Asymmetric Reductions catalysed by Chiral Shift Reagents

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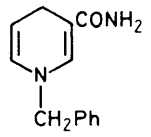
The reduction of methyl phenylglyoxylate to give optically active methyl mandelate by NADH models is catalysed by chiral shift reagents used as Lewis acids.

The reduction of activated aldehydes and ketones by NADH models is currently an active research area.[1] All systems and models described require $Mg(ClO_4)_2$ as a catalyst; in fact, it is always used in stoicheiometric amounts. Magnesium is thought to mimic the role of zinc which is present in the enzymatic system.[2] In the course of a study on asymmetric reduction of activated carbonyl groups by chiral NADH models, we checked the possibility of asymmetric induction by using achiral NADH models in the presence of chiral Lewis acids in catalytic amounts.

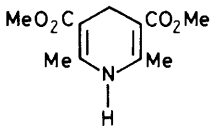
Table 1. Reduction of methyl phenylglyoxylate to methyl mandelate catalysed by lanthanide β-diketonates.

Entry	NADH model	Catalyst	Solvent (*t*/°C)	% Yield (time/day)	$[\alpha]_D$/°	% E.e.[e] (abs. conf.)
1	(**1a**)	$Eu(fod)_3$[a]	MeCN (70)	90 (7)		
2	(**1b**)	$Eu(fod)_3$[a]	MeCN (70)	39 (7)		
3	(**1a**)	$Nd(F_6acac)_3$[b]	MeCN (70)	68 (6)		
4	(**1b**)	$Nd(F_6acac)_3$[b]	MeCN (70)	69 (6)		
5	(**1a**)	$Eu(tfc)_3$[c]	CH_2Cl_2 (room temp.)	30 (8)	+58.5	44 (*S*)
6	(**1b**)	$Eu(tfc)_3$[c]	CH_2Cl_2 (room temp.)	28 (8)	+73.33	55 (*S*)
7	(**1b**)	$Eu(tfc)_3$[c]	MeCN (70)	>98 (3)	+33.8	25 (*S*)
8	(**1a**)	$Eu(hfc)_3$[d]	CH_2Cl_2 (room temp.)	20 (20)	+41.25	31 (*S*)
9	(**1b**)	$Eu(hfc)_3$[d]	MeCN (70)	75 (6)	+33.57	25 (*S*)

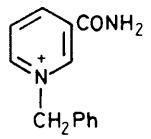
[a] Tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-octane-3,5-dionato)europium. [b] Tris-(1,1,1,5,5,5-hexafluoropentane-2,5-dionato)neodymium was prepared by the method in ref. 3. [c] Tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium. [d] Tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium. [e] From the optical rotation of pure (*S*)-methyl mandelate $[\alpha]_D^{30}$ + 133.9° (*c* 1.0, 95% aq. EtOH).



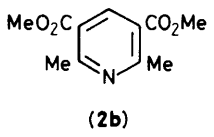
(**1a**)



(**1b**)



(**2a**)



(**2b**)

The reduction of methyl phenylglyoxylate to give methyl mandelate was first achieved by using *N*-benzyldihydronicotinamide (**1a**) or the dimethyl Hantzsch ester (**1b**) as NADH models in the presence of catalytic amounts of lanthanide β-diketonates [equation (1); Table 1; entries 1—4].†

$$PhCOCO_2Me + (\mathbf{1}) \xrightarrow{\text{Lewis acid}} Ph^*CH(OH)\text{–}CO_2Me + (\mathbf{2}) \quad (1)$$

We then studied chiral europium β-diketonates, shift reagents for the determination of enantiomeric excess (e.e.) by n.m.r. spectroscopy; the catalytic activity is somewhat lower at room temperature (entries 5, 6, and 8) but a significant degree of asymmetric induction did occur. The NADH models (**1a**) and (**1b**) behaved quite similarly; the most important feature is the nature of the chiral ligand, the trifluoromethyl ligands leading to better inductions than the heptafluoropropyl ones. In all cases, the chiral ligands derived from (+)-camphor and complexes led to methyl mandelate with excess of the (*S*)-enantiomer.

This is the first example of the use of shift reagents as catalysts in organic synthesis;[4] the only previous reports of chiral shift reagents concern the hetero Diels–Alder reaction.[5]

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† Reductions were carried out under nitrogen in inactinic glass flasks on a 2 mmol scale with a 1 : 1 : 0.1 molar ratio of substrate : NADH model : catalyst; dried and deaerated acetonitrile (20 ml) was added through a septum. After the appropriate heating time, the mixture was quenched with methanol (2 ml) and concentrated, and methyl mandelate was isolated by preparative layer chromatography (silica gel with $CHCl_3$–Et_2O, 95 : 5). Optical rotations were measured in ethanol, 95 °C.

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