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Asymmetric Reduction of *ortho*-Substituted Benzophenones with *B*-Chlorodiisopinocampheylborane: A Convenient Synthesis of Enantiomerically Enriched Benzhydrols

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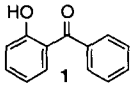
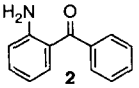
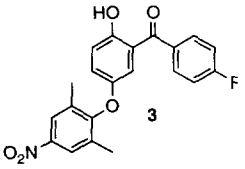
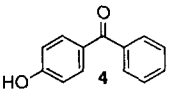
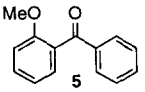
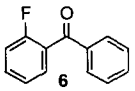
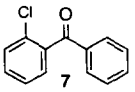
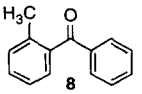
Abstract: A very efficient synthesis of chiral benzhydrols from *ortho*-substituted benzophenones is described which presumably utilizes a heteroatom-directed, intramolecular asymmetric reduction of ketones with *B*-chlorodiisopinocampheylborane.

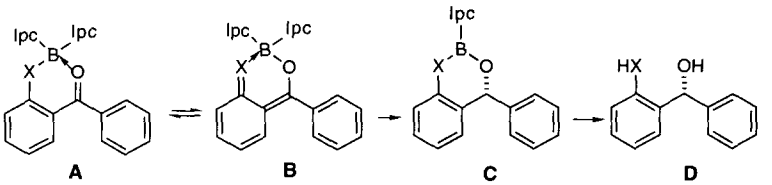
The asymmetric synthesis of benzhydrols has recently attracted considerable interest. Several novel methodologies have been described in the literature utilizing: (i) asymmetric reduction of benzophenones with chiral Grignard reagents[1] or lithium aluminum hydride-chiral amino alcohol complexes;[2] (ii) addition of chiral titanium reagents to aromatic aldehydes;[3] and (iii) resolution of benzhydrols by complexation with brucine.[4] Recently, an asymmetric reduction of *o*-hydroxyacetophenones with *B*-chlorodiisopinocampheylborane (DIP-Chloride™) has been reported by Brown.[5] Since both enantiomers of this reagent are commercially available in bulk quantity, we decided to investigate the asymmetric reduction of substituted benzophenones with DIP-Chloride™. In this communication, we report a practical and efficient synthesis of *o*-substituted benzhydrols with high enantioselectivity. This methodology provides an asymmetric synthesis of both enantiomers of CGS 26214: a potent LDL cholesterol lowering agent.[6]

This new asymmetric synthesis of benzhydrols was illustrated by the reduction of *o*-hydroxybenzophenone to *o*-hydroxybenzhydrol. Ketone **1** was added to a solution of (–)-DIP-Chloride™ (2 equiv) in THF solution at –15 °C and held for an additional 3 hours. The reaction mixture was warmed to ambient temperature and subsequently treated with triethanolamine and 3% H_2O_2 solution to provide, after extractive isolation and column chromatography on silica gel, the optically pure *o*-hydroxybenzhydrol **D** (X = O) in 77% yield (96.4% ee), whose absolute configuration has not yet been determined. Functional groups at the ortho position such as OH and NH_2 (entries 1 and 2) were required for our system to achieve high levels of enantioselectivity. Attachment of another bulky functionality at the *meta*-position did not depress the enantiomeric excess of benzhydrol at all (entry 3). After some experimentation, we discovered a relationship between the rate of reduction and enantiomeric excess (Table 1). The rate of reduction also depended on the functionality of ketone in the order of: OH > NH_2 > F > Cl > CH_3.[7] These relationships, as well as the fact that ketone **4** was recovered under the same experimental conditions, suggest an intramolecular reduction of benzophenones **1**, **2**, and **3** via complex **A** and **B**, which has a characteristic reddish color in THF.

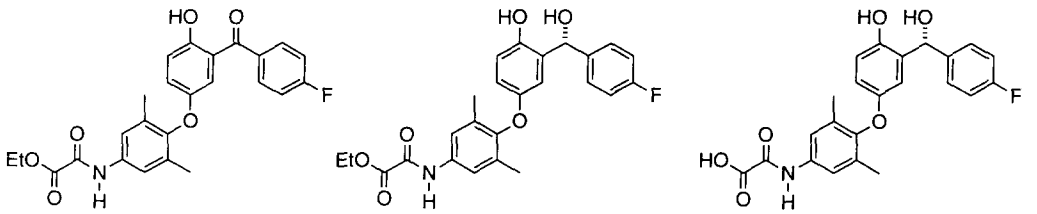
Table 1: Enantioselective Reduction of *o*-Substituted Benzophenones with (–)-*B*-Chlorodiisopinocampheylborane

entry	ketone	conditions	conversion, %	ee, %[a]
1	 1	-15 °C (3 h), 0 °C (15 min)	99[b]	96.4[c]
2	 2	25 °C (72 h)	99[b]	88
3	 3	25 °C (2 h)	99[b]	96.9
4	 4	-15 °C (3 h), 0 °C (15 min)	0[d]	—
5	 5	25 °C (96h)	99[e]	0
6	 6	25 °C (92 h)	99[e]	28
7	 7	25 °C (114 h)	66[e]	15
8	 8	25 °C (96 h)	33[e]	0

