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NADH Model Mediated Reduction of C=N Substrates: Enantioselective Synthesis of D- and L-Phenylglycinates.

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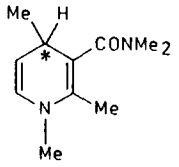
Abstract: Hydride transfer from N,N,1,2,4-pentamethyl-1,4-dihydronicotinamide, **1**, to methyl 2-methoxycarbonylimino-phenylacetate, **3**, was accomplished in an optical yield ≥ 95%.

Efficient chirality transfer from reduced NADH models to prochiral carbonyl substrates has i.a. been achieved with pentamethylated 1,4-dihydronicotinamide **1**.[1] In comparison with 1,4-dihydroquinoline analogues,[2] NADH model **1** is extremely reactive but equally stereoselective. In contrast to most other NADH models used, its oxidized form **2** is provided with stable axial chirality. The high asymmetric induction observed in the reduction of C=O substrates was accounted for by the adoption of a short-lived ternary complex, in which the amide carbonyl dipole and the transferred hydrogen adopt a *syn*-out-of-plane orientation as predicted previously by quantumchemical calculations.[3] Chelation by Mg^{2+} may rationalize the appropriate positioning of the substrate in the ternary complex.[1,4] With the aim of broadening the scope of the hydride transfer reactions with NADH model **1** and to further test the concept of *syn*-out-of-plane orientation, efforts were undertaken to achieve enantioselective reduction of C=N substrates. Herein we describe the NADH model **1**-mediated enantioselective conversion of methyl 2-methoxycarbonylimino-phenylacetate, **3**, into methyl N-carbomethoxy-phenylglycinate, **4**, and a cyclic process allowing the conversion of racemic phenylglycine derivatives into an enantiomer of choice.

Hitherto, the reduction of benzyliminoacetophenone with a 4-methyl-3-hydroxymethyl-1,4-dihydropyridine is the only example of an NADH model mediated enantioselective hydride transfer to C=N substrates.[5] When compared with ketones or aldehydes, the intrinsic chemical reactivity of imines towards a nucleophilic species will be significantly lower but that of iminium derivatives much higher. Taking into account the requirement of activation of carbonyl substrates either by an electron-withdrawing group (e.g., a geminal CO_2Me) or by a coordinating group at appropiate distance (e.g., an α-OH) for efficient, stereoselective hydride uptake, attention was focused initially on iminium substrates. However, all efforts to induce hydride transfer from NADH model **1** to the iminium compounds **5** and **6** failed, but instead addition of the enamine moiety of **1** to the iminium substrates occurred. This behaviour reflects the inability of the

reaction partners to build a suitable ternary complex. Attention was shifted then to N-substituted imino derivatives **7a-e**. However, none of these compounds was prone to hydride uptake when brought in contact with NADH model **1**, irrespective of the presence of $Mg(ClO_4)_2$ or $LiClO_4$. Reactions were limited to autoxido-reduction of **1**.[6,1]



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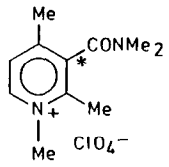

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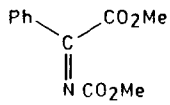

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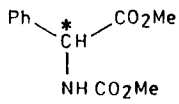

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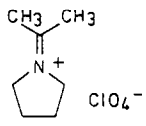

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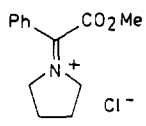

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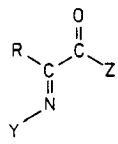
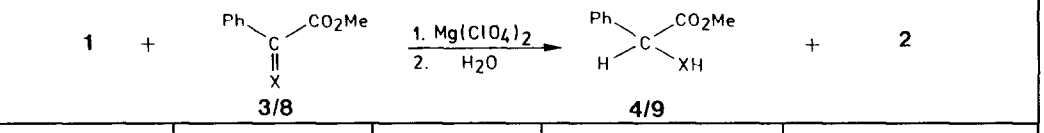


