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Enantioselective Reduction of C=O and C=N Compounds with NADH Model N,N,1,2,4-Pentamethyl-1,4-dihydronicotinamide

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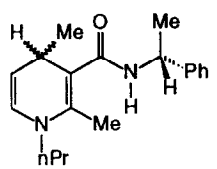
Abstract. The scope and mechanism of enantioselective hydride transfer from NADH model **4** to prochiral C=O and C=N compounds were investigated. Efficient chirality transfer from **4** to α-keto esters and α-methoxycarbonylimino esters was achieved. The resemblance in reactivity and stereochemistry of the prochiral C=O and C=N-CO_2Me functionalities in the hydride transfer reaction is attributed to the intervention of a similar $Mg(ClO_4)_2$-mediated ternary complex.

INTRODUCTION

The reversible and stereoselective hydride transfer from NADH to prochiral substrates under the influence of dehydrogenases has inspired many chemists to design NADH models useful as efficient enantioselective reducing agents.[1] Generally, magnesium or zinc perchlorate is used in vitro to enhance the reactivity and to create a well-organized transition state. One line of approach mimics the selective shielding of one of the diastereotopic C-4 hydrogens of NADH in the enzymic cavity by introducing a methyl substituent at C-4 of a 1,4-dihydronicotinamide, thus creating a stereocentre at the reaction centre, e.g., **1**[2], **2**[3] and **3**[4]. In our laboratory, efficient enantioselective hydride transfer has been achieved with N,N,1,2,4-pentamethyl-1,4-dihydronicotinamide (**4**).[5]



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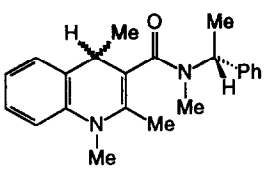

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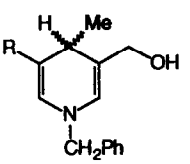

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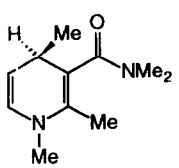
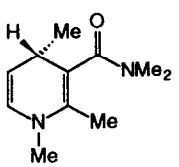
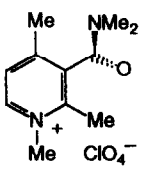


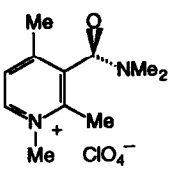
R-**4**



S-**4**



P-**5**



M-**5**

In contrast to most other C-4 methylated NADH models, **4** combines excellent stereoselectivity with high reactivity. Additionally, the stable axial chirality in the oxidized form **5** provides information about the mechanism of the hydride transfer. Hydride transfer from *S*-**4** to methyl benzoylformate afforded NAD^+ model *M*-**5** and *S*-methyl mandelate in an optical yield ≥ 95%. Only a transition state in which the migrating C-4 hydrogen and the amide carbonyl feature a *syn*-out-of-plane orientation may account for the observed stereochemistry.

The present paper deals with the scope and mechanism of hydride transfer reactions with NADH model **4**. The reactivity of several carbonyl and imino compounds towards NADH model **4** and the efficiency of the chirality transfer were investigated. Based on experimental evidence, the exact nature of the ternary complex(es) rationalizing the observed stereoselectivity is discussed.

RESULTS AND DISCUSSION

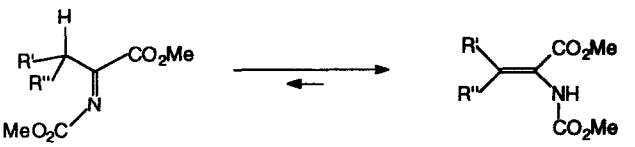
Reactivity of C=O compounds. The synthetic utility of hydride transfer from NADH model **4** to the C=O bond was screened with several reactive carbonyl compounds, e.g., 4,5-dihydro-4,4-dimethyl-2,3-furanedione (**6b**), ethyl 3-methyl-2-oxobutyrate (**6c**), 1-phenyl-1,2-propanedione (**6d**), 3-methyl-1,2-cyclopentanedione (**6e**) and 1,2-cyclohexanedione (**6f**). While α-keto esters **6b** and **6c** were reduced selectively upon equimolecular reaction with **4** in 100 and 56% yield, respectively, dione **6d** afforded a mixture of 2-hydroxy-1-phenyl-1-propanone and 1-hydroxy-1-phenyl-2-propanone, and the cyclic diketones **6e** and **6f** were not reduced at all. The reluctancy of **6e** and **6f** to undergo hydride transfer from **4** may find its origin in their predominant existence in the enol form. Earlier work[5,6] already showed that acetone doesn't react with **4** to an appreciable extent, but benzaldehyde does for ~60% and methyl pyruvate and benzoin do quantitatively.

