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A simple and convenient synthesis of β-amino alcohol chiral auxiliaries based on limonene oxide

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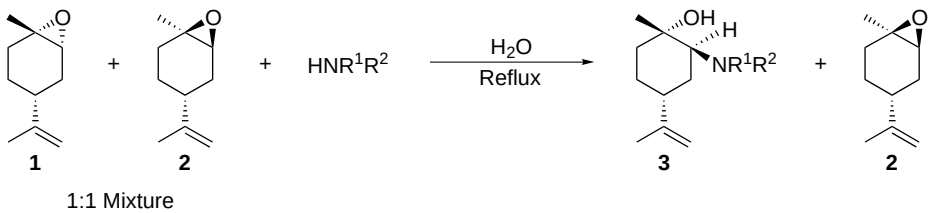
Abstract—A series of chiral β-amino alcohols was prepared by the reaction of secondary amines with a 1:1 mixture of *cis*- and *trans*-limonene oxide in the presence of water as a catalyst. The β-amino alcohol obtained was derived from the *trans*-limonene oxide, and the unreacted *cis*-limonene oxide was recovered from the reaction mixture. The β-amino alcohols are useful chiral auxiliaries for the addition of diethylzinc to benzaldehyde.



The literature abounds with examples of the use of β-amino alcohols as chiral auxiliaries in a variety of synthetic organic reactions.[1] In many instances, these materials are prepared by lengthy syntheses in which one-step involves 'classical resolution' or another separation technique to obtain one pure enantiomer. Several years ago, we recognized that one way to avoid enantiomer separation was to start the β-amino alcohol synthesis with a naturally occurring, readily available chiral material, such as a terpene. We demonstrated this concept with the synthesis of (1*R*,2*S*,3*S*,5*R*)-2-(dialkylamino)-6,6-dimethylbicyclo[3.1.1]heptan-3-ols via the hydroboration/oxidation of the corresponding enamines of (*R*)-(+)-nopinone.[2] The concept was further demonstrated by Masui and Shioiri who prepared (1*S*,2*S*,3*R*,5*S*)- and (1*R*,2*R*,3*S*,5*R*)-3-amino-2-hydroxypinane and demonstrated the utility of their oxazaborolidine derivatives in the asymmetric reduction of prochiral ketones.[3] Most recently, Nugent and coworkers have similarly taken advantage of the chirality present in (+)-3-carene to prepare a highly effective chiral auxiliary for the addition of lithium cyclopropylacetylide to an unprotected *N*-acylketimine in high enantiomeric excess.[4] In furthering our investigation of terpene based chiral auxiliaries, we now describe the synthesis of a series of new β-amino alcohol chiral auxiliaries from the reaction of (*R*)-(+)- or (*S*)-(−)-limonene oxide with secondary amines.

Obtaining β-amino alcohols via the opening of epoxides with amines is an approach that has been utilized as early as 1923.[5] (*R*)-(+)-Limonene oxide is a readily available and inexpensive starting material due to the natural abundance of its precursor, (*R*)-(+)-limonene.[6] However, epoxidation of the endocyclic double bond creates a 1:1 mixture of *trans*-limonene oxide (**1**) and *cis*-limonene oxide (**2**) which is difficult to separate.[7] Pure *cis*-(*R*)-(+)-limonene oxide (**2**) has been prepared from the corresponding diol.[8] Pure *cis*-(*R*)-(+)-limonene oxide (**2**) and *trans*-(*R*)-(+)-limonene oxide (**1**) have

