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(-)-Menthol as a source of new *N*,*N*-diamine ligands for asymmetric transfer hydrogenation

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ABSTRACT

The synthesis of new chiral *N*-monotosylated-1,2-diamines based on the (-)-menthol skeleton is presented. The elimination of HCl from neomenthyl chloride obtained from an Appel reaction led to p-menth-3-ene in excellent yield. Further functionalization of the double bond in p-menth-3-ene with chloramine-T gave the corresponding *N*-tosylaziridines, which upon reaction with sodium azide and subsequent reduction of the azide functional group, formed the 1,2-diamine system. The synthesized chiral ligands proved effective in the asymmetric transfer hydrogenation of aromatic ketones and an endocyclic imine.

Introduction

The 1,2-diamine structural motif is present in natural products and their derivatives and is often responsible for their biological activity. Chiral 1,2-diamines are often applied as chiral inductors in asymmetric catalysis and organocatalysis[1–6] and several synthetic diamine derivatives have been employed as valuable pharmaceuticals.[7] One of the best known group of compounds containing the diamine system are enantiomerically pure *trans*-1,2-diaminocyclohexane derivatives, which have been applied as chiral reagents and ligands in asymmetric synthesis,[8] as chelating agents[9,10] and as organocatalysts.[11,12] An inexpensive and simple way to obtain 1,2-diamines in enantiomerically pure form is the use of renewable natural resources. Among them, monoterpenes are readily available chiral precursors.[13] Based on the molecular skeleton of (+)-limonene and (+)-3-carene several diamines have been developed and employed as chiral ligands for the asymmetric transfer hydrogenation of ketones and for the enantioselective addition of dialkylzinc to aldehydes.[14–16] Recently, we described the synthesis of *trans*-1,2-diamines derived from natural (-)-menthol and demonstrated their effectiveness as chiral ligands in the asymmetric transfer hydrogenation of aromatic ketones and imines.[17]

Herein, we report the synthesis of new chiral monotosylated 1,2-diamines based on *p*-menth-3-ene, itself derived from (-)-menthol, and their application in the asymmetric hydrogenation of aromatic ketones and a selected 3,4-dihydro-β-carboline.

Results and discussion

Our synthetic approach to the synthesis of mono-*N*-tosylated *trans*-1,2-diamines from *p*-menth-3-ene is presented in Scheme 1. Initially, a concise method to transform natural menthol to the key intermediate *p*-menth-3-ene **3** was needed. Based on a literature survey we selected a procedure described by Appel and co-workers[18] and later by Ishmuratov and co-workers[19] leading to compound **3** in one synthetic step. Unfortunately under the proposed conditions the reaction between (-)-menthol and CCl_4/Ph_3P carried out in CH_3CN gave neomenthyl chloride **2** as the major product (37%) and *p*-menth-2-ene in 22% yield. The ^1H NMR analysis of the crude reaction mixture showed the presence of *p*-menth-3-ene in only 6% yield. Since the direct synthesis failed, we used the previously obtained neomenthyl chloride for the synthesis of compound **3**. According to Huckel and co-workers,[20] the elimination of hydrogen chloride from neomenthyl chloride **2** upon treatment with sodium ethoxide produces two isomeric menthenes: *p*-menth-2-ene and *p*-menth-3-ene in a ratio of about 1:3 (ESI, Table 1). Unfortunately, these isomeric menthenes have similar physical properties and could not be successfully separated.[21]

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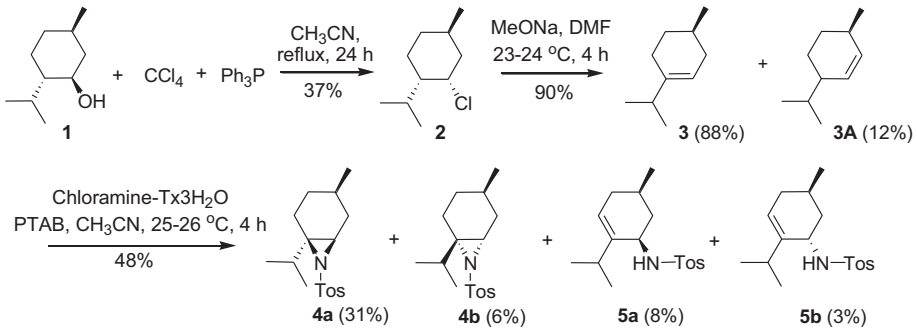

Scheme 1. Synthetic pathway towards aziridines **4a-b**.