Since NADH model **4** is not only capable of transferring a hydride to the carbonyl substrate but is also susceptible to autoxidoreduction in the presence of $Mg(ClO_4)_2$, many substrates are only partially or not at all reduced by NADH model **4**. The rapid formation of a reactive ternary complex consisting of the substrate, the NADH model and Mg^{2+} seems essential for an effective hydride transfer. Apparently, the presence of an α-carboalkoxy and to a smaller extent an α-hydroxyalkyl or an α-phenyl group in the carbonyl substrate facilitates the construction of a ternary complex, while steric crowding of bulky groups adjacent to the carbonyl bond strongly hampers its formation. In contrast to α-keto ester **6c**, the rigid cisoid structure of lactone **6b** overcomes the steric constraints imposed by the α-methyl substituent, rendering the reactivity of **6b** comparable to that of methyl benzoylformate (**6a**). In conclusion, only carbonyl compounds carrying a polar α-substituent and easily fitting in a ternary complex, are efficiently reduced by **4**.

Reactivity of C=N compounds. With the objective of broadening the scope of hydride transfer reactions with NADH model **4**, we also investigated the reduction of C=N substrates. Very few examples of enantioselective NADH model mediated reductions of C=N compounds have been reported up to now.[7,8] The lack of such transformations may rely both on steric constraints imposed by N-substitution and on the intrinsic chemical reactivity and complexation ability of C=N compounds. When compared to ketones, imines are significantly less reactive towards nucleophilic species, whereas iminium compounds are considerably more reactive. Recently, we briefly reported the prerequisites for the occurrence of hydride transfer from **4** to the C=N bond.[8] We found that

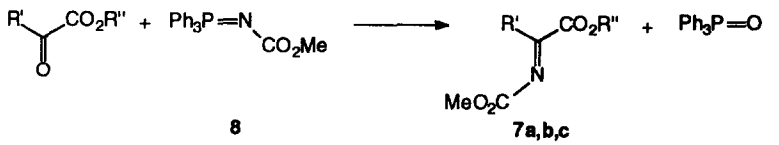
iminium compounds do not undergo hydride uptake from **4** but rather react with the enamine moiety of the dihydropyridine ring. We also found that only a strong activation of imino compounds, e.g., by introducing electron withdrawing carbomethoxy groups at both ends of the C=N bond, enables hydride transfer. Apparently, a high intrinsic reactivity together with the ability of the nitrogen lone pair to coordinate with Mg^{2+} is required for the hydride transfer reaction. Aiming at an enantioselective synthesis of α-amino acid derivatives, the reduction of α-methoxycarbonylimino esters was further investigated.

Due to their tendency to undergo cycloaddition, nucleophilic addition and polymerization, α-acylimino esters are not easily available.[9] In particular α-acylimino esters derived from naturally occurring α-amino acids and their optical antipodes, which are provided with weakly acidic β-protons, tend to isomerize into the more stable enamine tautomers (eq. 1), which are unreactive towards NADH model **4**. Enamine-tautomerization is avoided when the β-protons of the α-acylimino esters are masked by halogen atoms, as in **7c-e**. After hydride transfer to these halogenated imines, the non-halogenated α-amino acid derivatives might be obtained by catalytic hydrogenation of the C-halogen bond.



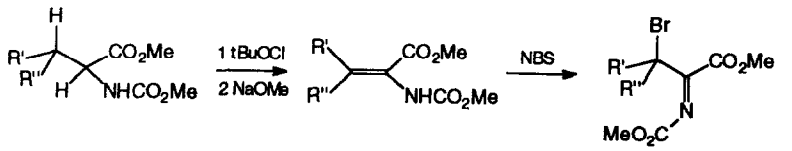
(eq. 1)

α-Methoxycarbonylimino esters **7a-c** were obtained from the corresponding α-keto esters via an aza-Wittig reaction with iminophosphorane **8** (eq. 2).[10,11] However, the drastic reaction conditions needed in the aza-Wittig reaction limits its use for a general synthesis of α-acylimino esters. The β-bromo-α-imino esters **7d** and **7e** were prepared by a recently reported method involving N-bromosuccinimide (NBS) oxidation of the α,β-didehydroamino acid derivatives **11**,[12] which derive from the corresponding protected racemic amino acids **10** (eq. 3).[13]



(eq. 2)

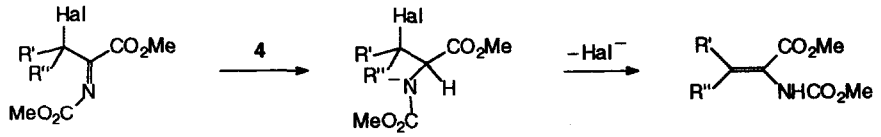
a: R' = Ph, R'' = Me; **b**: R', R'' = CMe_2CH_2; **c**: R' = CCl_3, R'' = Me



(eq. 3)

d: R' = R'' = Me; **e**: R' = Ph, R'' = H

^{1}H NMR monitoring of reactions at room temperature between equimolar amounts of imino substrates **7a-e** and racemic hydride donor **4** revealed the instantaneous disappearance of imino substrate and hydride donor and the formation of pyridinium compound **5**. Analysis of the organic fractions after aqueous workup indicated that imino substrates **7a** and **7b** had quantitatively been reduced into the corresponding α-amino acid derivatives, while imino substrates **7c-e** afforded the unexpected α,β-didehydroamino acid derivatives **11c-e**. In the latter three cases, the fast and quantitative conversion of **4** into **5** suggests that hydride transfer to the imino substrates had occurred indeed, but was followed immediately by elimination of a halide and rearrangement into the stable enamine derivatives **11** (eq. 4). Possibly, masking the β-protons of α-acylimino esters with weaker leaving groups, e.g., a dithioacetal, might afford a suitable hydride acceptor for NADH model **4**, without concomitant elimination of the reduction product. However, the high activation of the imino bond required for efficient hydride uptake from **4** and the instability of such imino compounds seriously limits the synthetic utility of this NADH model mediated reduction.



