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cis-2-Amino-1-acenaphthenol: Practical Resolution and Application to the Catalytic Enantioselective Reduction of Ketones

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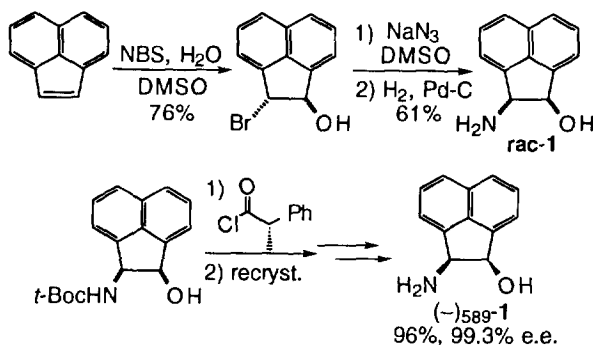
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Abstract: The chiral amino alcohol, *cis*-2-amino-1-acenaphthenol, was resolved via its (*R*)-2-phenylpropionic acid salt. This amino alcohol was used as the precursor of a chiral oxazaborolidine, which was an efficient chiral catalyst in the asymmetric reduction of prochiral ketones.

In recent years, the development of chiral auxiliaries and catalysts has received much attention. Many of chiral auxiliaries and catalysts are derived from natural homochiral compounds, but limitations in their structural modification is sometimes an obstacle to achieve an efficient asymmetric process. This problem is solved by using artificial chiral compounds, which can be suitably designed for each asymmetric process, and in fact some successful examples have been recently reported.¹

In the preparation of well-designed artificial chiral auxiliaries, the resolution of their racemic modifications is thought to be one of the most practical methods, because complicated multi-step transformations can be avoided to minimize the loss of optically active target compounds. In this context, the development of the method for the resolution of a particular racemic modification is essential.² In our study concerning the development of artificial chiral auxiliaries,³ racemic *cis*-2-amino-1-acenaphthenol (*rac*-1) was found to be efficiently prepared and resolved as shown in Scheme 1.⁴ However, this resolution method requires several protection and deprotection steps and therefore a more facile and practical method was desired. In this communication, we wish to report a new and efficient method for the resolution of *rac*-1 and application of enantiomerically pure **1** to the catalytic asymmetric reduction of prochiral ketones.

Scheme 1



At first, we examined the resolution of *rac-1* via diastereomeric salts with several kinds of chiral acids, such as camphorsulfonic acid, mandelic acid, tartaric acid, malic acid, and 2-phenylpropionic acid; the diastereomeric salts were recrystallized from water, ethanol, or their mixture. Among the resolving agents examined, 2-phenylpropionic acid was the most effective. Examination of several conditions for recrystallization (Table 1) revealed that diastereomeric salt **2a** was preferentially obtained in 37% yield with 98% d.e., when a 2:1 mixture of water and ethanol was used as a solvent (Entry 3). The d.e. value of the salt was determined by a chiral HPLC analysis (Daicel Chiralcel OD) of the *N,O*-diacetylated product **3**, which was obtained by treatment of the diastereomeric salt with acetic anhydride and pyridine. The absolute configuration was determined by comparison of the retention time of **3** on chiral HPLC with the reported values.⁴

On the other hand, recrystallization of a mixture of the diastereomeric salts from ethyl acetate gave the opposite diastereomer **2b** predominantly (Entry 5). Thus, upon combining the two recrystallization processes using two different kinds of solvents, both enantiomers of **1** became available very efficiently (Scheme 3). In this resolution, 2-phenylpropionic acid could be recovered almost quantitatively from each diastereomeric salt.

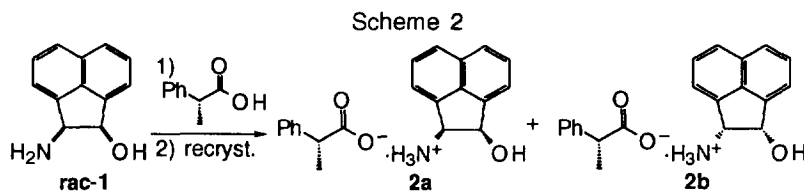
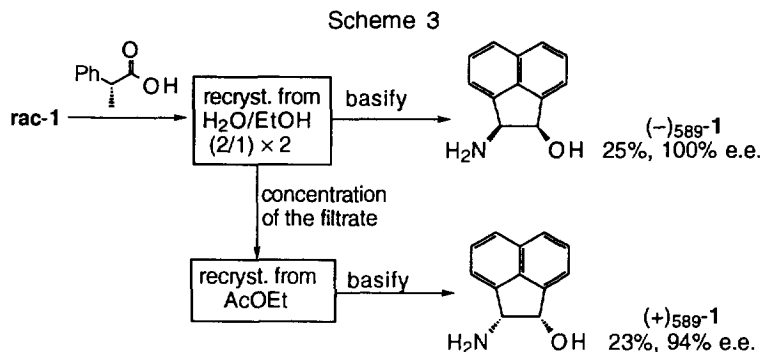
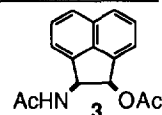


