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Boranes in Synthesis. 1. Asymmetric Synthesis of β-Amino Alcohols. A Facile Conversion of Enamines to the Corresponding β-Amino Alcohols in High Enantiomeric Purity

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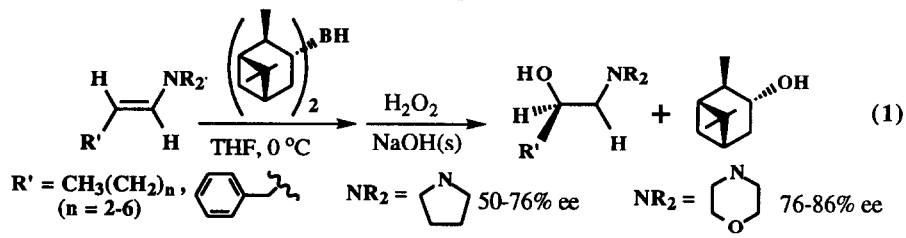
Summary: *The asymmetric hydroboration of aldehyde enamines with $^{d}Ipc_2BH$ at 0 °C, followed by oxidation with $NaOH(s)/H_2O_2$, yields the corresponding β-amino alcohols in good yields and high enantiomeric excess.*

We report herein that diisopinocampheylborane ($^{d}Ipc_2BH$) is highly effective for the asymmetric hydroboration of acyclic aldehyde enamines, such as 1-pyrrolidino-1-octene and 1-morpholino-1-pentene. Oxidation of the intermediate trialkylborane furnishes the corresponding β-amino alcohols in 50 to 86% ee. The stereogenic center of the carbinol carbon is consistently enriched in the *R*-enantiomer when $^{d}Ipc_2BH$ prepared from (+)-α-pinene is used as the hydroboration reagent (eq. 1).



Enantiomerically pure β-amino alcohols are assuming an increasingly important role in medicinal chemistry and organic synthesis. In medicinal chemistry,[1] β-amino alcohols, such as Propranolol[2] and Denopamine,[2] have been shown to be effective therapeutic agents, and the relationship of absolute configuration to pharmacological activity has been amply demonstrated,[1,2b,3] most notoriously by Thalidomide.[3] In organic synthesis, many important transformations of prochiral substrates into chiral compounds can be achieved in very high enantiomeric purity by utilizing a catalytic amount of an enantiomerically pure β-amino alcohol as a chiral auxiliary.[4]

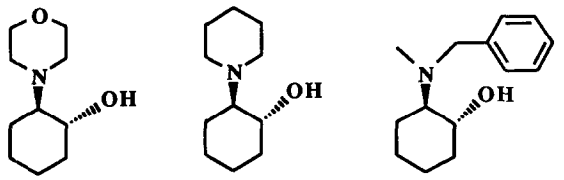
There are few methods available for the synthesis of racemic β-amino alcohols[5] and enantiomerically pure β-amino alcohols are obtained either from the reduction of amino acids or by resolution procedures.[2a;6a,b] The only general asymmetric syntheses of β-amino alcohols currently available are the homogeneous asymmetric hydrogenation of α-amino ketones, utilizing BINAP-Ru complexes and H_2 pressures of 50-100 atmospheres,[6c] and the asymmetric reduction of α-amino ketones with the chiral borohydride, K-Glucoride.[6d] We report herein a practical and useful alternative to these methodologies.

We sought to develop a simple, general procedure for the synthesis of racemic and enantiomerically pure β-amino alcohols, based on the hydroboration of a nitrogen-substituted carbon-carbon double bond.[5] Enamines were chosen as the substrates because the enamine double bond is significantly more reactive towards

hydroboration than the double bond of simple alkenes[7] and gives the corresponding β-amino alcohols in high yield by simple oxidation of the intermediate organoboranes.[5] Thus, we have shown that the hydroboration-oxidation of α,β- and β,β-disubstituted enamines with borane methyl sulfide (BMS) followed by alkaline hydrogen peroxide oxidation readily yields the corresponding β-amino alcohols.[5e,f]

Encouraged by the results obtained using achiral hydroborating reagents, we initiated a systematic study of the asymmetric hydroboration of enamines, using mono- and diisopinocampheylborane. Initially, we chose to investigate the hydroboration of enamines derived from 5-, 6-, and 7-carbon cycloalkanones with monoisopinocampheylborane ($^{d}IpcBH_2$). Since cycloalkanone enamines are structurally related to alkyl trisubstituted alkenes, in which the dialkylamino group has replaced an alkyl moiety, $^{d}IpcBH_2$, derived from (+)-α-pinene, seemed the best choice for carrying out the asymmetric hydroboration of these enamines.

Hydroboration of representative cycloalkanone enamines with $^{d}IpcBH_2$ at -40 °C in THF, followed by oxidation with $NaOH/H_2O_2$, gave the corresponding *trans*-2-(dialkylamino)cycloalkanols in very good isolated chemical yields (60-85%), although the enantiomeric excesses of the amino alcohols obtained were only modest (26-28% ee) as determined by capillary GC of the corresponding menthyl chloroformate[8] (MCF) esters (Fig.1).[9]



28% ee 26% ee 27% ee

Figure 1. Chiral β–amino alcohols synthesized from the corresponding enamines, using $^{d}IpcBH_2$ as the asymmetric hydroboration reagent.