7c,d,e **11c,d,e** (eq. 4)

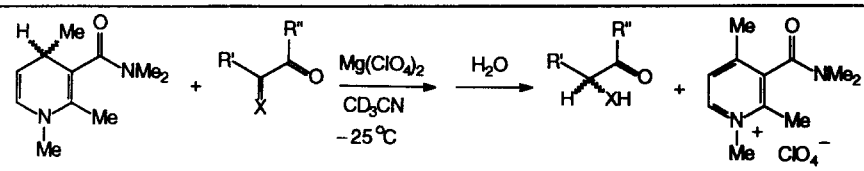
c: R', R'', Hal = Cl; **d**: R', R'' = Me, Hal = Br; **e**: R' = Ph, R'' = H, Hal = Br

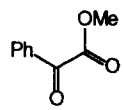
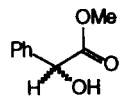
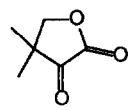
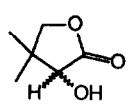
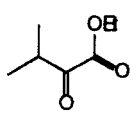
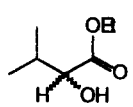
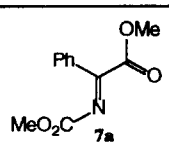
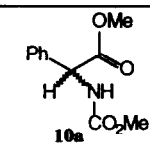
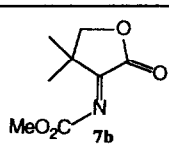
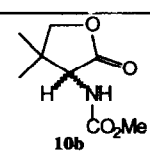
Stereoselectivity and mechanism of the hydride transfer. The stereoselectivity of the hydride transfer reactions was investigated with optically active **4**. Resolution of racemic **4** had previously been accomplished by medium pressure chromatography on a column packed with cellulose triacetate.[5] On repetition of the chromatographic separation, ee values exceeding 90% could be reached. This rather tedious resolution was optimized with the aid of HPLC. In one run, the resolution of 50 mg of racemic **4** into chemically pure (*R*)-**4** (ee > 95%) and (*S*)-**4** (ee > 90%) was accomplished with an overall yield of 70%. The assignment of the absolute configuration of **4** and conformation of **5** has been described previously.[5] Ee values of the reduction products were determined with the aid of ^{1}H- or ^{31}P-NMR utilizing the chiral shift reagent tris[3-[(heptafluoropropyl)hydroxymethylene]-d-camphorato]-europium(III) ((+)-Eu(hfc)$_3$ (for compounds **9a,b** and **10a**), or the chiral derivatizing agents 2-chloro-(4*R*,5*R*)-dimethyl-2-oxo-1,3,2-dioxophospholane (for compound **9c**) or (*R*)-α-methyl-benzylamine (for compound **10b**).

The stereochemical outcome of reductions with optically active **4** is depicted in Table 1. All reductions were conducted at -25°C in CD_3CN in the presence of one mole equivalent $Mg(ClO_4)_2$. Reaction of optically active **4** with C=X compounds **6a-c** and **7a,b** afforded axially chiral NAD^+ model **5** in ≥ 95% optical yield, while the optical yields of the corresponding alcohols and amino derivatives ranged from 70 to ≥ 95%. In all cases, the *R* configuration in NADH model **4** corresponds to the *R* configuration in the reduction products and to the *P* conformation in NAD^+ model **5**. Similarly, *S*-**4** yields the *S* reduction products and *M*-**5**. The striking similarity in stereochemistry between the hydride transfer to the prochiral C=N-CO_2Me and C=O functionalities suggests a similar mechanism in both cases. The observed chirality transfer to both

the C=O and the C=N bond may be explained by the intervention of a short lived, strictly organized ternary complex (**12a**) as was postulated previously.[5] In this complex Mg^{2+} coordinates with the carboxamide oxygen of the NADH model, thus enhancing the hydride donor ability of **4** by the out-of-plane rotation of the amide carbonyl dipole. Equally important, Mg^{2+} is responsible for activating the C=X substrate via Lewis acid complexation and for positioning the substrate in the ternary complex by chelation.

