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A simple route to chiral ferrocenyl alcohols

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Abstract

A chiral B-methylated oxazaborolidine, complexed with borane, has been shown to be a highly effective enantioselective reducing agent for a variety of acyl ferrocenes. The resulting chiral ferrocenyl alcohols are obtained in high overall yields and with very high optical purity (greater than 95% enantiomeric excess). Reactions times are less than 1 h and isolation and purification of the chiral alcohols is accomplished readily. The chiral material used in the synthesis of the optically-active oxazaborolidine can be recovered at the end of the reaction.

Key words: Iron; Ferrocene derivatives; Chirality; Enantioselective synthesis; Borane

1. Introduction

In recent years, considerable attention has been devoted to the preparation of optically active compounds, mainly alcohols and amines, bearing a ferrocenyl or other organometallic group at the alpha carbon atom. These compounds have been used in investigations of the stereochemistry of nucleophilic substitution reactions at the chiral center [1] as well as in investigations of the forces stabilizing carbocations generated from these chiral compounds [2]. One of these compounds, R-(−)-1-ferrocenylethylamine, has also proven useful in stereoselective peptide synthesis by a technique known as "four-component condensation" [3]. Originally, chiral ferrocene compounds were obtained by resolution of a racemic mixture of the alcohol or amine, a process which required approximately a week of laboratory work and involved 4–6 fractional recrystallizations of the diastereomeric salts [1,4]. A later process involved conversion of the alcohol to the corresponding racemic thioglycolic acid, resolution, and conversion to the chiral alcohol by treatment with mercuric chloride in water [5]. More recently microbial reduction of acetylferrocene [6] or enzymatic resolution of racemic 1-ferrocenylethanol by horse liver alcohol dehydrogenase [7] has been used to produce the pure enantiomers. While each of these processes yields the desired alcohol in high enantiomeric excess, they generally require extended lengths of time to produce significant quantities of material. This paper describes the enantioselective reduction of several ferrocenyl ketones to chiral alcohols by readily available reducing agents.

2. Results and Discussions

While lithium aluminum hydride and sodium borohydride readily reduce prochiral ketones to racemic modifications of enantiomeric alcohols, several modified reducing agents have been developed recently which achieve reductions with very high enantiomeric excess. Among the more efficient are Corey's oxazaborolidine complex (I) [8], Brown's chiral organoboranes (II) [9], and Mosher's $LiAlH_4$-"darvon alcohol" complex [10]. While each of these reagents, as well as structurally related reagents, has been shown to be effective in reducing particular prochiral compounds, no reports of their reaction with organometallic compounds such as ferrocene have appeared.

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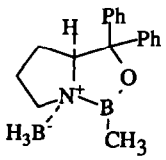
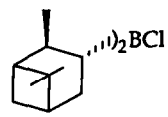


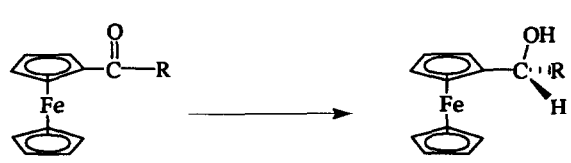
(I)



(II)

Prochiral ferrocenyl ketones (**III**) are readily available from Friedel-Crafts reactions with ferrocene. Reaction of acetylferrocene (**IIIa**) with (−)-diisopinocamphenylchloroborane [9] or with the $LiAlH_4$-"darvon alcohol" complex [10] followed by workup as described in the literature resulted in the production of low yields (< 10%) of 1-ferrocenylethanol contaminated with significant amounts of unidentified organometallic compounds. Moreover each of these procedures requires several hours of reaction time. On the other hand reactions with Corey's chiral oxazaborolidine catalyst were much more successful.

Table 1 lists the results obtained when borane THF and a catalytic amount of the chiral B-methylated oxazaborolidine were allowed to react with prochiral ferrocenyl ketones (**IIIa–c**) at 0–5°C for 5 min. The yields represent isolated and purified yields of the corresponding alcohols. Their physical and spectral (IR and NMR) properties were identical to those reported in the literature [11–14]. The sterically hindered ketones (**IIId, e**) resisted reduction under these conditions. When the reaction time was increased to 1 h, the 2-methyl-1-propanol derivative (**IVd**) was obtained in high yield; however, **IIIe** was not reduced even under these conditions. Optical rotations for all the alcohols were measured in benzene solution. Of these alcohols only the pure enantiomer of **IVa** had been reported previously [1,15] and it has been shown to have the *R* configuration. While the absolute configurations of the other alcohols have not been determined, it is assumed that they also possess the *R* configuration. Enantiomeric excesses were determined from proton NMR



(III) (IV)

a = -CH_3
b = -CH_2CH_3
c = -C_6H_5
d = -$CH(CH_3)_2$
e = -$C(CH_3)_3$

TABLE 1. Optically active ferrocenyl alcohols

Compound	Yield (%)	Specific rotation [a] $[\alpha]_D^{20}$	Enantiomeric excess [b] (%)
IVa	89	−31°	> 95
IVb	81	−51°	> 95
IVc	84	−85°	> 95
IVd	82	−73°	> 95

[a] (c, 0.034 g ml^{-1}; benzene; 1, 1.0 dm); [b] Determined by NMR.

spectra recorded in the presence of the chiral lanthanide shift reagent, $Eu(tfc)_3$ [16]. The presence of the other enantiomer of alcohols **IVa–d** could not be detected in the NMR spectra; therefore, the enantiomeric purity is at least 95% in all cases.

