Asymmetric Reduction with L-Proline Amide Derivatives of 1,4-Dihydronicotinamide

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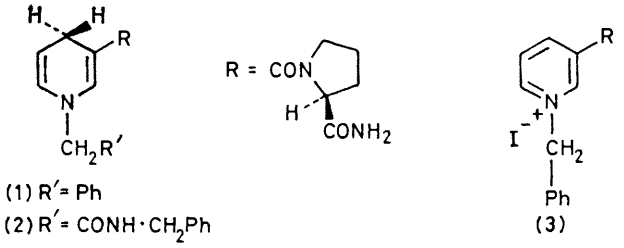
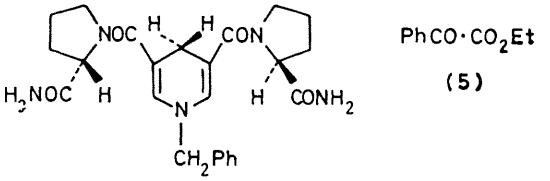
Summary The magnesium perchlorate-, zinc chloride-, and cobalt chloride-catalysed asymmetric reduction of ethyl benzoylformate with 1,4-dihydronicotinamides carrying an L-proline amide in the 3-carbamoyl side-chain afforded *R*-mandelate, the asymmetric yields being greatly affected by the catalyst metal species (5—83%).

The stereochemistry of NADH model reactions is interesting to bio-organic chemists who wish to characterise the nature of asymmetric induction for synthetic purposes The dependence of stereochemistry on the conversion,[1] the effect of the dimethyl groups in chiral 2,4-dimethyl-1,4-dihydronicotinamide on the product stereochemistry,[2] the peptide derivatives of an NADH model,[3] the incorporation of chiral 1,4-dihydronicotinamide into a crown ether ring,[4] and the electronic factors in asymmetric NADH model reactions have already been reported [5]

We now describe the asymmetric reduction of the prochiral carbonyl substrates (**5**) and (**6**) by the use of L-proline amide derivatives† of the 1,4-dihydronicotinamides (**1**), (**2**), and (**4**) using metal ion catalysts to give the corresponding alcohols with an asymmetric bias ranging from 5 to 83% enantiomeric excess (e e)



(1) R′= Ph
(2) R′= CONH·CH$_2$Ph
(3)



(4)

PhCO·CO$_2$Et
(5)

PhCO·CF$_3$
(6)

In a typical run, the 1,4-dihydronicotinamide (**1**) {u v λ_{max} (ethanol) 349 nm (ϵ 5040), $[\alpha]_D^{25}$ 67 6° (*c* 1 235, ethanol), 0 47 g, 1 43 mmol)}, anhydrous magnesium perchlorate (0 26 g, 1 14 mmol), and the substrate (**5**) (0 20 g, 1 14 mmol) in dry acetonitrile (13 ml), were stirred at 50 °C for 7 days under nitrogen After the usual work-up,[1b] the reduction product, ethyl mandelate (0 17 g, 84 0%), was isolated pure by preparative t l c (Kieselgel 60G, developed by benzene) {$[\alpha]_D^{25}$ −105 0° (*c* 1 11, chloroform), 83 2% e e }

As can be seen from the data in the Table, both the chemical and optical yields of ethyl mandelate attained a maximum with the simplest model (**1**), using magnesium perchlorate under the specified conditions Interestingly, the optical yield was greatly affected by replacing magnesium perchlorate with zinc and cobalt chloride (runs 1—3) as was the model reductant (**2**), which carries an additional amide group in the N-1 substituent In the latter case however, the highest optical yield was obtained in the cobalt chloride-catalysed reduction (run 6) which suggests the important role of metal ions in the stereochemical-determining transition state To our knowledge, this is the first observed example of a variation in the stereochemistry with metal ion species in NADH model reactions