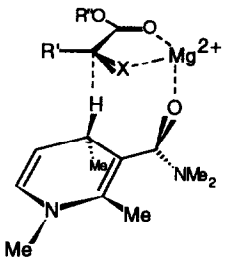
Table 1 Chirality transfer from optically active 4 to imino and keto substrates



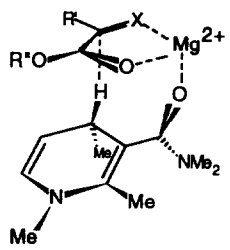
NADH model 4		substrate	product				NAD$^+$ model 5		
conf	ee[a] %			conf	ee %	Y[b] %	conf	ee %	Y[b] %
R[c]	96			*R*	92	95	*P*	93	97
S	90	**6a**	**9a**	*S*	88	98	*M*	84	93
R	95			*R*	59	62	*P*	91	96
S	90	**6b**	**9b**	*S*	68	76	*M*	87	97
R	95			*R*	67	70	*P*	85	89
S	90	**6c**	**9c**				*M*	82	91
R	93			*R*(-)	89	96	*P*	90	97
S	55	**7a**	**10a**	*S*(+)	50	91	*M*	53	96
R	95			*R*(-)[d]	80	84	*P*	88	93
S	90	**7b**	**10b**	*S*(+)[e]	70	78	*M*	84	93

[a] Enantiomeric excess determined by HPLC. [b] Optical yield corrected for ee of **4**. [c] From reference 5. [d] $[\alpha]^{20}_D$ -34° (c=1, $CHCl_3$), *R*-configuration tentatively assigned to the (-)-enantiomer based on ^1H NMR-data. [e] $[\alpha]^{20}_D$ +24° (c=1, $CHCl_3$).

Assuming a hexavalent arrangement of Mg^{2+} in the ternary complex, coordination of Mg^{2+} with the lone pairs of three hetero atoms allows the formation of only 2 chelated complexes: one complex in which the C=X dipole is lying over the dihydropyridine ring and is orientated towards C-3 (**12a**, anti-parallel orientation of C=X and dihydropyridine dipoles), and one in which it points away from this ring (**12b**, parallel dipoles). Apparently, complex **12a**, leading to the formation of the *S*-reduction product from *S*-**4**, is energetically favoured over complex **12b**. MINDO/3 calculations on a ternary complex consisting of NADH model **4**, Mg^{2+} and 2-oxo-3-butynoic acid also indicated a preference for an orientation of the C=O dipole in the direction of C-3 (difference in ΔH: 3 kcal. mol^{-1}).[14]



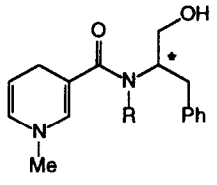
12a



12b

The importance of the formation of a chelated ternary complex during the hydride transfer is clearly demonstrated in the reaction of *S*-benzoin with racemic **4**.[6] Whereas *R*-**4** and *S*-benzoin easily fit in a chelated ternary complex with Mg^{2+}, thus enabling a fast hydride transfer reaction, *S*-**4** is unable to form a productive ternary complex with *S*-benzoin and hence no hydride transfer takes place.

Results obtained with NADH models **13** and **14**,[15] which carry the same chiral auxiliary for stereodifferentiation of the diastereotopic C-4 hydrogens, support the relevance of a *syn*-out-of-plane orientation of the transferring hydrogen and the carboxamide dipole of the NADH model for an efficient chirality transfer. The much higher ee values obtained with **14** presumably arise from the incorporation of the carboxamide group in a cyclic structure, forcing the amide oxygen and one of the C-4 hydrogens into a *syn* orientation.



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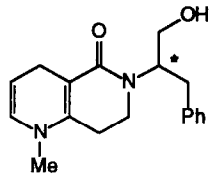

14

The intervention of two chelated ternary complexes offers an explanation for the lower ee values of **9b** and **9c** in comparison with **9a**. Van der Waals interaction of the α-methyl groups in the carbonyl compounds **6b** and **6c** with the dihydropyridine ring hampers to some extent the formation

of complex **12a**, rendering complex **12b** competitive. This leads to a lower enantiomeric excess of the alcohol, while leaving the ee of the pyridinium compound unaffected. The same phenomenon is observed for imino substrates **7a** and **7b**.

To achieve chelation of the imino substrates 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 the imine is required. The single set of ^1H and ^{13}C NMR signals observed for imino derivatives **7a** and **7b** reveals that either a fast *E-Z* isomerization takes place or that only one isomer exists in solution. The first option seems more likely,[16] so that the *E* isomer is believed to be accommodated in the ternary complex, while the *Z* isomer, being unable to form a productive chelate, easily isomerizes into the *E* form.

CONCLUSION

Efficient enantioselective hydride transfer from NADH model **4** to α-keto esters and α-methoxycarbonylimino esters was achieved. The chirality transfer to both the C=O and the C=N bond may be explained by the intervention of a $Mg(ClO_4)_2$ mediated ternary complex in which the carboxamide dipole and the transferring hydrogen of the NADH model feature a *syn*-out-of-plane orientation and in which the substrate is positioned by chelation with Mg^{2+}. The need for highly activated keto or imino substrates, however, seriously limits the application of NADH model **4** as a versatile chiral reducing agent. Important drawbacks of **4** are its autoxidoreduction in the presence of Mg^{2+} and its stoichiometric use. To obtain an efficient enantioselective hydride donor, which may be used catalytically, chirality at C-4 of the NADH model should be avoided. Therefore, efforts are being undertaken to exploit axial chirality induced by C-2 or C-3 substitution for efficient stereodifferentiation of the diastereotopic C-4 hydrogens.

EXPERIMENTAL

NMR spectra were recorded on a Bruker AC400 spectrometer (^1H NMR at 400.1 MHz, ^{13}C NMR at 100.6 MHz and ^{31}P NMR at 162.0 MHz). All reactions involving dihydronicotinamide **4** or imino compounds **7** were performed under an argon atmosphere.