	R	Y	Z
7a	Me	OCH_2Ph	OCH_2Ph
7b	Me	CH_2Ph	$NHCH_2Ph$
7c	Me	CH_2Ph	OCH_2Ph
7d	Ph	CH_2Ph	OMe
7e	Ph	CH_2Ph	OEt

From all these negative results, we concluded that only imines more reactive than α-benzylimino-substrates **7b-e**, but still capable of coordination, could possibly serve as efficient and stereoselective hydride acceptors from NADH model **1**. Therefore methoxycarbonylimino derivative **3** was selected as potential substrate. Treatment of compound **3** with racemic NADH model **1** in CD_3CN at room temperature in the presence of $Mg(ClO_4)_2.2aq$ gave NAD^+ model **2** together with methyl mandelate, **9**, instead of the expected amino acid derivative **4**, due to the fast hydration of the imino substrate and subsequent elimination to methyl carbamate and methyl benzoylformate.[7] By carefully drying the CD_3CN and $Mg(ClO_4)_2$ to keep the water content in the reaction medium below one equiv and by operating below -10°C, the appropriate conditions were created for efficient hydride transfer from NADH model **1** to imine **3**. After aqueous work-up and chromatographic purification of the apolar fraction, compound **4** was isolated in >55% yield. In Table 1 the stereochemical outcome of reactions between imine **3** and optically active **1** is depicted and compared with that recorded for methyl benzoylformate, **8**.[1] The assignment of the absolute configuration and conformation of **1** and **2**, respectively, and their ee determinations have been described previously.[1] The absolute configuration of **4** was unequivocally established by independent synthesis of *S*-**4** from *S*-phenylglycine and the ee was determined by (+)-Eu(hfc)$_3$-induced enantiotopic differentiation of the C-carbomethoxy proton signals in hexadeuteriobenzene ($\Delta\delta_R > \Delta\delta_S$). Obviously, hydride transfer occurs with high asymmetric induction as well with regard to axially chiral NAD^+ model **2** as to phenylglycinate **4**. When starting the reaction at -25°C the ee values measured for **2** and **4** are very close and the optical yields exceed 95%. The *R* (resp *S*) configuration in NADH model **1** corresponds to the *R* (resp *S*) configuration in the amino acid derivative **4** and to the *P* (resp *M*) conformation in NAD^+ model **2**.

Table 1. Enantioselective hydride transfer from NADH model **1** to imine **3**[a] and its oxo-analogue **8**.[b]



config	ee %	X	initial temp °C	config	ee %	opt y %	conform	ee %	opt y %
S	55±2	N-CO_2Me	-10	*S*	50	91	*M*	53	96
R	93±2	N-CO_2Me	-25	*R*	89	96	*P*	90	97
S	69±2	O	0	*S*	57	83	*M*	60	87
R	96±2	O	-25	*R*	91.5	95	*P*	93	97

[a]Procedure: A cooled solution of dry $Mg(ClO_4)_2$ (0.2 mmol) in CD_3CN (0.2 ml) was treated under argon with a solution of imine **3** (0.2 mmol) in CD_3CN (0.4 ml) and NADH model **1** (0.2 mmol) in CD_3CN (0.4 ml) consecutively. The reaction mixture was allowed to reach room temperature within one hour. After addition of NH_4Cl (0.1 M, 4 ml) the solvent was evaporated and the residue partitioned between CH_2Cl_2 and H_2O. Column chromatography of the organic layer on silica gel (2 g, CH_2Cl_2 as eluent, R_f 0.15) afforded pure **4**, and evaporation of the aqueous layer NAD^+ model **2**. [b]Reference 1.

The striking similarity between the reaction conditions and the stereochemical outcome of the hydride transfer to **3** and **8**, respectively, clearly demonstrates the close parallel in behaviour of the prochiral C=N-CO_2Me and C=O functions. Therefore a ternary complex, entirely analogous to that postulated for the reduction of methyl benzoylformate, is proposed as transition state (Figure 1). Mg^{2+} is herein responsible for the out-of-plane fixation of the amide carbonyl dipole of **1**, which concomitantly enhances its hydride donor ability, and for the positioning via chelation of the imino substrate, which renders the latter more electron deficient. The developing positive charge at N-1 may be stabilized by the increasing electron density at the imino nitrogen.

