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Suitably designed chiral amino alcohols: synthesis, resolution and application to the catalytic enantioselective reduction of aryl alkyl ketones

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Abstract: The amino alcohol *rac*-1-(1,2,3,4-tetrahydroisoquinoline-1-yl)-cyclopentanol was resolved via its O,O′-dibenzoyl-tartaric acid salt. These enantiomeric amino alcohols were used in the enantioselective reduction of prochiral aryl alkyl ketones. The resulting secondary alcohols were obtained in high enantiomeric excess. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Introduction

Asymmetric synthesis has evolved rapidly over recent years. Preparation of chiral auxiliaries from homochiral amino acids and their application has been intensively investigated.[1] The use of such natural products imparts a limitation in their structural modification. Furthermore there is often only one enantiomer available in sufficient amounts. The synthesis of both enantiomeric forms is important for our investigations about intramolecular vs. intermolecular induction in the catalytic reduction of chiral compounds.[2] The different configurations of the catalysts are necessary to control the stereochemistry of the products. In this context, the development of chiral compounds, which can be suitably designed for each asymmetric process, has recently been drawing considerable attention. Some successful examples have been reported.[3]

In this paper, we wish to report a new and efficient method for the synthesis of novel enantiomerically pure rigid amino alcohols via resolution of the racemic modification and their application in the enantioselective catalytic reduction of prochiral ketones.

Results and discussion

The target chiral ligand for the catalytic enantioselective reduction of ketones is a β-amino alcohol with a cyclopentanol building block and an aromatic system. Rigid amino alcohols containing a five membered ring system derived from amino acids have been used successfully in stereoselective applications.[2,4] For this reason, the racemic amino alcohol *rac*-**1** was prepared according to the literature.[5] 1,2,3,4-Tetrahydroisoquinoline was transformed into the stabilized 1-carbanion and addition of cyclopentanone gave the desired benzylic substituted product *rac*-**1** (Scheme 1).

In the next step, optically active acids, such as (*R*)-mandelic acid and (+)-O,O′-dibenzoyl-D-tartaric acid, were checked for the separation of the enantiomers by fractional crystallization of the diastereomeric salts. The racemic compound *rac*-**1** was then resolved by selective crystallization of the amino alcohol as its (+)-O,O′-dibenzoyl-D-tartaric acid salt. The first crystallization from ethanol gave a salt containing predominantly the (+)-enantiomer of **1**, which crystallized well. After recrystallization, the amino alcohol (+)-**1** was isolated in 50% (25% wrt the racemate) yield with an enantiomeric excess of (+)-**1** of >99%.

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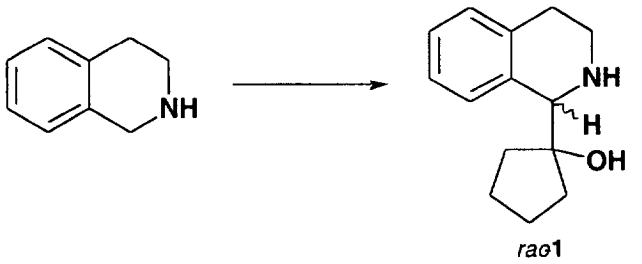
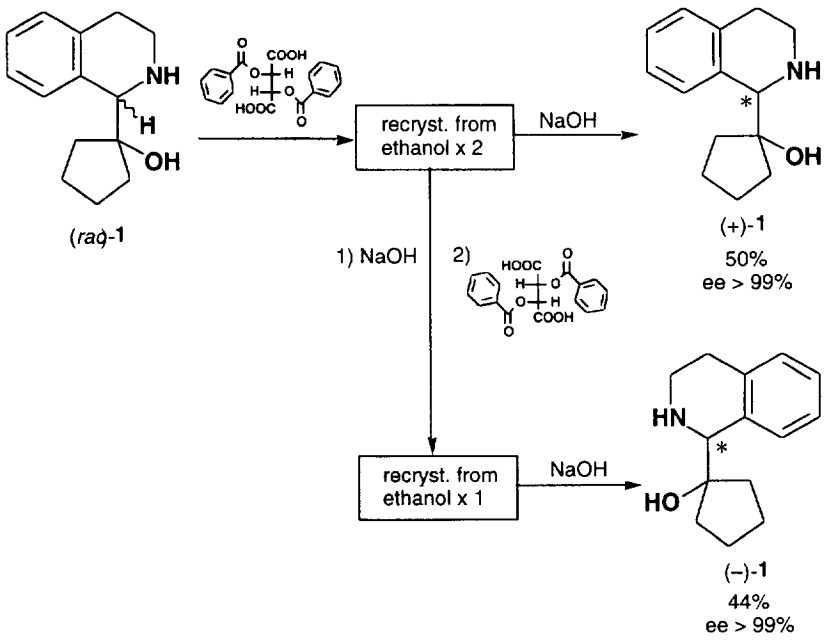