N,N,1,2,4-Pentamethyl-1,4-dihydronicotinamide, 4. The synthesis of racemic **4** in 3 steps from N,N-dimethylacetoacetamide was outlined previously.[5] Resolution of **4** (35 mg, dissolved in *n*-hexane/*i*-PrOH (4:1, 120 μL)) was accomplished with HPLC (cellulose triacetate column, Merck 16362, 15-25 μm, 30 g, 300 mm x 16 mm, 12 bar, 4 mL.min^{-1}). Elution with *n*-hexane/*i*-PrOH (7:3) afforded pure (*R*)-**4** (10 mg, ee > 95%) and (*S*)-**4** (15 mg, ee > 90%).

Methyl 2-Methoxycarbonylimino-phenylacetate, 7a.[9] (Aza-Wittig reaction). A neat mixture of iminophosphorane **8** (1.65 g, 5 mmol) and methyl benzoylformate (**6a**, 0.83 g, 5 mmol) was heated at 150°C during 4 h. Et_2O (10 mL) was added to the cooled reaction mixture. After filtration to remove precipitated triphenylphosphinoxide, the filtrate was concentrated. In vacuo chromatography (silica gel, CH_2Cl_2), afforded **7a** as a pale yellow oil (R_f 0.42, 0.31 g, 28%) contaminated with traces of **6a** (R_f 0.64). ^1H NMR (CD_3CN): δ 3.84 (s, 3H, N-CO_2CH_3); 3.91 (s, 3H, C-CO_2CH_3); 7.51 (tr, *J* = 8 Hz, 2H, m-Ar H); 7.63 (tr, *J* = 8 Hz, 1H, p-Ar H); 7.88 (d, *J* = 8 Hz, 2H, o-Ar H). ^{13}C NMR (CD_3CN): δ 54.0 and 54.7 (OCH_3); 129.9 (p-, m-Ar C); 132.9 (o-Ar C); 134.5 (ipso-Ar C); 163.0 (C=N); 164.0 and 164.2 (C=O).

4,5-Dihydro-4,4-dimethyl-3-methoxycarbonylimino-2-(3H)-furanone, 7b. Reaction of 4,5-dihydro-4,4-dimethyl-2,3-furanedione (**6b**) and iminophosphorane **8** under the conditions used for the synthesis of **7a** afforded **7b** as a pale yellow oil (0.34 g, 36%). ^1H NMR (CD_3CN): δ 1.31 (s, 6H, CH_3); 3.81 (s, 3H, OCH_3); 4.33 (s, 2H, CH_2). ^{13}C NMR

($CDCl_3$): δ 23.9 (CH_3); 39.1 (C-4); 53.6 (OCH_3); 77.7 (CH_2); 159.5 (C=N); 161.3 and 166.2 (C=O). Accurate mass calcd for $C_8H_{11}NO_4$: 185.069. Found: 185.069.

Methyl 2-Methoxycarbonylimino-3,3,3-trichloropropionate, 7c.[17] A solution of methyl 3,3,3-trichloropyruvate[18](4.11 g, 20 mmol) and iminophosphorane **8** (6.71 g, 20 mmol) in toluene (40 mL) was gently boiled under reflux during 4 h. The solvent was removed in vacuo and the residue taken up in hexane (20 mL). After removal of precipitated triphenylphosphinoxide, the filtrate was concentrated and distilled under reduced pressure affording **7c** (2.50 g, 50%). Bp 93°C/1.0 mm Hg. ^1H NMR ($CDCl_3$): δ 3.94 and 3.97 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 54.0 and 54.3 (OCH_3); 91.8 (CCl_3); 155.9 (C=N); 157.4 and 159.2 (C=O).

Methyl 3-Bromo-2-methoxycarbonylimino-3-methylbutyrate, 7d.[12] A solution of N-Bromosuccinimide (NBS, 0.90 g, 5 mmol) and enamine **11d** (0.94 g, 5 mmol) in CH_2Cl_2 (25 mL) was stirred for 20 h at room temp. The solvent was evaporated and the residue taken up in boiling n-pentane. After cooling in an ice bath, the suspension was filtered and the filtrate concentrated to afford **7d** (1.06 g, 80%). ^1H NMR ($CDCl_3$): δ 2.07 (s, 6H, CH_3); 3.86 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 31.3 (CH_3); 52.9 (OCH_3); 53.8 (OCH_3); 59.5 (CBr); 161.1 (C=O and C=N); 166.2 (C=O).

