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ENANTIOSELECTIVE PROTONATION/DIASTEREOSELECTIVE REDUCTION WITH SODIUM NAPHTHALENIDE-ACETAMIDE; A NEW SYNTHESIS OF CHIRAL *trans*-2-PHENYLCYCLOHEXANOL

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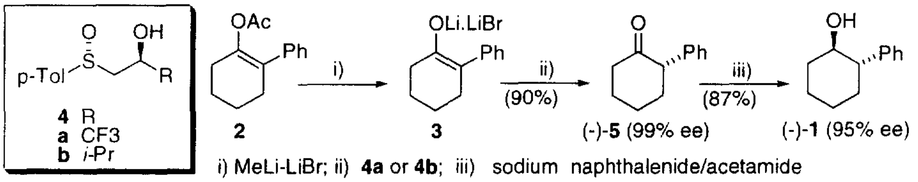
Abstract: An efficient synthesis of *trans*-2-phenylcyclohexanol has been achieved by enantioselective protonation of the enolate of 2-phenylcyclohexanone with α-sulfinyl alcohols and subsequent reduction of the chiral ketone by sodium naphthalenide in the presence of acetamide. Interestingly, the chirality source is not consumed in the synthesis of the chiral target. © 1999 Elsevier Science Ltd. All rights reserved.

Cyclohexyl based chiral auxiliaries play an important role in asymmetric synthesis.[1] Included in this group is *trans*-2-phenylcyclohexanol **1**, an efficient chiral auxiliary reagent introduced by Whitesell.[2]

Several synthetic routes to enantiomerically pure *trans*-2-phenylcyclohexanol **1** *via* either resolution methods[3] or asymmetric synthesis, including hydroboration,[4] epoxidation[5] or osmium catalyzed dihydroxylation[6] of phenylcyclohexene, have been reported. In addition, the enantioselective reaction of cyclohexene oxide with phenyllithium promoted by chiral Schiff bases has recently been described.[7] This last result has prompted us to communicate another approach to the synthesis of enantiomerically enriched *trans*-2-phenylcylohexanol. Our method consists of the enantioselective protonation of 2-phenylcyclohexanone enolate with α-sulfinyl alcohols, followed by diastereoselective reduction of the corresponding ketone. The diastereoselective reduction uses a new procedure based on the use of sodium naphthalenide in the presence of a proton source. An important feature of our method is that the chiral reagent used, the sulfinyl alcohol, is almost completely recovered and available from menthol, a cheap chiral source.



i) MeLi-LiBr; ii) **4a** or **4b**; iii) sodium naphthalenide/acetamide

The enolate of 2-phenylcyclohexanone **3** was generated and then submitted to protonation following the optimal conditions described by us previously for enantioselective protonation using α-sulfinyl alcohols.[8] Specifically, the precursor **2**[9] was treated with a methyl lithium/lithium bromide (2.1 eq) complex and the resulting enolate **3** protonated with (*S,Rs*)-**4a** (-100 °C) or (*S,Rs*)-**4b** (-50 °C). This led to the corresponding (-)-(*S*)-2-phenylcyclohexanone **5** with a high chemical yield (90% of isolated product) and complete stereoselection (> 99% ee) in both cases. Compound (-)-**5** was characterized by comparison using data from the literature.[10]

The stereoselective reduction of (-)-**5** to (-)-**1** has two important drawbacks: i) the steric hindrance of the α-substituent that favours the formation of the *cis* alcohol when hydrides are used[11] and ii) the racemization of the stereocenter in a basic medium, such as in the reduction with sodium/ethanol.

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To circumvent these problems we developed the reduction of (-)-**5** with sodium naphthalenide[12] in the presence of acetamide as a proton source. When the chiral ketone (-)-**5** was added to a THF solution of sodium naphthalenide/acetamide for a short period of time (7 min.), a slight racemization of the ketone took place and *trans*-2-phenylcyclohexanol **1** was obtained with only 87% ee. We were able to improve on this result by slow addition of the ketone over 90 minutes. In this way (-)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol **1** was obtained with 95% ee. A typical procedure for reduction of the chiral ketone (-)-**5** is as follows: small pieces of sodium (4.25×10^{-3} atm-gr) were added to a solution of naphthalene (3.78 mmol) in THF (10 ml). After sonication for 3h in an ice bath, the resulting dark green solution was diluted with THF (10 ml) and cooled to -78 °C, after which acetamide (3.02 mmol) was added. A solution of (-)-**5** (0.378 mmol) in THF (7 ml) was then added dropwise over a period of 90 min. The reaction was quenched with methanol (5 ml) and poured into phosphate buffer. The usual workup gave (-)-(1*R*,2*S*)-*trans*-2-phenylcylohexanol **1** with an 87% yield and 95% ee (determined by ^{1}H-NMR of the corresponding MTPA ester).[13]

The use of sodium naphthalenide in combination with a suitable proton donor for the reduction of ketones to alcohols has not been reported previously in the synthetic literature. While the scope and limits of this new method must be further investigated, it can currently be applied successfully to the stereoselective reduction of hindered cyclic ketones. A substituent α to the carbonyl group, along with the presence of a proton donor in the medium, are crucial factors for the inhibition of ketyl radical coupling.[14] Since reduction by metal hydrides of cyclic 2-substituted ketones does not yield the corresponding *trans* alcohols with acceptable stereoselection,[11] our method represents a useful approach for working with this type of compound. It has many advantages over the classical methods such as Na/EtOH and Na/NH_3(l), which require more drastic reaction conditions. This is an essential feature in the context of the synthesis of chiral alcohols because racemization of the chiral ketone precursor must be avoided.

Further work to apply the method to the synthesis of other interesting substrates is in progress.

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