Therefore we tested different conditions for the dehydrochlorination of neomenthyl chloride with a base to obtain 3-menthene in higher purity. The screening of this reaction revealed that the elimination of HCl is best achieved using MeONa in DMF at 23–24 °C and gave a mixture of *p*-menth-2-ene and *p*-menth-3-ene in a ratio of about 1:8. Alcohols such as MeOH and EtOH are not favorable solvents for this elimination reaction; aprotic solvents like DMF or DMSO gave better results. The dehydrochlorination using potassium *tert*-butoxide occurred very rapidly even at room temperature but with low selectivity (1:2). As a result of our screening, we obtained *trans*-*p*-menth-3-ene with a purity of 88%, which was converted to aziridines **4** using the direct *N*-tosylaziridination reaction (Scheme 1).[22,23] The reaction between **3** and Chloramine-T trihydrate in the presence of phenyltrimethylammonium tribromide (PTAB) carried out at 25–26 °C resulted in the formation of a mixture of *cis*/*trans*-aziridines **4a,b**, which were isolated in 37% combined yield. Additionally, the dehydrobromination products **5a,b** were isolated in 11% yield. Based on ^{1}H NMR analysis, the ratio of aziridines **4** to unsaturated derivatives **5** is 70:30 and the ratios of **4a:4b** and **5a:5b** are *ca.* 78:22. When the reaction was carried out at 45 °C the main product **4** was isolated in 25% yield with a similar ratio of aziridines. Compounds **4** and **5** were easily isolated by column chromatography on silica-gel with hexane/ethyl acetate. The aziridines **4a,b** were eluted using 0–4% AcOEt and the alkenes **5a,b** were eluted using 8–10% AcOEt. Finally, isomers **4a,b** and **5a,b** were separated by fractional crystallization from hexane or a dichloromethane/hexane mixture, respectively. The absolute configuration of compounds **4a** and **5a** was determined by the single crystal X-ray analysis (Figs. 1–2).

Next, *N*-tosylaziridines **4a** and **4b** were treated with sodium azide in DMF at 60 °C (Scheme 2). Interestingly in both cases this transformation was regio- and diastereoselective and led directly to the azide derivatives **6a** (60%) and **6b** (55%), respectively. Additionally, unreacted substrates **4a** and **4b** were isolated in 30% and 20% yield, which suggests that these isomers were formed as the main products during the reaction.

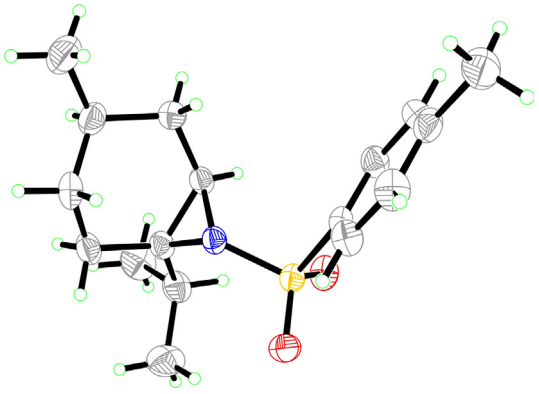

Figure 1. ORTEP diagram for the X-ray analysis of compound **4a**.

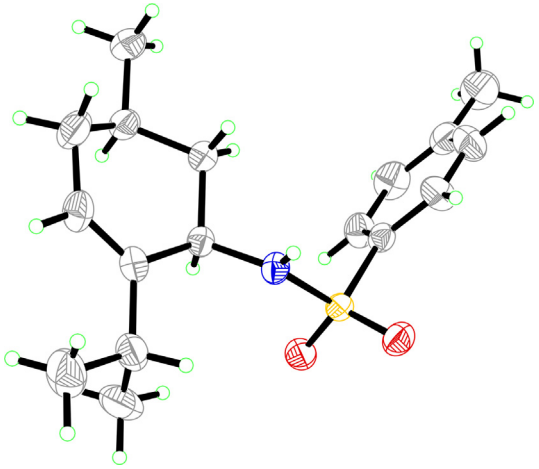

Figure 2. ORTEP diagram for the X-ray analysis of compound **5a**.

The absolute configuration of compound **6a** was determined by single crystal X-ray analysis (Fig. 3).

The pure isomers **6a** and **6b** were individually hydrogenated over 10% Pd/C to afford the diamines **7a** and **7b** in 92% and 88% isolated yield, respectively. Suitable crystals for X-ray analysis were obtained for amine **7b** and its absolute configuration was determined by single crystal X-ray analysis (Fig. 4).

In order to evaluate the utility of amines **7a** and **7b** as chiral inductors, the Ru(II) complexes **8a** and **8b** were prepared and tested against 1-methyl-3,4-dihydro-β-carboline and various model aromatic ketones under asymmetric transfer hydrogenation conditions.[24–27] The ruthenium complexes were prepared *in situ* by mixing $[RuCl_2(benzene)]_2$ with the monotosylated diamines **7a** and **7b** and triethylamine (Ru:amine:Et_3N molar ratio = 1:2.4:2) in acetonitrile or by heating the metal precursor with the ligand (Ru:amine molar ratio = 1:2.4) in 2-propanol at 80 °C. Initially, the model reduction reaction of 1-methyl-3,4-dihydro-β-carboline was tested. The hydrogenation using a HCOOH/Et_3N mixture was carried out at 30 °C and the reaction progress was monitored by TLC. The products were isolated by short-path column chromatography and the enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. The results of the reduction are summarized in Table 1. Complex **8a** in which the methyl and isopropyl substituents are in the *syn*-orientation shows significantly higher asymmetric induction and gave the amine with 72% ee. Considering the promising activity of the tested complexes **8a,b** in imine reduction, we applied them to a model hydrogenation of several aryl ketones. 2-Propanol and a HCOOH/Et_3N mixture were