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Boranes in Synthesis. 2. Asymmetric Synthesis of β-Amino Alcohols. A Facile Conversion of 2-Amino Acetophenones to the Corresponding β-Amino Alcohols in High Enantiomeric Purity

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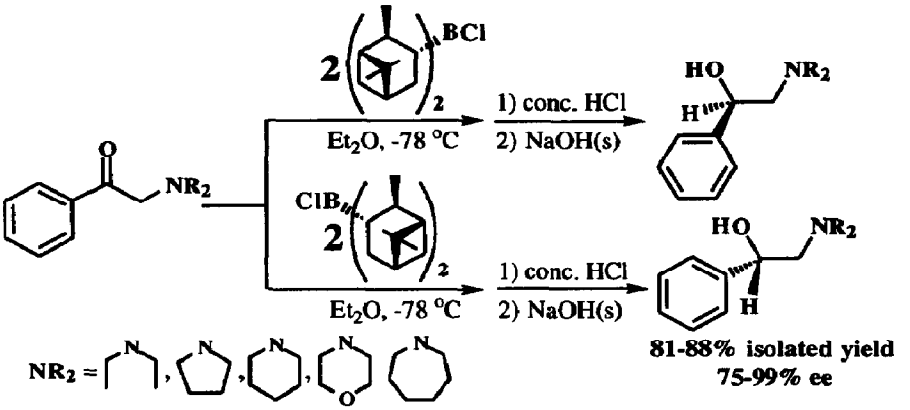
Summary: *The asymmetric reduction of 2-amino acetophenones with Ipc_2BH or Ipc_2BCl at -78 °C, yields the corresponding β-amino alcohols in good to excellent yields. Although only modest (12-45% ee) enantiomeric excesses were obtained with Ipc_2BH, 75-99% enantiomeric excesses were obtained when Ipc_2BCl was used as the asymmetric reducing agent.*

We report herein that *B*-chlorodiisopinocampheylborane (Ipc_2BCl) is highly effective for the asymmetric reduction of 2-amino acetophenones, such as 2-(4-morpholino)acetophenone. A simple acid work-up furnishes the corresponding β-amino alcohols in 75 to 99% ee. The stereogenic center of the carbinol carbon is consistently enriched in the *R*-enantiomer when $^{d}Ipc_2BCl$ prepared from (+)-α-pinene is used as the asymmetric reducing agent and in the *S*-enantiomer when $^{l}Ipc_2BCl$ prepared from (-)-α-pinene is used (eq. 1).



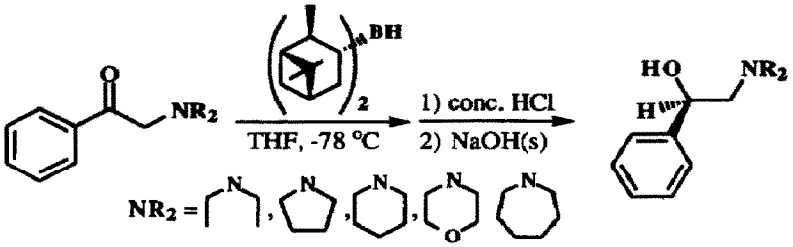
(1)

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 general asymmetric syntheses of β-amino alcohols currently available. We recently reported on the asymmetric hydroboration/oxidation of enamines as an effective asymmetric synthesis of β-amino alcohols.[5] Other general asymmetric syntheses of β-amino alcohols involve the reduction of 2-amino ketones, utilizing either

BINAP-Ru complexes and H_2 pressures of 50-100 atmospheres[6c] or the chiral borohydride, K-Glucoride.[6d] We sought to develop a simple, general procedure for the synthesis of enantiomerically pure β-amino alcohols that would complement our asymmetric hydroboration/oxidation of enamines methodology.[5] We report herein a practical and useful addition to these methodologies that requires no specialized equipment and utilizes *B*-chlorodiisopinocampheylborane (Ipc_2BCl) as the asymmetric reducing agent.[7]

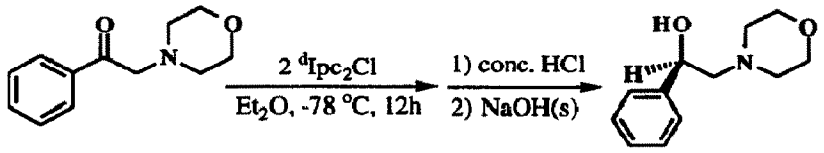
Initially, we investigated the asymmetric reduction of 2-amino acetophenones using diisopinocampheylborane (Ipc_2BH) as the asymmetric reducing agent. When 2-(1-pyrrolidino)acetophenone was reduced in THF at -78 °C with diisopinocampheylborane followed by a simple acid work-up, optically active 2-(1-pyrrolidino)-1-phenylethanol was obtained in 81% isolated yield. The enantiomeric excess of the β-amino alcohols were determined by chiral HPLC of the underivatized β-amino alcohols using a Daicel brand CHIRALPAK AD chiral stationary phase.[5c] The enantiomeric excesses found ranged from 12%-45%, and the β-amino alcohols were enriched in the *R*-enantiomer (eq. 2).[8]



80-90% isolated yield
12-45% ee (2)