Table 1 Optimization of Recrystallization Conditions

Entry	Solvent	Volume of solv./ml ^{a)}	Yield/% ^{b)}	2a:2b ^{c)}
1	EtOH	5	18	56:44
2	H ₂ O/EtOH (2/1)	10	52	66:34
3		20	37	99: 1
4	H ₂ O/EtOH (4/1)	25	30	94: 6
5	AcOEt	17	81	39:61

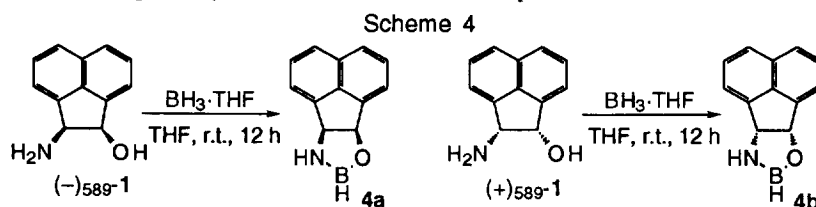
a) 0.5 g of salt was used in each entry.

b) Based on *rac-1*. c) Determined by a chiral HPLC analysis (Daicel Chiralcel OD) of **3** obtained by treatment of **2** with Ac₂O and Pyridine.



Next we applied this chiral amino alcohol in a catalytic asymmetric synthesis. Amino alcohol **1** has a structural characteristic that the orientation of the amino and hydroxyl groups is fixed due to the fused ring system of acenaphthene. Thus, we considered that this structural feature would be suitable to construct a rigid transition state for the catalytic enantioselective reduction of ketones by borane. On the basis of this consideration, we used this amino alcohol as the precursor of a chiral oxazaborolidine.⁵

Chiral oxazaborolidines **4a** and **4b** were easily prepared by the reaction of $\text{BH}_3\cdot\text{THF}$ complex with $(-)\text{-}589\text{-}1$ and $(+)\text{-}589\text{-}1$, respectively, and used without isolation or purification.⁶



Reduction of acetophenone was carried out at $0\text{ }^\circ\text{C}$ by using **4a** (10 mol% of acetophenone), prepared *in situ*, and $\text{BH}_3\cdot\text{THF}$ complex (2 eq. of acetophenone) to give (*R*)-1-phenylethanol of 95% e.e. (Table 2, Entry 1).⁷ In a similar manner, reduction of several kinds of prochiral ketones gave the corresponding alcohols in good to excellent selectivity (Table 2). The absolute configurations of the products were in good agreement with the expectation based on a proposed transition state model for the reduction with a chiral oxazaborolidine/ BH_3 complex.⁸ It is noteworthy that both enantiomers of this artificial amino alcohol are readily available and that consequently both enantiomers of the desired alcohols should be equally easy to obtain (Table 2, Entries 1 and 2).

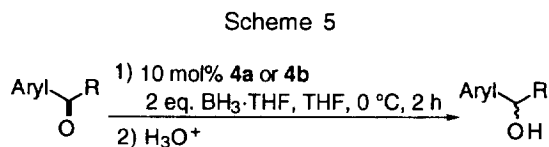
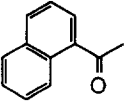
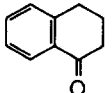


Table 2 Catalytic Enantioselective Reduction of Various Ketones

Entry	Cat.	Ketone	Yield/%	% e.e. (Config.) ^{a)}
1	4a	PhCOCH_3	89	95 ^{b)} (<i>R</i>)
2	4b	PhCOCH_3	65	94 ^{b)} (<i>S</i>)
3	4b	$\text{PhCOCH}_2\text{CH}_3$	70	80 ^{c)} (<i>S</i>)
4	4a		87	92 ^{c)} (<i>R</i>)
5	4a		81	91 ^{c)} (<i>R</i>)

a) The absolute configuration was determined on the basis of the sign of the specific rotation.

b) Determined by a chiral HPLC analysis (Daicel Chiralcel OJ).

c) Determined by a 270 MHz $^1\text{H-NMR}$ analysis of the MTPA ester of the product.

In summary, enantiomerically pure *cis*-2-amino-1-acenaphthenol, which is easily available in both enantiomeric forms via resolution, can be effectively employed as the precursor of a chiral catalyst in an asymmetric reduction. Other applications of this chiral amino alcohol in asymmetric syntheses are now under investigation.

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References and notes

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7. A representative procedure for the enantioselective reduction of prochiral ketones catalyzed by **4a** is as follows. To a suspension of (1*R*,2*S*)-(-)₅₈₉-2-amino-1-acenaphthenol ((-)₅₈₉-**1**, 37 mg, 0.2 mmol) in THF (4 ml) was added BH₃·THF (1.0 M in THF, 4 ml), and the mixture was stirred for 12 h. Then, a THF solution (2 ml) of acetophenone (240 mg, 2.0 mmol) was added to the mixture in a period of 2 h at 0 °C. After being stirred for an additional 20 min, the mixture was treated with MeOH (5 ml). The usual workup gave (*R*)-1-phenylethanol (220 mg, 1.79 mmol, 89%).
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