The results shown in Figure 1 demonstrate that, even at -40 °C, $^{d}IpcBH_2$ is not sterically hindered enough to significantly enhance the facial selectivity of its reaction with the enamine double bond, thereby resulting in an enantioselective hydroboration of only modest enantiomeric excess.

We then investigated enamines derived from acyclic aldehydes. Even though aldehyde enamines are structurally related to *trans*-alkenes, the reactivity of the enamine double bond suggested that the more sterically demanding diisopinocampheylborane ($^{d}Ipc_2BH$) could be successfully used to give a highly enantioselective hydroboration. We speculated that the increased electron density at the β-carbon of the enamine[7c] would facilitate this hydroboration reaction. Our experimental results (**Fig. 2**) show that the enhanced reactivity of the enamine double bond is apparently offset by the significantly more sterically demanding $^{d}Ipc_2BH$, resulting in a much slower and more enantioselective hydroboration. Since $^{d}Ipc_2BH$ is only sparingly soluble in tetrahydrofuran (THF) at 0 °C, dissolution of the solid $^{d}Ipc_2BH$ indicated the completion of the reaction. Oxidation of the intermediate trialkylborane furnished the corresponding β-amino alcohols in good chemical yields (60-85% isolated yields) and high enantiomeric purity (**Fig. 2**).[10] The enantiomeric excesses of the underivatized β-amino alcohols were determined using HPLC and a Daicel brand CHIRALPAK AD chiral stationary phase.[11]

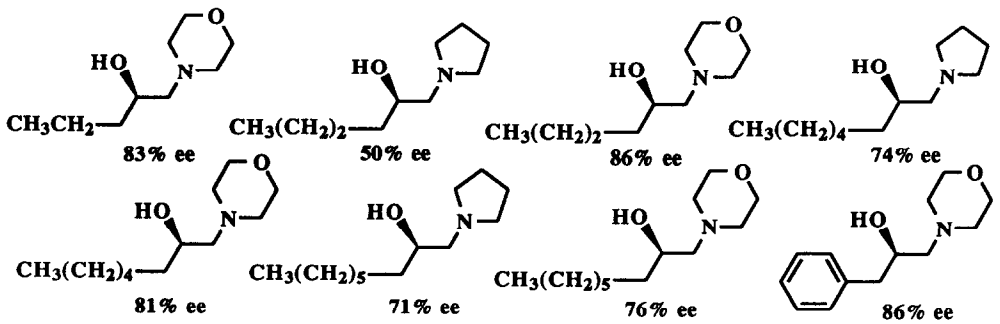
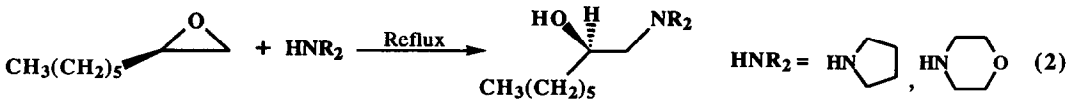


Figure 2. Chiral β–amino alcohols synthesized from the corresponding enamines, using $^{d}Ipc_2BH$ at 0 °C.

Since the absolute configurations of the β-amino alcohols prepared in this study have not been reported previously, we prepared representative enantiomerically pure samples of 1-(dialkylamino)-2-octanols from the appropriate amine and (*R*)-1,2-epoxyoctane (eq. 2).[12]



Enantiomeric separation of the β–amino alcohols[11] revealed that $^{d}Ipc_2BH$ affords β–amino alcohols enriched in the *R*-enantiomer. Based on this result, we are proposing a lowest-energy transition state for the hydroboration of acyclic aldehyde enamines with $^{d}Ipc_2BH$ that is consistent with these experimental observations (**Fig. 3**).[13]

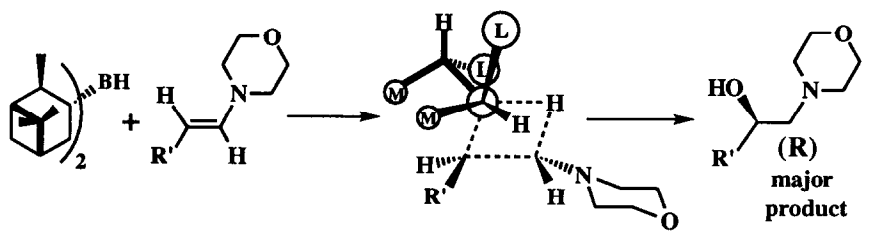


Figure 3. Proposed transition state for the hydroboration of aldehyde enamines with $^{d}Ipc_2BH$.

In the case of simple *trans*-alkenes, steric interaction between the "inside" L-group and the alkyl group is large enough to slow the reaction considerably.[13] However, in the case of acyclic aldehyde enamines, the energetically favorable coordination of the β-carbon of the double bond to the boron atom apparently overcomes the steric repulsion between the L-group and the dialkylamino group.

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