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# Syntheses of chiral amino alcohols and diols

Mariappan Periasamy

School of Chemistry, University of Hyderabad Hyderabad - 500134, INDIA

**Abstract:** Convenient methods of synthesis of chiral α,α-diphenyl-pyrrolidinemethanol from S-proline and novel, convenient methods of resolution of racemic 1,2-diphenylethanediols and 2,2'-binaphthols using S-proline and its derivatives are described.

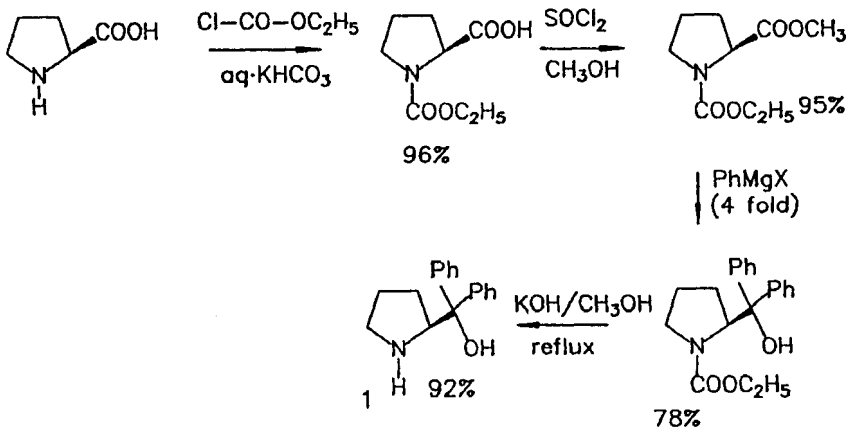
In the course of studies directed towards understanding of the mechanisms of hydroboration of olefins and reduction of ketones, we have synthesized the borane complexes of several amines. It was observed that these complexes give up to 54% e.e in the reduction of aryl-alkyl ketones in the presence of $F_3B{:}OEt_2$ (1, 2). Also, chiral alcohols could be obtained in up to 20% e.e in the hydroboration of certain prochiral olefins after $H_2O_2/NaOH$ oxidation (3). Initially, our interest was on the mechanisms of these interesting reactions. However, these studies led us to examine the development of relatively simple procedures for asymmetric transformations using readily accessible reagents.

The best recipe available now for the catalytic asymmetric reduction of ketones is the Itsuno - Corey amino alcohol - $BH_3$ combination (4-6). Corey *et. al* discovered that the transformation can be carried out using catalytic amounts of the amino alcohol (5). They have also observed that the catalyst (CBS reagent) prepared using α,α - diphenylpyrrolidinemethanol **1** gives better results. Although results of several amino alcohol - $BH_3$ combinations have since appeared, the CBS reagent system has been most widely utilized (7). However, there has been some operational difficulties with these methods and reports describing convenient procedures appeared for the synthesis of both CBS catalyst and its precursor (8, 9). We have decided to examine this problem with an objective of developing methods utilizing readily accessible, inexpensive reagents.

**Convenient Methods of Synthesis of the CBS Reagent Precursor**

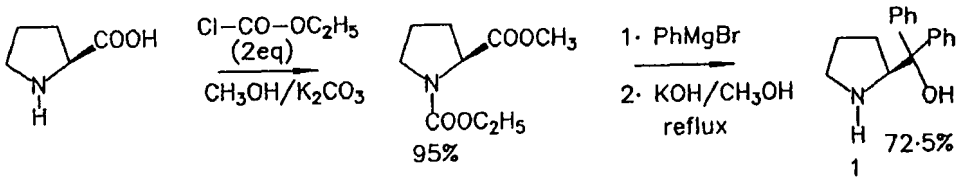
The reported procedure of synthesis of the CBS reagent precursor involves the conversion of S-proline to the corresponding carbamate derivative using the relatively expensive benzyl chloroformate as in the final step the corresponding carbamate could be readily cleaved using $Pd/C/H_2$ (8). However, in a report describing an asymmetric synthesis of the CBS precursor, it has been described

that the corresponding N-t-butyloxycarbamate derivative can be readily cleaved by refluxing in $NaOH/CH_3OH$ (10). Since such alkaline hydrolysis would involve a tetrahedral intermediate, it should be possible to perform these operations using inexpensive ethyl chloroformate. Indeed, this was observed (Scheme 1).




Scheme 1

The synthesis can be made very simple by carrying out the N- and O-protections in a single pot operation (11) (Scheme 2).

