Homogeneous Catalytic Asymmetric Hydrogenolysis of Sodium Epoxysuccinate: the First Example of Asymmetric Hydrogenolysis of an Epoxide

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As the first example of asymmetric hydrogenolysis of an epoxide, the homogeneous catalytic asymmetric hydrogenolysis of sodium epoxysuccinate was accomplished by using rhodium catalysts containing chiral phosphine ligands.

Homogeneous asymmetric catalysis is one of the most important breakthroughs in organic synthesis in the last two decades. The wide application of this technology is reflected both in the large number of publications in the literature and in its successful uses in commercial processes.[1–4] In most previously studied asymmetric catalysis systems, there is a critical step involving the bond formation of the chiral centres produced.[1] In contrast, asymmetric catalytic synthesis based on a bond-breaking process is relatively rare.[5,6]

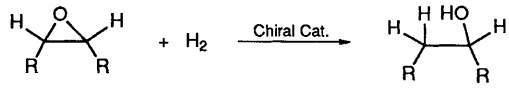
In this paper we present the first example of the asymmetric catalytic hydrogenolysis of an epoxide, in which the chiral product is formed *via* a critical *bond-breaking* process (Scheme 1). The focus of this paper is on the asymmetric catalytic hydrogenolysis of sodium epoxysuccinate (Scheme 2). The L- or D-malic acid products are useful chiral synthons for a variety of products.[2]

In our initial study of this reaction we chose rhodium–phosphine complexes as catalyst precursors because of the amount of information in the literature on their synthesis, characterisation and wide applications in asymmetric hydrogenation reactions.[1] Since the sodium salt of epoxysuccinic acid is not soluble in most organic solvents, mixtures of water and polar organic solvents (such as methanol) are usually used as the reaction medium.

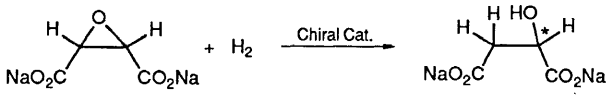
Our initial experimental results indicate that most commonly used (bisphosphine)rhodium (I) catalysts are active for the hydrogenolysis of sodium epoxysuccinate under mild conditions (ambient temperature, 5 atm of H_2 pressure).

The hydrogenolysis reaction is quite chemoselective. Except for the small amount of sodium tartrate which is generated by the hydrolysis of the starting material, virtually no other side-product is observed. When a chiral phosphine ligand is used in the catalyst system, enantioselectivity in the malic acid product is observed. The highest optical yield in our screening study is 62%, when Rh(nbd) (npepnnp)Cl† is used as catalyst precursor.‡ To our knowledge, this is the first example of asymmetric catalytic hydrogenolysis of an epoxide. The results of the screening of commonly used chiral rhodium catalysts are summarized in the Table 1. Several notable observations in this study are: (*i*) the enantioselectivity of the catalyst systems is independent of hydrogen pressure within a practical range (1 to 200 atm). (*ii*) The rate of reaction is faster under higher H_2 pressure. (*iii*) The enantioselectivity is lower at higher reaction temperature. (*iv*) When an alcohol such as methanol is used as a cosolvent, hydrogenolysis can take place without an external source of H_2; the H_2 source in this case is probably the methanol solvent.[8] These results have not been optimised and there is good potential for further improvement.

Although a detailed mechanistic study is not yet complete, several observations during this study did shed some light on a possible mechanism for this reaction. When sodium epoxysuccinate was allowed to react with D_2 in a D_2O–MeOD solvent mixture with a Rh catalyst, the resulting product clearly showed the incorporation of deuterium on the β-carbon (Scheme 3). ^1H NMR of this deuteriated product showed the α-H at δ 4.33 and a β-H at δ 2.69. The β-H at δ 2.41 in sodium malate was missing owing to its replacement by deuterium. ^{13}C NMR (proton-decoupled) also showed the β-carbon at δ 45.3 with a C–D coupling constant of 19.7 Hz.



Scheme 1



Scheme 2

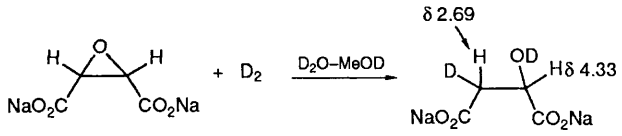
Table 1 A comparison of catalysts for the asymmetric hydrogenolysis of sodium epoxysuccinate[a]