Methyl 3-Bromo-2-methoxycarbonylimino-3-phenylpropionate, 7e.[12] A solution of NBS (1.42 g, 8 mmol) and enamine **11e** (1.88 g, 8 mmol) in CH_2Cl_2 (50 mL) was stirred for 36 h at room temp. The solvent was evaporated and the residue taken up in boiling n-pentane (25 mL). The cooled suspension was filtered and the filtrate concentrated to afford **7e** (1.20 g, 48%). ^1H NMR ($CDCl_3$): δ 3.80 and 3.82 (s, 3H, OMe); 6.13 (s, 1H, CH); 7.30 - 7.40 (m, 3H, m- and p-Ar H); 7.47 (m, 2H, o-Ar H). ^{13}C NMR ($CDCl_3$): δ 48.2 (CH); 53.5 (2 x OCH_3); 128.5 - 129.1 (o-, m- and p-Ar C); 134.6 (ipso-Ar C); 158.2 (C=N); 158.4 and 161.0 (C=O). Accurate mass calcd for $C_{12}H_{12}{}^{79}BrNO_4$: 312.995. Found: 312.995.

N-Carbomethoxy-triphenylphosphinimine, 8.[11] A solution of diethyl azodicarboxylate (3.48 g, 20 mmol) in dry THF (20 mL) was added dropwise within 30 min to a stirred and cooled (0°C) solution of triphenylphosphine (5.24 g, 20 mmol) and methyl carbamate (3.50 g, 20 mmol) in dry THF (40 mL). After additional stirring for 4 h at room temp, the reaction mixture was concentrated in vacuo. $CHCl_3$ (15 mL) was added, the solution cooled in an ice-bath for 15 min and the precipitated N,N'-dicarbethoxyhydrazine removed by filtration (1.80 g, 52%). The filtrate was concentrated and the resultant suspension crystallized from EtOAc/*n*-hexane (1 : 1, 10 mL) to afford pure phosphinimine **8** (3.68 g, 55%). Mp 134 - 136°C. ^1H NMR ($CDCl_3$): δ 3.63 (s, 3H, OCH_3); 7.45 - 7.75 (m, 15H, Ar H). ^{13}C NMR ($CDCl_3$): δ 52.6 (d, $J_{P\text{-}C}$= 4 Hz, OCH_3); 127.9 (d, $J_{P\text{-}C}$ = 100 Hz, ipso-Ar C); 128.5 (d, $J_{P\text{-}C}$= 12 Hz, m-Ar C); 132.2 (d, $J_{P\text{-}C}$= 3 Hz, p-Ar C); 132.9 (d, $J_{P\text{-}C}$= 10 Hz, o-Ar C); 162.5 (d, $J_{P\text{-}C}$= 3 Hz, NCO). ^{31}P NMR ($CDCl_3$): δ 21.6. Anal. calcd for $C_{20}H_{18}NO_2P$ (MW 335.34): C, 71.63; H, 5.41; N, 4.18. Found: C, 71.77; H, 5.57; N, 4.15.

N-Carbomethoxy-α-amino acid esters. General procedure. To a stirred and cooled (0°C) solution of the amino acid ester hydrochloride[19] (10 mmol) in H_2O (10 mL) were added dropwise aqueous Na_2CO_3 (1M, 11 mL) and $ClCO_2Me$ (1.11 g, 12 mmol). Then the ice-bath was removed and the reaction mixture stirred at room temp for 3 h. Subsequent extraction with Et_2O (3 x 20 mL), drying ($MgSO_4$) and concentration of the organic layer gave the crude N-carbomethoxy-α-amino acid ester, which was purified by crystallization from EtOAc/*n*-hexane (1 : 2).

Methyl N-Carbomethoxyphenylglycinate, 10a. Yield 92%. Mp 89.5°C. ^1H NMR ($CDCl_3$): δ 3.67 (s, 3H, N-CO_2CH_3); 3.72 (s, 3H, C-CO_2CH_3); 5.37 (d, J = 7 Hz, 1H, CH); 5.80 (d, J = 7 Hz, 1H, NH); 7.34 (m, 5H, Ar H). ^{13}C NMR ($CDCl_3$): δ 51.6 and 52.0 (OCH_3); 57.4 (CH); 126.7 (p-Ar C); 127.9 (o-Ar C); 128.3 (m-Ar C); 136.2 (ipso-Ar C) 155.9 (N-$\underline{C}O_2Me$); 170.9 (C-$\underline{C}O_2Me$). Anal. calcd for $C_{11}H_{13}NO_4$ (MW 223.23): C, 59.19; H, 5.87: N, 6.27. Found: C, 59.77; H, 6.03; N, 6.37.

N-Carbomethoxypantoninelactone, (4,5-dihydro-4,4-dimethyl-3-carbomethoxyamino-2(3H)-furanone), 10b. Compound **10b** was obtained from pantoninelactone hydrochloride[20] in 78% yield. Mp 122°C. ^1H NMR ($CDCl_3$): δ 1.05 and 1.25 (s, 3H, CH_3); 3.70 (s, 3H, OCH_3); 4.05 (s, 2H, OCH_2); 4.45 (d, J = 8.0 Hz, 1H, CH); 5.70 (d, J = 8.0 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 19.5 and 22.7 (CH_3); 40.5 (CMe_2); 52.3 (OCH_3); 59.6 (CH); 76.5 (OCH_2); 157.2 and 174.9 (C=O). Anal. calcd for $C_8H_{13}NO_4$ (MW 187.20): C, 51.33; H, 7.00; N, 7.48. Found: C, 51.86; H, 7.20; N, 7.50.