Scheme 1.

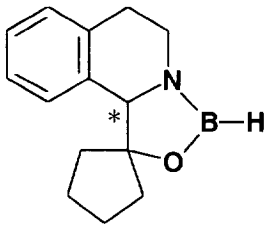


Scheme 2.

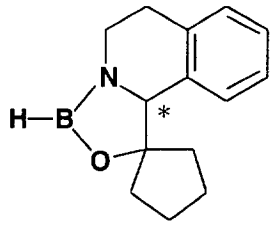
The enantiomeric excess of (+)-**1** was determined by ^{1}H-NMR-analysis using (*R*)-mandelic acid as chiral solvating agent[6] (CSA). The proton at the stereogenic center of the amino alcohol shows a chemical shift nonequivalence of 0.16 ppm ($CDCl_3$).

The (−)-enantiomer of **1** was isolated from the mother liquor of the described crystallization. The remaining solid was treated with 2 N NaOH to liberate the amino alcohol **1**, enriched with the (−)-enantiomer. Reaction of (−)-O,O′-dibenzoyl-L-tartaric acid with this compound gave the salt after only one crystallization with an enantiomeric excess of (−)-**1** of >99%. The free amino (−)-**1** alcohol was isolated from the corresponding salt by treatment with 2 N NaOH in 44% yield (22% wrt the racemate). According to this procedure, both enantiomers of **1** are easily available in good yield and high enantiomeric excess (Scheme 2).

Next the homogenous catalytic reduction of aromatic ketones with *in situ* formed oxazaborolidine catalysts (*S**)-**2** and (*R**)-**2** was investigated. Conversion of the β-amino alcohols (+)-**1** and (−)-**1** to oxazaborolidines **2** was accomplished by treating with BH_3·THF and used without isolation or purification (Scheme 3).

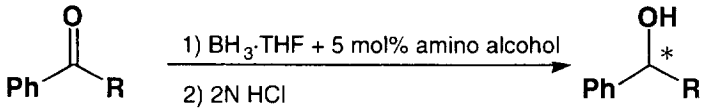


(*S**)-**2**



(*R**)-**2**

Scheme 3.



Scheme 4.

Table 1. Catalytic enantioselective reduction of aromatic ketones

Amino Alcohol	Oxazaborolidine[a)]	Ketone	Yield [%]	*ee* [%][b)]	Config.[c)]
(+)-**1**	(*S**)-**2**	$PhCOCH_3$	94	88	*R*
(−)-**1**	(*R**)-**2**	$PhCOCH_3$	94	88	*S*
(+)-**1**	(*S**)-**2**	$PhCOCH_2CH_3$	92	76	*R*
(−)-**1**	(*R**)-**2**	$PhCOCH_2Cl$	93	88	*R*

a) Prepared in situ (see experimental section) b) Determined by chiral GC analysis (SGE Cydec-B, chiral). c) The absolute configuration of the obtained secondary alcohol was determined via chiral GC analysis by comparison with authentic samples.

Acetophenone, propiophenone and ω-chloroacetophenone were used as model substrates for the enantioselective catalytic reduction with borane (Scheme 4). The enantiomeric excess (*ee*) of the resulting alcohols were determined by chiral GC analysis. The results of the reduction with the oxazaborolidines (*S**)-**2** and (*R**)-**2** are listed in Table 1.