We then investigated the use of *B*-chlorodiisopinocampheylborane (Ipc_2BCl). This reagent has been shown to be highly effective in the asymmetric reductions of aryl alkyl ketones, α-tertiary alkyl ketones, and β-and γ-haloketones.[7] However, the direct asymmetric reduction of 2-amino ketones with Ipc_2BCl was never attempted, even though ^{11}B-NMR published earlier[7c] suggested that an α-amino ketone with a trisubstituted nitrogen would not complex with the Ipc_2BCl and could, therefore, be effectively reduced. Chiral γ- and δ-amino alcohols were synthesized by first reducing β-halo- and γ-haloketones to the optically active halohydrins with Ipc_2BCl and then subjecting these halohydrins to S_N2 displacement of the halide by an amine to give optically active β- and γ-amino alcohols.[7d] The potent anti-depressant drugs Tomoxetine, Fluoxetine, and Nisoxetine were synthesized in high optical purity in this manner.[7d]

When we attempted the reduction of 2-(4-morpholino)acetophenone with Ipc_2BCl, we found that the Ipc_2BCl did, in fact, complex with the nitrogen of the 2-amino ketone, resulting in a low yield of the desired β-amino alcohol along with uncharacterized side-products. We then employed two equivalents of Ipc_2BCl, reasoning that, since the first equivalent of Ipc_2BCl was complexed to the amino ketone nitrogen, a second equivalent of Ipc_2BCl would be necessary to effect the desired asymmetric reduction. We were gratified to find that this methodology gave 2-(4-morpholino)-1-phenylethanol in 82% isolated yield and >99% enantiomeric excess (eq. 3).



82% isolated yield
99% ee (3)

Similar results were obtained for the reductions of a variety of other 2-amino acetophenones. As expected, the absolute configuration of the product β-amino alcohol was determined by the stereochemistry of the enantiomer of α-pinene used to make the Ipc_2BCl (**Table 1**).[7]

Table 1. Asymmetric Synthesis of β-Amino Alcohols By DIP-Chloride Reduction of 2-Amino Acetophenones

α–amino ketone	β-amino alcohol[a]	yield,%[b]	ee, %[c]	abs. config.[d]
2-*N,N*-diethylamino acetophenone	2-*N,N*-diethylamino-1-phenylethanol	85[e]	80	*S*
2-(1-pyrrolidino)-acetophenone	2-(1-pyrrolidino)-1-phenylethanol	81[f]	75	*R*
2-(1-piperidino)-acetophenone	2-(1-piperidino)-1-phenylethanol	88[e]	93	*S*
2-(4-morpholino)-acetophenone	2-(4-morpholino)-1-phenylethanol	82[f]	99	*R*
2-(1-hexamethyleneimino)-acetophenone	2-(1-hexamethyleneimino)-1-phenylethanol	86[f]	77	*R*

[a]Fully characterized by 250 MHz ^{1}H- and ^{13}C-NMR. [b]Isolated yields. [c]Enantiomeric excesses of the underivatized amino alcohols determined by chiral HPLC using a Daicel CHIRALPAK AD chiral stationary phase[5,8] or by chiroptical comparison. [d]Absolute configuration determined by a combination of chiral HPLC analysis[5,8] and chiroptical comparison. [e]Synthesized as follows: (1) $^l Ipc_2BCl$/EE, -78 °C, 12h; (2) conc. HCl; (3) NaOH(s). [f]Synthesized as follows: (1) $^d Ipc_2BCl$/EE, -78 °C, 12h; (2) conc. HCl; (3) NaOH(s).

General Procedure For DIP-Cl Asymmetric Reduction of 2-Amino Acetophenones. All glassware, needles, and syringes were oven-dried at 120 °C for 24 hours prior to use and cooled to room temperature under a nitrogen atmosphere. All operations were performed under a nitrogen atmosphere. The 2-amino acetophenones were synthesized by reacting 2-bromo acetophenone (phenacyl bromide) with one equivalent of amine in THF in the presence of a 10% excess of triethylamine. The 2-bromo acetophenone was purchased from the Aldrich Chemical Company and used without further purification. The following procedure for the synthesis of 2-(4-morpholino)-1-phenylethanol is representative. A 30-mL Pyrex serum vial equipped with a magnetic stirring bar was charged with $^d Ipc_2BCl$ (8.0g, 25 mmol). The $^d Ipc_2BCl$ was dissolved in anhydrous diethyl ether (EE, 10 mL) and cooled to -78 °C. 2-(4-Morpholino)acetophenone (2.1g, 10 mmol) was dissolved in anhydrous EE and added dropwise with stirring to the $^d Ipc_2BCl$ solution. The reaction mixture was stirred until it reached ambient temperature (~12h). The reaction was quenched with methanol (1 mL, 25 mmol), followed by concentrated HCl (12M, 2 mL, 24 mmol) and stirred for an additional 30 min. The aqueous and organic fractions were separated, and the aqueous fraction was washed with hexanes (3 X 5 mL). The aqueous fraction was layered with fresh EE

(~20 mL) and solid NaOH was added until the reaction mixture was strongly basic to litmus. The ether fraction was separated, the aqueous fraction was extracted with ether (3 X 5 mL), the organic fractions combined, dried over $MgSO_4$ (anhydrous), and filtered. Crude 2-(4-morpholino)-1-phenylethanol was isolated by vacuum removal of solvent to give a pale orange powder (1.9g, 82% yield, >99% ee).

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(8) Chiral HPLC analysis of the racemic mixtures of the corresponding β-amino alcohols gave two peaks of equal intensity.

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