Methyl N-Carbomethoxyvalinate, 10d.[22] Yield 90%. Mp 42°C (Lit.[22] 40°C). ^1H NMR ($CDCl_3$): δ 0.91 and 0.97

(d, 3H, CH_3); 2.16 (m, 1H, CH); 3.69 (s, 3H, N-CO_2CH_3); 3.75 (s, 3H, C-CO_2CH_3); 4.29 (dd, 1H, CH); 5.54 (br d, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 17.3 and 18.7 (CH_3); 31.0 (CH); 51.8 and 52.0 (OCH_3); 58.8 (CH); 156.7 and 172.5 (C=O).

Methyl N-Carbomethoxyphenylalaninate, 10e. Yield 89%. ^1H NMR ($CDCl_3$): δ 3.08 (ABX, 2H, CH_2Ph); 3.61 (s, 3H, N-CO_2CH_3); 3.68 (s, 3H, C-CO_2CH_3); 4.63 (m, 1H, CH); 5.51 (br d, 1H, NH); 7.13 (d, 2H, o-Ar H); 7.2-7.3 (m, 3H, m- and p-Ar H). ^{13}C NMR ($CDCl_3$): δ 37.8 (CH_2); 52.0 (OCH_3); 54.6 (CH); 126.8-129.0 (o-, m- and p-Ar C); 135.7 (ipso-Ar C); 156.1 and 171.9 (C=O).

Methyl N-Carbomethoxy-α,β-didehydrovalinate, 11d.[13,23] To a stirred and cooled (0°C) solution of methyl N-carbomethoxyvalinate (**10d**) (1.55 g, 8.0 mmol) in dry Et_2O (50 mL) were consecutively added t-BuOCl[21] (1.40 g, 13 mmol) and a solution of NaOMe (0.7 g, 13 mmol) in MeOH (2 mL). After removal of the ice bath, the solution was stirred for 15 min and then the solvent was removed in vacuo. The residue was taken up in $CHCl_3$ (50 mL), washed with H_2O (2 × 5 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded methyl N-carbomethoxy-N-chlorovalinate as a colourless oil (1.80 g, 100%). The crude oil (1.12 g, 5 mmol) was dissolved in Et_2O (50 mL), DBU (0.76 g, 5 mmol) was added and the solution was gently boiled under reflux during 2 h. After cooling in an ice bath, the precipitated DBU.HCl was filtered off and the filtrate was concentrated. The residue was taken up in $CHCl_3$ (40 mL), washed with diluted HCl (2 × 10 mL) and saturated $NaHCO_3$ (2 × 10 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded **11d** (0.87 g, 97%). Mp 66°C (Lit.[23] 67°C). ^1H NMR ($CDCl_3$): δ 1.89 (s, 3H, CH_3-syn); 2.16 (s, 3H, CH_3-anti); 3.71 (s, 3H, N-CO_2CH_3); 3.75 (s, 3H, C-CO_2CH_3); 6.17 (s, 1H, NH).

Methyl N-Carbomethoxy-α,β-didehydrophenylalaninate, 11e.[13] Compound **11e** was prepared from **10e** according to the procedure described for **11d**, and was recrystallized from EtOAc/*n*-hexane (1 : 1). Yield 80%. Mp 88°C. ^1H NMR ($CDCl_3$): δ 3.66 (s, 3H, N-CO_2CH_3); 3.82 (s, 3H, C-CO_2CH_3); 6.57 (s, 1H, NH) 7.2 - 7.4 (m, 4H, vinylic H and m-, p-Ar H); 7.52 (d, 2H, o-Ar H). ^{13}C NMR ($CDCl_3$): δ 52.4 (OCH_3); 52.6 (OCH_3); 124.3 (C-β); 128.4 - 129.6 (o-, m- and p-Ar C); 131.7 (C-α); 133.4 (ipso-Ar C); 154.5 (C=O); 165.6 (C=O). Anal. calcd for $C_{12}H_{13}NO_4$ (MW 235.24): C, 61.27; H, 5.57; N, 5.95. Found: C, 61.23; H, 5.27; N, 5.90.

Reduction of keto and imino compounds with racemic NADH model 4. General procedure. To a stirred and cooled (0°C) solution of $Mg(ClO_4)_2$ (45 mg, 0.2 mmol) in CD_3CN (0.4 mL) were consecutively added a solution of the keto or imino compound (0.2 mmol) in CD_3CN (0.3 mL) and a solution of racemic dihydropyridine **4** (40 mg, 0.2 mmol) in CD_3CN (0.3 mL). A ^1H NMR spectrum taken after 15 min showed that the reaction was complete (disappearance of vinylic proton signals of **4** (4.4 and 5.7 ppm); appearance of aromatic proton signals of **5** (7.7 and 8.5 ppm). Aqueous NH_4Cl (0.1 M, 4 mL) was added and the CD_3CN was evaporated. The residue was extracted with CH_2Cl_2 (2 × 8 mL). The organic layer was washed with H_2O (2 × 1 mL), dried over $MgSO_4$ and concentrated. The products were identified by ^1H NMR. Successful reductions (**6b,c** and **7a,b**) were repeated with optically active **4**.