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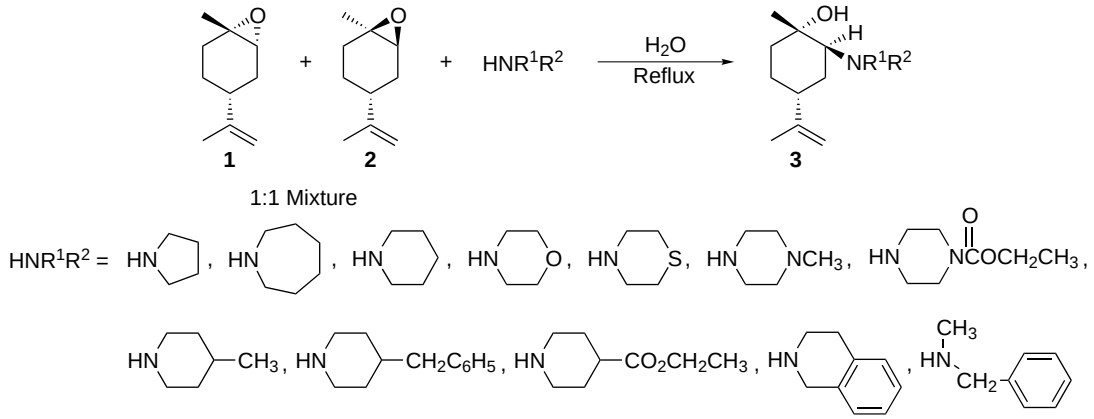


Scheme 1.

been prepared by Hofmann degradation of the two isomeric amino alcohols obtained from the reaction of the mixture of **1** and **2** with aqueous dimethylamine.[9,10] The reaction of ammonia and lower alkylamines with a 1:1 mixture of **1** and **2** has been reported to give the corresponding mixture of amino alcohol diastereomers which have been separated by selective crystallization of acid salts.[10,11] Consequently, limonene oxide has not been used as a precursor for the synthesis of β-amino alcohol chiral auxiliaries.

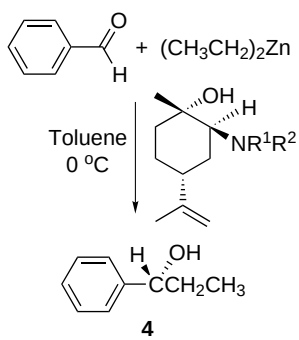
We now report here conditions which permit the diastereoselective preparation of β-amino alcohols from the 1:1 mixture of **1** and **2**, and the use of these new β-amino alcohols as chiral auxiliaries in the addition of diethylzinc to benzaldehyde.

We selected a series of secondary amines for our study. The initial reaction was run with morpholine. The reaction was conducted neat with approximately three equivalents of morpholine to the 1:1 mixture of **1** and **2**, and the progress of the reaction was monitored by capillary GC. Surprisingly, even after 7 days at 110°C, only 11% reaction occurred. Addition of *p*-toluenesulfonic acid (PTSA) did not improve the rate of the reaction.

We found, however, that water was an excellent catalyst for the reaction. The capillary GC analyses of the reaction of morpholine with the 1:1 mixture of **1** and **2** in the presence of a catalytic amount of water indicated that one diastereomer was reacting much faster than the other. Spiking a reaction sample with authentic *cis*-(*R*)-(+)-limonene oxide (**2**) confirmed that **1** was reacting with morpholine much faster than **2**. We thus found that it was possible to stop the reaction after approximately 12 hours and isolate diastereomerically pure β-amino alcohol **3** and unreacted **2**. The diastereoselectivity observed in the reaction between a 1:1 mix of **1** and **2** with secondary amines can be explained in terms of conformational differences in the transition states.[12] Attack of secondary amine at C-2 of **1** proceeds through a favorable 'chair-like' transition state, while attack at C-2 of **2** cannot occur due to the development of an energetically unfavorable 'boat-like' transition state.

Encouraged by these results, we reacted the series of secondary amines with the 1:1 mixture of **1** and **2** in the presence of water at reflux to give a corresponding series of β-amino alcohols **3** derived from the reaction of **1** (Scheme 1).[†]

The *cis*-limonene oxide (**2**) was recovered from the reaction mixture by simple distillation, leaving the crude β-amino alcohol. The crude β-amino alcohol was purified by isolation of the oxalate salt, followed by treatment with potassium hydroxide to give the free



Scheme 2.

[†] The reaction sequence shown in Scheme 1 shows (*R*)-(+)-limonene oxide as the starting material to give the corresponding (1*S*,2*S*,4*R*)-2-dialkylamino-1-methyl-4-(1-methylethenyl)cyclohexanol (**3**). Identical reactions were carried out with (*S*)-(−)-limonene oxide to give the corresponding (1*R*,2*R*,4*S*)-2-dialkylamino-1-methyl-4-(1-methylethenyl)cyclohexanol.