In a relevant system,[1b] the initial addition of the oxidised NADH model to the reduction mixture remarkably improved the e e of the product mandelate In order to discover whether such a chelate control is operative here, a similar reduction was carried out with the oxidised form (**3**) initially added to this system which, unexpectedly, lowered the asymmetric bias to 42% (run 7) In addition, the use of a smaller amount of metal ion (compare runs 10 and 8) and of a binary solvent medium (methylene chloride–acetonitrile) of reduced polarity brought about a decline in the asymmetric yield (run 11) Asymmetric reduction of trifluoroacetophenone under the same optimised conditions using (**1**) resulted in barely 31% e e of the corresponding product alcohol (run 12)

Whitesell and Felman[6] noticed that the asymmetric bias was doubled by the introduction of C_2 symmetry in the alkylation of chiral enamines, so we designed and prepared another model compound (**4**) for testing the symmetry effect The observed e e (47% in run 13) was lower than that in run 9 in which the reductant (**1**) of C_1 symmetry was used under exactly the same conditions Accordingly,

Table Reduction of ethyl benzoylformate and trifluoroacetophenone with chiral NADH models

Run	NADH model	Substrate	Metal catalyst	Metal model ratio	Reaction T/°C	Reaction t/days	% Yield	$[\alpha]_D^{25}$/°(*c*)[a]	% e e[b] *R*
1	(1)	(5)	$Mg(ClO_4)_2$	0 80	r t	12	37 2	−99 7(0 824)	79 1
2	(1)	(5)	$ZnCl_2$	0 80	r t	12	8 4	−5 8(0 463)	4 6
3	(1)	(5)	$CoCl_2$	0 80	r t	12	5 0	−17 1(0 784)	13 5
4	(2)[c]	(5)	$Mg(ClO_4)_2$	0 74	r t	10	43 3	−42 8(2 289)	18 5
5	(2)	(5)	$ZnCl_2$	0 74	r t	13	18 0	−41 4(1 027)	32 9
6	(2)	(5)	$CoCl_2$	0 74	r t	13	23 2	−74 6(0 911)	59 1
7	(1)	(5)	$Mg(ClO_4)_2$	1 00[d]	50	7	70 6	−52 9(1 303)	41 9
8	(1)	(5)	$Mg(ClO_4)_2$	0 80	50	7	84 0	−105 0(1 113)	83 2
9	(1)	(5)	$Mg(ClO_4)_2$	1 50	60	2 83	58 4	−83 2(1 089)	66 3
10	(1)	(5)	$Mg(ClO_4)_2$	0 40	r t	0 50	36 1	−89 1(1 152)	70 6
11[e]	(1)	(5)	$Mg(ClO_4)_2$	0 80	50	0 042	70 7	−89 1(0 846)	70 6
12	(1)	(6)	$Mg(ClO_4)_2$	1 00	50	7	21 5	+3 9(1 082)[f]	31 0
13	(4)[g]	(5)	$Mg(ClO_4)_2$	1 50	60	2 83	33 8	−59 4(1 079)	47 1

[a] Measured in chloroform [b] Based on the reported maximum rotation of ethyl mandelate +126 2° in chloroform (R Roger *J Chem Soc* , 1932, 2168), and of phenyltrifluoromethylcarbinol, +13 4° in benzene (J Jurczak A Konowal, and Z Krawczyk *Synthesis*, 1977, 258) [c] U v λ_{max} 342 nm(ϵ 3950 ethanol) $[\alpha]_D^{25}$ 54 8° (*c* 3 508, ethanol) [d] Compound (**3**) added (m p 192—194 °C) [e] A mixture of acetonitrile (8 ml) and methylene chloride (4 ml) was used as solvent [f] Measured in benzene [g] U v λ_{max} 370 nm (ϵ 5920, ethanol), $[\alpha]_D^{25}$ 32 0° (*c* 0 75, ethanol)

† All the compounds reported herein gave i r , u v , and ^{1}H n m r spectra consistent with the assigned structures

such a symmetry element effect is not operative in this system.

Finally, the stereospecificity attained here with chiral NADH models may reasonably be due to the conformational rigidity of the transition state associated with pyrrolidine and dihydropyridine heteroatoms as well as the substrate carbonyl through the metal ion-mediated chelative interactions.

The importance of such a chelation control in systems involving heteroatoms has been of acute interest[7] in asymmetric syntheses.

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