Reduction reactions with optically active 4: To a stirred and cooled (-25°C) solution of $Mg(ClO_4)_2$ (45 mg, 0.20 mmol) in CD_3CN (0.2 mL) were consecutively added a solution of the keto or imino substrate (0.20 mmol) in CD_3CN (0.4 mL) and a solution of optically active **4** (40 mg, 0.20 mmol) in CD_3CN (0.4 mL). The stirred mixture was allowed to attain room temp within 1 h. Aqueous NH_4Cl (0.1 M 2 mL) was added and the CD_3CN evaporated below 30°C. The residue was partitioned between CH_2Cl_2 (8 mL) and H_2O (4 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by column chromatography on silica gel. The combined aqueous layers were concentrated in vacuo below 30°C. The residue was suspended in CH_3CN, filtered and the filtrate concentrated to give pyridinium perchlorate **5**. ^1H NMR (CD_3CN): δ 2.48 (s, 3H, C-4 Me); 2.60 (s, 3H, C-2 Me); 2.90 (s, 3H, *anti* N-Me); 3.20 (s, 3H, *syn* N-Me); 4.17 (s, 3H, N-1 Me); 7.65 (d, 1H, H-5); 8.55 (d, 1H, H-6). To a solution of **5** (20 mg) in CD_3CN (0.4 mL) was added (+)-Eu(hfc)$_3$ (100 mg) and the ee was calculated from the resolved *syn* N-Me ^1H NMR signals: δ 5.10 (*M*-**5**); 5.24 (*P*-**5**).

Ee determination of pantolactone, 9b. To a solution of **9b** (22.4 mg, 0.17 mmol) in C_6D_6 (0.4 mL) was added (+)-Eu(hfc)$_3$ (12.8 mg, 0.01 mmol) and the ee was calculated from the resolved ^1H NMR signals: *R*-**9b**: δ 1.01 (s, 3H, *anti* C-4 Me); 1.42 (s, 3H, *syn* C-4 Me); 3.62 (d, 1H, *anti* H-5); 3.73 (d, 1H, *syn* H-5); 4.69 (s, 1H, H-1). *S*-**9b** : 0.98 (s, 3H, *anti* C-4 Me); 1.30 (s, 3H, *syn* C-4 Me); 3.57 (d, 1H, *anti* H-5); 3.68 (d, 1H, *syn* H-5); 4.64 (s, 1H, H-1).

Ee determination of ethyl 2-hydroxy-3-methylbutyrate, 9c.[24] To a solution of **9c** (14.6 mg, 0.1 mmol) in C_6D_6 (0.5 mL) were added Et_3N (19 µL, 0.15 mmol), 4-dimethylamino-pyridine (2 mg, 0.01 mmol) and 2-chloro-(4*R*, 5*R*)-dimethyl-2-oxo-1,3,2-dioxaphospholane (13 µL, 0.1 mmol). The resultant suspension was filtered into an NMR tube

and the ee calculated from the ^{31}P NMR signals of the diastereomeric phosphates: *R*-butyrate: δ 14.86; *S*-butyrate: 14.80.

Ee determination of methyl N-carbomethoxyphenylglycinate, 10a. To a solution of **10a** (8 mg) in C_6D_6 (0.4 mL) was added (+)-Eu(hfc)$_3$ (23 mg) and the ee was calculated from the resolved C-CO_2CH_3 ^1H NMR signals: *S*-**10a**: 3.49; *R*-**10a** 3.58.

Ee determination of N-carbomethoxypantonine lactone, 10b.[25] To a stirred and cooled (0°C) suspension of $AlCl_3$ (9.0 mg, 0.07 mmol) in $ClCH_2CH_2Cl$ (0.1 mL) was added Et_3N (12.5 µL, 0.09 mmol). A solution of lactone **10b** (11.0 mg, 0.06 mmol) and *R*-(+)-α-methylbenzylamine (10 µL, 0.08 mmol) in $ClCH_2CH_2Cl$ (0.1 mL) was added and the mixture was stirred at room temp for 20 h. Ice-water (1 mL) was added and, after filtration, the filtrate was extracted with $ClCH_2CH_2Cl$ (2 x 2 mL). The organic layer was dried ($MgSO_4$) and concentrated affording an oil (8 mg, 43%). The ee was calculated from the ^1H NMR signals of the diastereomeric amides in C_6D_6: (-,+)-diastereomer: δ 0.78 (s, 3H, CH_3); 0.90 (s, 3H, CH_3); 1.20 (d, 3H, CH_3); 3.30 (s, 3H, OCH_3); 3.40 (br d, 2H, CH_2); 4.40 (d, 1H, CH); 5.25 (m, 1H, CH); 6.19 (d, 1H, NH); 6.62 (d, 1H, NH); 7.0 - 7.3 (m, 5H, Ph). (+,+)-diastereomer: δ 0.92 (s, 3H, CH_3); 1.08 (s, 3H, CH_3); 1.22 (d, 3H, CH_3); 3.25 (s, 3H, OCH_3); 3.50 (d, 2H, CH_2); 4.40 (d, 1H, CH); 5.25 (m, 1H, CH); 6.12 (d, 1H, NH); 6.52 (d, 1H, NH); 7.0 - 7.3 (m, 5H, Ph).

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