The reduction of several kinds of prochiral ketones gave the corresponding alcohols in high enantiomeric excesses up to 88% *ee*. In summary, the amino alcohols (+)-**1** and (−)-**1** have been synthesized via resolution of the racemic compound *rac*-**1**. The corresponding oxazaborolidines **2** are highly effective catalysts in enantioselective reductions of several aryl alkyl ketones. This method offers the possibility to synthesize suitably designed chiral auxiliaries by variation of the amines and electrophiles. The preparation of other new chiral amino alcohols is under investigation.

Experimental section

All reactions were carried out in oven dried glassware, under argon atmosphere and using anhydrous solvents. Melting points were taken on a melting point apparatus according to Dr. Linström and are uncorrected. Optical rotations were measured on a Perkin–Elmer automatic polarimeter. IR spectra were recorded on a Philips PU 9706 spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were

registrated on a Bruker AM 300 spectrometer using TMS as internal standard. Mass spectra were recorded on a Finnigan-MAT 212 (data system 300; CI, *i*-butane). Elemental analyses (C, H, N) were performed on a Carlo Erba Stumentalione (MOD 1104) analyzer. Gas chromatography (GC) was performed using a Shimadzu (GC-15A) instrument, 25 m column: SGE Cydex-B (chiral), w_i=0.25 mm, film thickness 0.25 µm, 1 µl product in *n*-hexane, detection: FID, carrier gas: nitrogen. Commercially available chemicals were used.

The racemic amino alcohol *rac*-1-(1,2,3,4-tetrahydroisoquinoline-1-yl)-cyclopentanol *rac*-**1** was prepared by the method reported in the literature,[5] mp 103°C (lit. [5] 102–103°C).

(+)-1-(1,2,3,4-Tetrahydroisoquinoline-1-yl)-cyclopentanol (+)-1

1.03 g *rac*-**1** (4.7 mmol) and 0.6 g (+)-O,O′-dibenzoyl-D-tartaric acid·H_2O (1.6 mmol) were dissolved in 90 ml ethanol on heating. While slowly stirred, the mixture was cooled to room temperature. The suspension was kept at −20°C for 14 days. The colourless crystals formed were filtered off, washed with two portions of ethanol (5 ml each) and dried. The colourless solid was recrystallized from 60 ml of ethanol and the mother liquor of the crystallisation was used to isolate the other enantiomer (see below). Next, the resulting salt was treated with 20 ml 2 N NaOH and 20 ml CH_2Cl_2 and stirred for 1 hour. The aqueous layer was extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Yield: 0.26 g, (50%); m.p. 128–129°C; $[\alpha]_{20}^{D}$=+34.1 (*c*=0.25, $CHCl_3$); IR (KBr): ν=3320–3200 cm^{-1} (NH, OH); ^{1}H-NMR ($CDCl_3$): δ=1.53–1.86 (m, 8H, $-(CH_2)_4-$), 2.57–3.31 (m, 6H, $-(CH_2)_2-$, NH, OH), 4.08 (s, 1H, CH–N), 7.08–7.26 (m, 4H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ=22.91, 23.94, 37.46, 38.46 ($-(CH_2)_4-$), 30.27 (C-4), 40.94 (C-3), 61.93 (C–OH), 84.50 (C-1), 125.34, 126.37, 128.16, 129.04, 135.60, 137.12 (aromatic C); MS (CI, *i*-butane): 218 (MH^+, 100%); Anal. calc. for $C_{14}H_{19}NO$ (217.3): C, 77.38; H, 8.81; N, 6.45. Found: C, 77.14, H, 8.75; N, 6.19.