The enantioselective reduction of these ketones is thought to proceed by preferential orientation of the molecule in the transition state of the reduction reaction as shown in Fig. 1 [8]. The bulky ferrocene group strongly directs this orientation—even in competition with groups such as isopropyl and phenyl. Apparently these groups can orient themselves in such a manner as to reduce strain in the transition state. However, the bulky *tert*-butyl group apparently prevents the ketone from coming close enough to the catalyst to be activated and reduced.

In summary, Corey's chiral B-methylated oxazaborolidine complex has been determined to be a highly effective reagent for the reduction of several ferrocenyl ketones. The system reacts rapidly, giving a high yield of product uncontaminated by other compounds, with very high enantioselectivity. We are currently evaluating the use of this and similar reagents with other organometallic systems.

3. Experimental section

3.1. Instrumentation

The NMR spectra were obtained on a Varian Gemini 200 MHz instrument, using $CDCl_3$ as solvent, and TMS as internal standard. The IR spectra were obtained on a Perkin-Elmer 1600 FT-IR. Optical rotations were measured in benzene solutions on a Rudolph Model 70 Research Polarimeter.

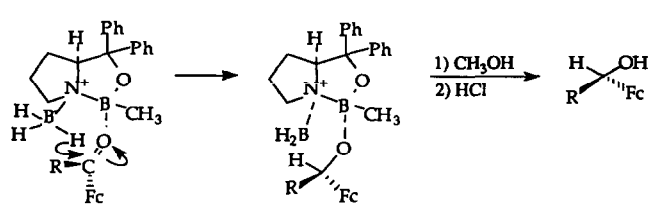


Fig. 1. Mechanism of enantioselective reduction.

3.2. Starting materials

The ferrocenyl ketones were prepared according to literature procedures [11,14,17,18]. The racemic alcohols were prepared by reduction of the ketones with $LiAlH_4$ [11–14]. S-(−)-2-(diphenylhydroxymethyl)pyrrolidine and tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium (**III**) were purchased from Lancaster Synthesis, Inc. The other chemicals were purchased from Aldrich Chemical Company and used as received.

3.3. Synthesis of Chiral B-methylated Oxazaborolidine

A slight modification of Corey's procedure [19] was followed to produce the compound. A mixture of 0.50 g of S-(−)-2-(diphenylhydroxymethyl)pyrrolidine, 0.12 g of methylboronic acid, and 25 ml of toluene was placed in a round-bottom flask fitted with a Dean-Stark trap and a condenser. The mixture was refluxed under a N_2 atmosphere for 3 h with continual removal of water. The solvent was removed under reduced pressure and the residue placed on a high vacuum pump until it solidified as a white powder. This material is stable for at least one week at room temperature under a N_2 atmosphere.

3.4. General Procedure of Enantioselective Reductions with Chiral B-methylated Oxazaborolidine

To a 50 ml 3-necked round-bottom flask was added 0.15 g (0.54 mmol) of B-methylated oxazaborolidine and 2 ml of anhydrous THF. The flask was fitted with a condenser topped with a N_2 inlet-outlet tube and the other necks sealed with septa. The reaction flask was placed in an ice-water bath and 0.5 ml (0.50 mmol) of borane THF was added by syringe. The mixture was allowed to react for five minutes while 4.0 mmol of the acyl ferrocene was dissolved in 3 ml of anhydrous THF. The acyl ferrocene solution and an additional 2 ml (2.0 mmol) of borane THF were added to the reaction flask simultaneously. After a reaction time of five minutes (except with **IIId** where the reaction time was 1 h), 2 ml of methanol was added. After another 10 min, 0.2 ml of ether saturated with HCl gas was added. The ice-bath was removed and the stirring was continued for 40 min. At the end of this time, the solvent was removed under reduced pressure. Anhydrous ethyl ether was added to the residue and the solution was chilled in an ice bath. The hydrochloride salt of S-(−)-2-(diphenylhydroxymethyl)pyrrolidine precipitated from the ether solution and was isolated by filtration. The solvent was removed from the filtrate to yield the crude alcohol which was purified by chromatography over alumina using petroleum ether/ethyl ether as the eluant.

3.5. Measurement of Enantiomeric Purity

A proton NMR spectrum of 0.08 g of the racemic 1-ferrocenyl alcohol dissolved in 0.6 ml of deuterated chloroform was obtained. To this solution was added 0.08 g of tris[3-(trifluoromethylhydroxymethylene-*d*-camphorato]europium (**III**) and a second spectrum obtained. This procedure was used to establish the position of the peaks corresponding to each enantiomer. Following exactly the same procedure with the optically active 1-ferrocenyl alcohols allowed for determination of the enantiomeric purity. The presence of the other enantiomer could not be detected in any of the alcohols produced by reduction with Corey's reagent.

Acknowledgments

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