Chemoenzymatic synthesis of a novel ligand for rhodium-catalysed asymmetric hydrogenation

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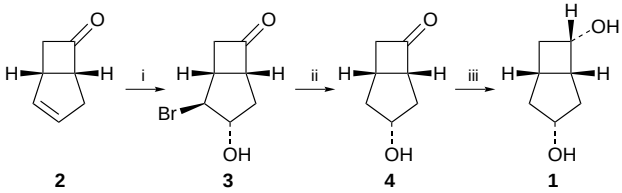
The hydrogenation of alkenes 7a–g using a chiral rhodium catalyst 6 (based on a bicyclo[3.2.0]heptane framework) takes place to give the phenylalanine derivatives 8a–g with remarkably high stereoselectivity (59–92% ee).

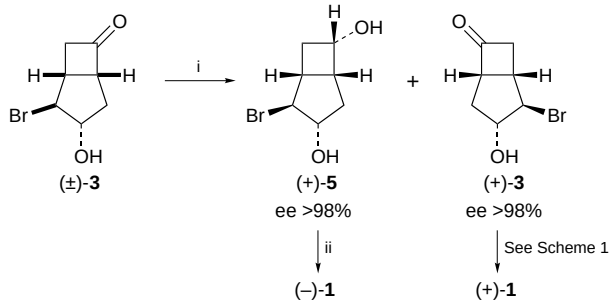
The relatively inflexible, angular shape of the bicyclo[3.2.0]heptane ring system means those substituents on the concave (*endo*) face of the molecule are positioned close together in space. Molecular modelling studies suggested that the hydroxy groups in bicyclo[3.2.0]heptan-3-*endo*, 6-*endo*-diol would be positioned in such a way that derivitization to form bis(diarylphosphinyl) groups may provide a novel chiral ligand for organorhodium-catalysed hydrogenation reactions.[1]

Optically pure diol **1** may be prepared from (−)-bicyclo[3.2.0]hept-2-en-6-one[2] **2** by the route described in Scheme 1. Thus, formation of the bromohydrin[3] **3**, hydrodebromination (furnishing **4**) and stereocontrolled reduction by delivery of hydride ion from the more exposed *exo*-face afforded the diol **1** in 50% overall yield.



Scheme 1 *Reagents and conditions*: i, *N*-Bromosuccinimide, acetone, H_2O, 6 h, 80%; ii, Bu_3SnH, AIBN, toluene, heat, 82%; iii, $NaBH_4$, MeOH, −78 °C, 76%

However, since both enantiomers of the diol **1** were required as intermediates to the chiral ligands it seemed more sensible to perform a kinetic resolution further along the synthetic sequence. Kinetic resolution of the racemic alcohols **1** and **4** using lipase-catalysed acylation reactions were unsuccessful. The bromohydrin (±)-**3** was resolved by employing *Pseudomonas fluorescens* lipase in vinyl acetate[4] but a more satisfactory



Scheme 2 *Reagents and conditions*: i, Yeast, H_2O, 6 h, 100% crude yield; ii, Bu_3SnH, AIBN, toluene, heat, 86%

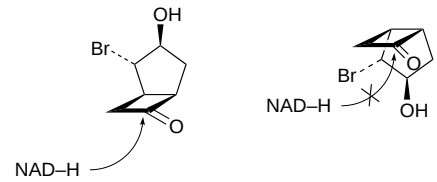


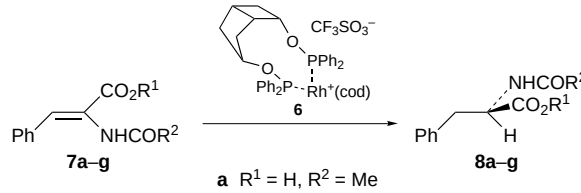
Fig. 1 Delivery of hydride to **3**

and efficient biocatalytic method utilised a yeast-catalysed highly enantio- and stereo-selective reduction of racemic ketone **3** (Scheme 2).