(−)-1-(1,2,3,4-Tetrahydroisoquinoline-1-yl)-cyclopentanol (−)-1

The mother liquor of the crystallisation of the salt formed from (+)-**1** and (+)-O,O′-dibenzoyl-D-tartaric acid·H_2O was evaporated and treated with 20 ml 2 N NaOH and 20 ml CH_2Cl_2. After stirring for 1 hour the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 ml). The combined organic layers was dried ($MgSO_4$) and evaporated under reduced pressure. The resulting solid and 0.38 g (−)-O,O′-dibenzoyl-L-tartaric acid·H_2O (1.0 mmol) were dissolved in 20 ml ethanol on heating. After cooling to room temperature the mixture was kept at −20°C for 7 days. The colourless crystals were filtered of. This salt was treated with 15 ml 2 N NaOH and 15 ml CH_2Cl_2. After extraction of the aqueous layer the organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Yield: 0.23 g, (44%); m.p. 128–129°C; $[\alpha]_{20}^{D}$=−35.2 (*c*=0.25, $CHCl_3$); IR (KBr): ν=3320–3200 cm^{-1} (NH, OH); ^{1}H-NMR ($CDCl_3$): δ=1.53–1.86 (m, 8H, $-(CH_2)_4-$), 2.56–3.31 (m, 6H, $-(CH_2)_2-$, NH, OH), 4.08 (s, 1H, CH–N), 7.08–7.27 (m, 4H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ=22.93, 23.95, 37.47, 38.47 ($-(CH_2)_4-$), 30.27 (C-4), 40.95 (C-3), 61.94 (C–OH), 84.51 (C-1), 125.36, 126.38, 128.16, 129.05, 135.58, 137.12 (aromatic C); MS (CI, *i*-butane): 218 (MH^+, 100%); Anal. calc. for $C_{14}H_{19}NO$ (217.3): C, 77.38; H, 8.81; N, 6.45. Found: C, 77.21, H, 8.67; N, 6.16.

Determination of the enantiomeric excess of (+)-1 and (−)-1

For the determination of the enantiomeric excess 0.06 mmol amino alcohol (+)-**1** or (−)-**1** and 0.07 mmol (*R*)-mandelic acid were dissolved in 1 ml $CDCl_3$. This solution was used directly for the ^{1}H-NMR analysis. Resonances for the proton at the stereogenic center of *rac*-**1**: δ=4.23 ppm and 4.39 ppm (Δδ=0.16 ppm). We used the racemic compound *rac*-**1** to prove this method and obtained an enantiomeric ratio of 50:50. Based on this method the enantiomeric excess of (+)-**1** and (−)-**1** was established to be >99%.

Enantioselective reduction of aromatic ketones (typical procedure)

The oxazaborolidines (*S**)-**2** and (*R**)-**2** were prepared *in situ* from 0.05 g of the amino alcohols (+)-**1** and (−)-**1** (0.25 mmol) in 5 ml of dry THF and 5.25 ml of a 1 M $BH_3 \cdot THF$ solution (5.25 mmol) at −70°C. The reaction mixture was stirred for 2 hours at 30°C. A solution of the ketone (5 mmol) in 5 ml dry THF was added with stirring to this solution within 60 min at 30°C. After stirring for 3 hours at this temperature the reaction mixture was hydrolyzed with 12.5 ml 2 N HCl and extracted three times with 10 ml *tert*-butylmethyl ether. The combined organic layers were successively washed with 12.5 ml 2 N NaOH and 10 ml NaCl solution, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to distillation (Kugelrohr) under vacuum to afford the pure alcohol. The obtained secondary alcohols were analysed by chiral gas chromatography (GC) analysis. The absolute configuration of the products was determined via chiral GC analysis by comparison with authentic samples. 1-Phenylethanol: temperature programme 100°C, 5°C/min up to 140°C, 5 min isotherm, retention times (*R*)-1-phenylethanol: 7.98 min, (*S*)-1-phenylethanol: 8.12 min; 1-phenyl-1-propanol: temperature programme 100°C, 4°C/min up to 125°C, 10 min isotherm, retention times (*R*)-1-phenyl-1-propanol: 13.12 min, (*S*)-1-phenyl-1-propanol: 13.46 min; 2-chloro-1-phenylethanol: temperature programme 100°C, 5°C/min up to 150°C, 10 min isotherm, retention times (*S*)-2-chloro-1-phenylethanol: 15.55 min, (*R*)-2-chloro-1-phenylethanol: 15.79 min.

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