Table 1. Limonene oxide-derived β-amino alcohols as chiral auxiliaries for the addition of diethylzinc to benzaldehyde

Entry	β-amino alcohol	% **4**	% ee	$[\alpha]_D^{25}$
1	(1*S*,2*S*,4*R*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol	98	78	37.5
2	(1*S*,2*S*,4*R*)-1-methyl-4-(1-methylethenyl)-2-(1-pyrrolidinyl)cyclohexanol	80	85	43.0
3	(1*S*,2*S*,4*R*)-1-methyl-4-(1-methylethenyl)-2-(1-piperidinyl)cyclohexanol	80	82	39.4
4	(1*S*,2*S*,4*R*)-2-(benzylmethylamino)-1-methyl-4-(1-methylethenyl)cyclohexanol	80	85	43.0

base, which was subsequently distilled or recrystallized.[‡] Four of the β-amino alcohols derived from (*R*)-(+)-limonene oxide were utilized as chiral auxiliaries in the addition of diethylzinc to benzaldehyde to produce (*R*)-1-phenyl-1-propanol (**4**) with 78–85% ee (Scheme 2, Table 1).[§]

In summary, we have demonstrated a simple and convenient synthesis of a new family of chiral β-amino alcohol chiral auxiliaries in both enantiomeric forms from readily available and inexpensive (*R*)-(+)-limonene and (*S*)-(−)-limonene, via their epoxides, and a variety of secondary amines. The utility of these new β-amino alcohols as chiral auxiliaries is currently under investigation.

[‡] **General procedure: (−)-(1*R*,2*R*,4*S*)-1-Methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol.** A 250 mL, single-neck flask equipped with a magnetic stirring bar and a reflux condenser fitted with a nitrogen bubbler was charged with 54.78 g (0.360 mol) of (*S*)-(−)-limonene oxide, 90 mL of morpholine, and 10 mL of deionized water. The mixture was heated to reflux and held there for 68.5 h. The reaction mixture was cooled to room temperature. The excess morpholine and limonene oxide were distilled off at reduced pressure to give 64.38 g of crude amino alcohol as a dark orange, viscous oil. The crude amino alcohol was dissolved in 90 mL of methanol. To the stirred solution, a solution of 33.00 g (0.366 mol) of oxalic acid in 300 mL of methanol was slowly added. A heavy slurry of white solid formed immediately. The slurry was cooled with an ice bath and stirred for 0.5 h. The solid was isolated by filtration, air dried, washed with 75 mL of cold (ice bath) methanol, and vacuum dried at 60°C to give 54.55 g of the oxalate salt of (−)-(1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol as a white solid, mp 206–207°C (dec.). The oxalate salt (53.55 g) was transferred to a separatory funnel and mixed with 600 mL of 1N potassium hydroxide and 200 mL of diethyl ether. The mixture was shaken and the layers separated. The aqueous layer was extracted with two 200 mL portions of diethyl ether. The combined ether fractions were washed with 100 mL of deionized water. The ether solution was dried over anhydrous magnesium sulfate. The diethyl ether was removed in vacuo (rotary evaporator) leaving 35.56 g of (−)-(1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol as a pale yellow oil. A few seed crystals of (−)-(1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol from a previous batch were added, and crystallization began immediately. The oil completely crystallized, and was broken up with a spatula to give a white solid, mp 43–44°C.

[§] **General procedure for (*R*)-1-phenyl-1-propanol (4).** To a 25 mL, round-bottom flask charged with the β-amino alcohol (1 mmol) was added diethylzinc in toluene (10.0 mL, 10 mmol) under nitrogen. The solution was stirred for 25 min at room temperature and then cooled to 0°C. Benzaldehyde (1.0 mL, 10 mmol) was added dropwise via syringe, and the reaction mixture was allowed to reach room temperature while stirring over night. The reaction mixture turned yellow upon addition of the benzaldehyde, but became colorless after stirring for 24 h. The reaction was acidified with 12 M hydrochloric acid and extracted with diethyl ether (5×30 mL). The combined ether extracts were dried and the solvent removed in vacuo. The resulting oil was distilled under reduced pressure to give (*R*)-1-phenyl-1-propanol, bp 47–50°C (1.0 Torr). Optical rotation (see Table 1) $c = 1.0$ in cyclohexane).

Acknowledgements

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