It is noteworthy that reduction takes place to give only the (6*S*)-bromodiol **5**, unlike the corresponding non-enantioselective bioreduction on the parent compound **2** which gave (1*S*,5*R*,6*S*)-bicyclo[3.2.0]hept-2-en-6-*endo*-ol and (1*R*,5*S*,6*S*)-bicyclo[3.2.0]hept-2-en-6-*exo*-ol in almost equal quantities.[5] Presumably delivery of the hydride ion from the concave face of (+)-**3** is prohibited by unfavourable steric interactions within the active site of the dehydrogenase (Fig. 1).

The diol (−)-**1** was converted into the rhodium complex **6** using standard methodology, and this complex was used to catalyse the asymmetric hydrogenation of compounds **7a–g** to afford the (*R*)-phenylalanine derivatives **8a–g** in excellent yield and moderate to good enantiomeric excess (Table 1). Indeed,

Table 1 Asymmetric hydrogenation of some enamide esters, **7a–g**



a R^1 = H, R^2 = Me
b R^1 = R^2 = Me
c R^1 = H, R^2 = Ph
d R^1 = Me, R^2 = Ph
e R^1 = Pr^i, R^2 = Ph
f R^1 = Bu^t, R^2 = Ph
g R^1 = Pr^i, R^2 = Me

Starting material	Product	Enantiomeric excess[a] (%)	Yield (%)
7a	**8a**	81	> 95
7b	**8b**	73	> 95
7c	**8c**	76	> 95
7d	**8d**	59	> 95
7e	**8e**	61	> 95
7f	**8f**	66	> 95
7g	**8g**	77	> 95

[a] Estimation by HPLC using a Chirasil-Val column.

Table 2 Asymmetric hydrogenation of enamide ester **7a**

T/°C	Volume of solvent/ml	Enantiomeric excess of product (%)
25	15	81
12	15	83.5
2	15	87.5
25	10	88
25	5	91.5
2	5	92.5

given the subtlety of the chirality of the bicyclo[3.2.0]heptane framework, the observed level of enantioselectivity is surprisingly high. The reaction rates were perfectly satisfactory (the reaction was completed in 2–10 min) using 1 mmol substrate and 0.01 mmol catalyst in MeOH (15 ml) under an atmosphere of hydrogen. Using similar conditions, itaconic acid was reduced to (2*S*)-methylsuccinate in quantitative yield and 80.5% ee.

The reaction conditions for the asymmetric reduction of substrate **7a** were investigated further. Lowering the temperature of the reaction and increasing the concentration of the reactants both proved to be beneficial, with a satisfactory 92.5% ee for product **8a** being obtained at low temperature and high concentration (Table 2).† The concentration effect may be explained by the effect on the rate of delivery of hydrogen to the catalyst, which will be slower in the reactions using small amounts of solvent. Thus, in the more concentrated solution the catalyst may experience a lower 'effective' hydrogen concentration.[6]

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Footnotes and References

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† Experimental procedure for the asymmetric hydrogenation of compound **7a**. A mixture of complex **6** (8 mg, 0.01 mmol) and α-acetamidocinnamic acid **7a** (205 mg, 1 mmol) was cooled (2 °C) under a nitrogen atmosphere. Dry, degassed MeOH (5 ml) was added to the mixture, which was stirred vigorously. The flask was evacuated, filled with hydrogen and stirred for 10 min. A 0.5 ml aliquot was removed from the reaction vessel and treated with Me_3SiCHN_2 (2.0 M solution in hexane) in order to convert the acid to the methyl ester. The solvent was evaporated and the residue was treated with diethyl ether; filtration and evaporation gave a crude residue (21 mg). The enantiomeric excess of the product **8a** was determined to be 92.5% by chiral gas chromatography, using a Chirasil-Val-III column.

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