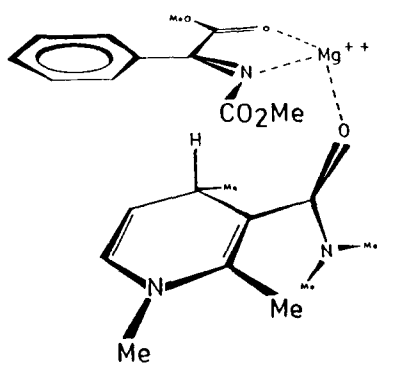


Figure 1.
Chirality transfer from *S*-**1** to *S*-**4** and *M*-**2**.

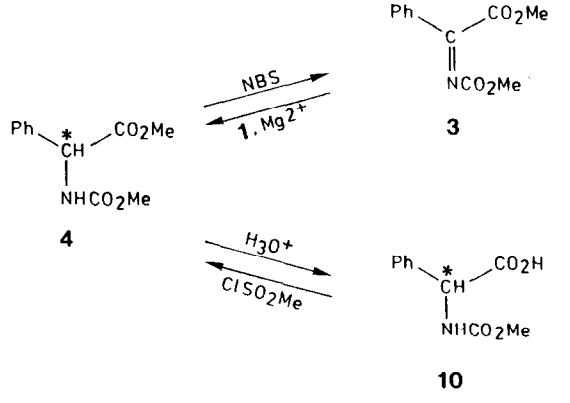


Figure 2.
Conversion of **10** and **4** into an enantiomer of choice.

To achieve chelation in the ternary complex the N-carbomethoxy group has to occupy a position remote from Mg^{2+} and hence the intermediacy of the *E* isomer of **3** is required. A fast *E-Z* isomerization due to the contribution of a dipolar form, in which the imine nitrogen adopts an sp hybridization,[8] may explain the single set of ^1H and ^{13}C NMR signals observed for imino derivative **3**. Therefore, the intrinsically more reactive *E* isomer of **3** is believed to be accomodated in the ternary complex, while the *Z* isomer, being unable to form a productive, chelated complex easily isomerizes to the *E* isomer.

As depicted in Figure 2, the enantioselective hydride transfer process was incorporated in a synthetic cycle, enabling the conversion of phenylglycine derivatives into an enantiomer of choice. Racemic **4** was synthesized in 92% yield under Schotten-Baumann conditions, and smoothly dehydrogenated to **3** by N-bromosuccinimide,[7] and re-obtained in optically active form upon reaction with optically active **1**. Acidic hydrolysis of optically active **4** gave carbamate **10**[9] without racemization, but further deprotection to phenylglycine.hydrochloride was accompanied by significant loss of optical purity (ee $\approx$ 50% after 48 h of reflux in 6M HCl). Conversely, the double protection of *S*-phenylglycine leads to optically pure *S*-**4**, as judged from (+)-Eu(hfc)$_3$-mediated ^1H NMR spectra in C_6D_6. Thus a synthetic cycle was developed allowing the interconversion of (racemic) **10** and **4** into either their *R* or their *S* enantiomers.

In conclusion, a strong activation of the iminosubstrate by carbomethoxy groups on both ends of the C=N bond, as in compound **3**, is essential for the occurrence of a stereoselective hydride transfer from **1**. Acylation of the imine nitrogen reduces its electron-donating properties to a large extent,rendering imino substrate **3** comparable to oxo substrate **8**, both in chemical reactivity and in ligand forming properties. In both cases the *R* chirality in the hydride donor corresponds to the *R* chirality in the reduction product (**4** and **9**, respectively) and to the *P* helicity (CO down) of the NAD^+ model **2**. These results provide further evidence for the intervention during hydride transfer from NADH models of a Mg^{2+}-mediated chelated ternary complex in which the transferred hydrogen and the amide carbonyl dipole are positioned in a *syn*-out-of-plane orientation. Future research will concentrate on the elaboration of the "imino approach" for the enantioselective synthesis of naturally occurring α-amino acids and their antipodes.

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