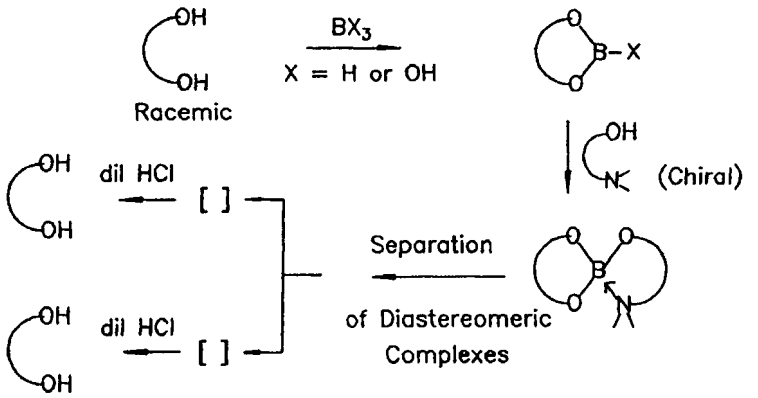



Scheme 2

We have also developed convenient methods of preparation of the oxazaborolidine catalyst *in situ* utilizing borane complexes prepared using the $I_2/NaBH_4$ combination (12).

**Novel Optical Resolution Procedures for the Synthesis of Chiral Diols**

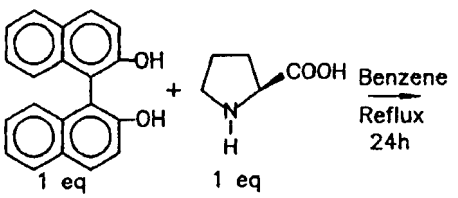
Chiral diols have proven synthetic applications in stoichiometric and catalytic asymmetric transformations. Although several chiral diols are now available, there have been sustained efforts towards resolution of the racemates, especially in the case of the 2,2'-binaphthol 2. The most widely utilized resolution method involves the synthesis of the corresponding cyclic phosphoric acid followed by complexation/derivatization using a chiral amine or a chiral alcohol. After the separation of the diastereomers, it is necessry to cleave the phosphate derivatives using $LiAlH_4$ to obtain the chiral 2,2'-binaphthol (13). We have envisaged the synthesis of the diasteremeric borate complexes of racemic diols using certain chiral amino acid derivatives which can be readily converted back to the chiral diols by dil.HCl treatment after resolution (Scheme 3).




Scheme 3

The synthesis has been carried out by passing $B_2H_6$ through a solution of the amino alcohol in benzene followed by refluxing with the racemic diols or refluxing a mixture of the amino acid, $B(OH)_3$ and the racemic diols. Unfortunately, no clean crystalline complex could be obtained in any case. However, refluxing of a 1:1:1 mixture of the racemic 1,2-diphenylethanediols 3 with $B(OH)_3$ and S-proline in benzene in a Dean-Stark set up followed by cooling gave a precipitate which after dil.HCl treatment yielded the 3-R,R derivative in 99% e.e (50%). The solution on dil.HCl treatment and work up gave the 3-S,S isomer in 30% e.e (14).

Similar experiments with the racemic 2,2'-binaphthols 2 posed some difficulties. Fortunately, however, it was discovered that the resolution can be attained in this case without using $B(OH)_3$. It was observed that refluxing of a 1:1 mixture of racemic 2,2'-binaphthols and S-proline in benzene leads to a precipitate and a benzene solution (Scheme 4).

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|---|---|---|
| R,S(±), 0% e·e | S(−), 65% e·e (43%) | R(+), 44% e·e (51%) |
| S(−), 10% e·e | S(−), 64% e·e (65%) | R(+), 70% e·e (25%) |
| S(−), 65% e·e | S(−), 87% e·e (66%) | S(−), 6% e·e (22%) |
| R(+), 44% e·e | R(+), 90% e·e (45%) | R(+), 6% e·e (41%) |
| S(−), 87% e·e | S(−), 100% e·e (77%) | S(−), 35% e·e (11%) |
| R(+), 90% e·e | R(+), 98% e·e (70%) | R(+), 28% e·e (18%) |

Scheme 4

Upon separation and evaporation of the benzene solution and ether/dil.HCl treatment **2** enriched in the R isomer (44% ee) was obtained. The precipitate on ether/dil.HCl treatment gave **2** enriched in the S isomer in 65% ee. Similar experiments using **2** enriched in one of the enantiomers lead to further enrichment as outlined in Scheme **4**. The racemic 2,2'-binaphthols can be resolved to give essentially pure enantiomers in three successive repetitions of this procedure (Scheme 4). Interestingly, both enantiomers of **2** are obtained in essentially pure forms using the readily accessible natural S-proline (15).

The nature of the complex formed in this case is not clearly understood. Very recently, we have found that treatment of the racemic **2** and S-proline in methanol also leads to a precipitate which on dil.HCl treatment gives **2** enriched in the S isomer (45% ee). The mother liquor upon evaporation and dil.HCl treatment yields the R isomer in 52% ee (16). We are actively pursuing research in delineating the nature of the complexes involved and also in the further development of resolution methods utilizing the readily accessible amino acids and their derivatives.

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