in which either chelation of the substrate or the blocking of one face is inefficient.

Although these reactions are stoichiometric, upon completion the pyridinium salts can be isolated, reduced with sodium dithionite and crystallised to afford the corresponding homochiral 1,4-dihydronicotinoyl derivatives **6** and **7** in 70–80% yield.

In conclusion, we have demonstrated that 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. Directional control is achieved by the incorporation of a sterically demanding chiral auxiliary at C-3 while

orientational control is achieved by incorporating a β-hydroxycarboxamide at C-5.

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