[a]Determined by chiral HPLC analysis of the crude benzhydrols on Daicel Chiralcel OJ column. [b]Determined by TLC analysis. [c]The ee was improved to 99% by crystallizing from hexane, $[\alpha]^{25}_{D} = -10.0°$ (c = 1.04, CH_3CN). [d]The starting material was recovered. [e]Determined by ^1H NMR analysis.



A useful application of our methodology was demonstrated by an enantioselective reduction of ketone **9** with (–)-DIP-Chloride™ affording an asymmetric synthesis of CGS 28935, the (–)-enantiomer of CGS 26214.[8] The ketone was cleanly reduced with two equivalents of (–)-DIP-Chloride™ to give alcohol **10** in 97% ee. However, literature workup using diethanolamine,[9] acetaldehyde,[10] or acetone/potassium sodium tartrate[11] failed to liberate the desired alcohol product. Treatment of the reaction mixture with alkaline ($NaHCO_3$) hydrogen peroxide afforded alcohol **10** and a significant amount (10-30%) of acid **11**, which was generated during both reduction and workup as indicated by HPLC analyses of reaction aliquots. This complication, due to the presence of a highly labile ester functionality, could be avoided completely by carrying out the reduction in the presence of pyridine (2 equiv). The pyridine reduced the rate of reduction from 3 h (0 °C) to 16 h (25 °C).[12] However, subsequent hydrogen peroxide workup afforded the desired alcohol **10** in quantitative yield (>99%) and high optical purity (92.5% ee). Similarly, the (+)-enantiomer of CGS 26214 was obtained by treating ketone **9** with (+)-DIP-Chloride™.



9 **10, CGS 28935** **11**

We have demonstrated that *ortho*-hydroxy or *ortho*-aminobenzophenones can be cleanly reduced with DIP-Chloride™ to the corresponding chiral benzhydrols with high enantioselectivity. This work also provides another demonstration of the synthetic utility of DIP-Chloride™, leading to the asymmetric synthesis of an important biological compound in high enantiomeric excess and chemical yield.

Enantioselective Reduction of Ketone 9 with (–)-DIP-Chloride™. To a solution of (–)-DIP-Chloride™ (1 g, 3.12 mmol) in 2 mL of THF at -15 °C was slowly added pyridine (0.51 mL, 6.3 mmol). To the subsequent white suspension, a solution of ketone **9** (0.64 g, 1.42 mmol) in THF (2 mL) was added dropwise. The mixture was stirred at -15 to -5 °C for 1 h, warmed to ambient temperature and stirred for an additional 16 h. An aliquot analyzed by HPLC on a C-18 column (Metachem Inertsil ODS-2, 0.5 mL conc H_3PO_4 in 450 mL water and 550 mL acetonitrile) confirmed that the reduction was complete and with greater than 99% presence of alcohol **10**. The mixture was cooled to –15 °C and treated with a solution of 30% H_2O_2

(0.8 g) in water (3 mL). The product was extracted into ethyl acetate, washed sequentially with 10% $NaHSO_3$, H_2O, and sat. NaCl and then concentrated. Most of the α-pinene and isopinocampheol by-products were removed by triturating the residue with hexane to obtain crude **10** as an off-white solid (0.68 g), which was purified by flash chromatography (silica gel 60Å, 200-400 mesh) using EtOAc/hexane (1/1) as eluant to yield 0.58 g (91%) of (–)-alcohol **10** (92.5% ee) as a white solid: mp 151-152 °C; $[\alpha]^{25}_D$ –21.7 (c = 1, CH_3CN); ^1H NMR ($CDCl_3$, 270 MHz) δ 8.79 (s, 1H), 7.28-7.40 (m, 5H), 7.04 (t, 2H, *J* = 8.7 Hz), 6.78 (d, 1H, *J* = 8.8 Hz), 6.55 (dd, 1H, *J* = 8.8, 3.0 Hz), 6.37 (d, 1H, *J* = 2.9 Hz), 5.89 (s, 1H), 4.44 (q, 2H, *J* = 7.1 Hz), 3.07 (s, 1H), 2.09 (s, 6H), 1.43 (t, 3H, *J* = 7.1 Hz). Anal. Calcd for $C_{25}H_{24}FNO_6$: C, 66.22; H, 5.33; N, 3.09; F, 4.19. Found: C, 66.33; H, 5.35; N, 2.97; F, 4.23.

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