Catalyst[b]	E.e. (%)
[Rh(nbd)(npepnnp)]BF_4	62
[Rh(nbd)(phpnnp)]BF_4	37
[Rh(nbd)(dipamp)]BF_4	7
[Rh(nbd)(skewphos)]BF_4	28
[Rh(nbd)(diop)]BF_4	30
[Rh(nbd)(diphol)]BF_4	33
[Rh(nbd)(binap)Cl	20
[Rh(nbd)(bppm)]BF_4	23
Rh(nbd)(prophos)Cl	18
[Rh(nbd)(chiraphos)]BF_4	6
[Rh(nbd)(cycphos)]BF_4	23

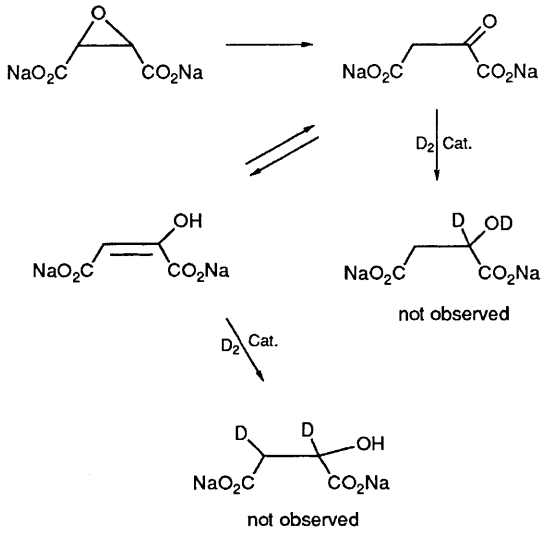
[a] Reaction conditions: 25°C, 80 psig H_2, 14 h; substrate : catalyst, 50 : 1 to 500 : 1; solvent, mixture of H_2O–MeOH (1 : 2 ~ 1 : 3, v : v). [b] Abbreviations used: dipamp = (*R*,*R*)-1,2-bis[(2-methoxyphenyl)-phenylphosphino] ethane; skewphos = (−)-(2*S*, 4*S*)-2,4-bis(diphenylphosphino)pentane; diop = 4,5-bis[(diphenylphosphinyl)-methyl]-2,2-dimethyl-1,3-dioxolane; diphol = 4,5-bis[(5*H*-dibenzophosphol-5-yl) methyl]-2,2-dimethyl-1,3-dioxolane; binap = 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl; bppm = (2*S*, 4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphino-methylpyrrolidine; prophos = (*R*)-(+)-1,2-bis(diphenylphosphino)-propane; chiraphos = (*S*,*S*)-2,3-bis(diphenylphosphino)butane; cycphos = 1,2-bis(diphenylphosphino)-1-cyclohexylethane.

† Abbreviations used: nbd = norbornadiene; npepnnp = *N*,*N*′-bis[(*S*)-α-(1-naphthyl)ethyl]-*N*,*N*′-bis(diphenylphosphino)ethylene-diamine.[7]

‡ GLC method[9] for the determination of product enantiomeric excess (e.e.). The malic acid (or the corresponding salt) product was converted to the dimethyl ester by stirring in HCl-saturated methanol solution overnight. The small amount of water generated in the esterification was removed with 2,2-dimethoxypropane (5–10 ml). Evaporation of all the solvent in a rotary evaporator generated the dimethyl ester. For GLC analysis, 5–10 mg of sample was heated with isopropyl isocyanate (1 ml) at 100°C for 1 h. The mixture was evaporated to dryness at ambient temperature with a stream of N_2 gas. The residue was diluted with methylene chloride (0.5 ml). The GLC was performed on a Varian 3700 chromatograph with a Chirasil-Val-L column (25 meters) at 140 °C (isothermal). Excellent baseline separation was achieved. The method was calibrated with mixtures of L- and D-malic acid of known e.e.s and was found to be accurate within ±1%.



Scheme 3



Scheme 4

This deuterium labelling study has revealed an important aspect of the epoxide hydrogenolysis reaction. The epoxide hydrogenolysis proceeds *via* a direct C–O bond cleavage instead of an epoxide to ketone isomerisation followed by ketone or enol hydrogenation (Scheme 4). The absence of deuterium on the α-carbon of the malic acid product clearly excludes the possibility of this reaction as a dominant route in the epoxide hydrogenolysis.

Epoxides without carboxy functionalities, *e.g.* styrene oxide, are not hydrogenolysed under similar conditions, indicating that the hydrogenolysis reaction is assisted by the coordination of the carboxy group. This is probably due to the weak coordinating effect of epoxides which cannot sustain a significant catalyst–substrate interaction. The presence of a carboxylate anion helps to bring the substrate to the catalyst centre *via* the coordination of the carboxy group. The origin of the enantioselectivity of the catalyst system probably resides in the influence of the chiral phosphine ligands on the coordination of the epoxide to the Rh centre. More in-depth studies to elucidate the exact mechanism are in progress.

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