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An Efficient and Enantioselective Synthesis of A Chiral Primary Amine

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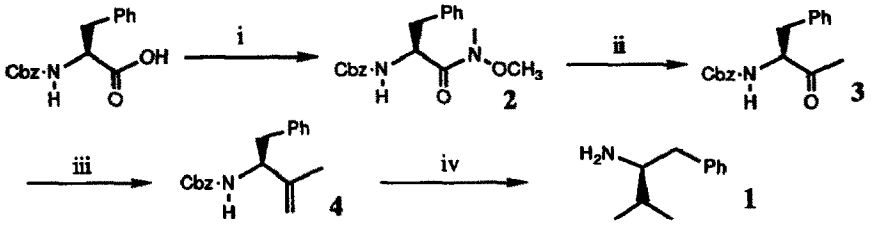
Abstract: An efficient and enantioselective method for the preparation of a chiral primary amine has been developed. Starting from N-protected L or D-amino acid the sequence involves coupling with N-methoxy-N-methylamine, acylation, olefination with potassium bis(trimethylsilyl)amide, and hydrogenation.

The chiral amines have received considerable attention because of their potential as a key intermediate for synthetic drugs. Racemic amines were readily obtained by various synthetic methods and it was necessary to separate them into their enantiomers. Although there are many acidic resolving agents[1] available, the yields and purities were not satisfactory.

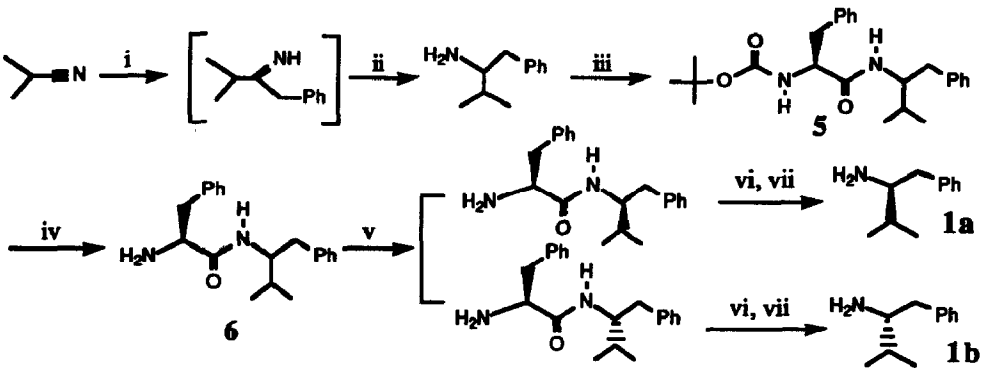
In an effort to develop an efficient method for the preparation of an optically active primary amine such as **1**, we investigated the use of amino acids. The use of chiral amino acids as starting materials attracted our attention because they are ubiquitous in nature.



Scheme 1. Reagents: i) i-BuOCOCl, N-methylmopholine, N,O-dimethylhydroxylamine hydrochloride; ii) CH_3MgBr, THF; iii) Ph_3PCH_3Br, KHMDS, toluene; iv) Pd / C, H_2

As shown in Scheme 1, the target amine **1** was synthesized from Cbz-L-phenylalanine. The N-methoxy-N-methylamide **2** obtained by mixed anhydride coupling method[2] was acylated by excess methylmagnesium bromide to afford the desired methyl ketone **3** in good yield[3]. Olefination of **3** was effected by use of potassium bis(trimethylsilyl)amide in toluene at -20 ^{0}C to give **4** without racemization. As a final step, hydrogenation with 10% Pd/C catalyst afforded the target compound **1**. The yields of all the steps in Scheme 1 were higher than 85%.

The reference compounds for **1** were prepared from isobutyronitrile *via* independent route as depicted in Scheme 2. The amines were prepared by the addition of benzylmagnesium chloride to isobutyronitrile to give the ketemine intermediate. This was followed by *in situ* reduction with $NaBH_4$-methanol. The amide diastereomers **5** obtained from the coupling of the racemic amine with N-(t-butoxycarbonyl)-L-phenylalanine provided only a small degree of separation on TLC. However, removal of the N-t-butoxycarbonyl group



Scheme 2. Reagents: i) $PhCH_2MgBr$, THF; ii) $NaBH_4$, MeOH; iii) EDC, HOBT, DMF, ^{t}BOC-L-phenylalanine; iv) TFA, CH_2Cl_2; v) column chromatography; vi) phenylisothiocyanate, CH_2Cl_2, reflux, 2 hours; vii) TFA

provided a much better separation of the two diastereomers. After separation on silica gel column chromatography, each diastereomer was subjected to Edman degradation. [α]$_D$ Value of compound **1a** was -38.1 compared to -37.4 for compound **1**, which was proved to be as high as 98% ee.

Various L or D amino acids[4] were subjected to the same method in Scheme 1 to provide optically active amines in the following Table.

Table : $[\alpha]_D$ Values of Chriral Amines.

Amine	$[\alpha]_D$ (Amine)	ee (%)
(R)-$PhCH_2CH(i\text{-}Pr)NH_2$	-37.3 (c=0.12, CH_2Cl_2)	98
(R)-$PhCH(i\text{-}Pr)NH_2$	+6.88* (c=0.11, methanol)	98
(S)-$PhCH(i\text{-}Pr)NH_2$	-6.89* (c=0.11, methanol)	98
(S)-$Ph(CH_2)_2CH(i\text{-}Pr)NH_2$	-23.2 (c=0.24, CH_2Cl_2)	96
(R)-$Ph(CH_2)_2CH(i\text{-}Pr)NH_2$	+23.3 (c=0.24, CH_2Cl_2)	96
(S)-$Ph(CH_2)_3CH(i\text{-}Pr)NH_2$	-20.5 (c=0.12, CH_2Cl_2)	96
(R)-$Ph(CH_2)_3CH(i\text{-}Pr)NH_2$	+20.5 (c=0.12, CH_2Cl_2)	96

* : Rotation of HCl salt

Thus, we have developed a simple, practical and enantioselective method for the synthesis of a chiral primary amine using L or D amino acid as a starting material with very high ee.

References and Notes

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