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Levopimaric acid derived 1,2-diamines and their application in the copper-catalyzed asymmetric Henry reaction

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ABSTRACT

Levopimaric acid, a readily available starting material, was used in efficient syntheses of new enantiopure diamines and Schiff bases with good yields. The synthetic procedure is based on the fumaropimaric acid monomethyl ester conversion into the optically pure *trans*-1,2-diamine via a Curtius rearrangement. New diamines were studied as ligands in the copper-catalyzed asymmetric Henry reaction.

1. Introduction

Natural products are a convenient and promising source of renewable raw materials for organic synthesis. Chiral natural compounds are widely used in drug discovery, asymmetric synthesis, and enantiomers separation. Metal complexes with chiral ligands based on amino acids, terpenes, carbohydrates, alkaloids have been applied as catalysts for enantioselective reactions.[1–4] Starting from natural monoterpenes a large variety of its nitrogen derivatives (diamines, amino alcohols, Schiff bases, imidazolines) have been synthesized and employed as chiral inducers in asymmetric catalysis.[5–11] The application of diterpenes for this purpose is much less studied. Among the few examples known, dehydroabietylamine and isosteviol were used as chiral moieties incorporated into organocatalysts.[12–16] Diterpene resin acids are a promising chiral source for the construction of various optically active substances as they are commercially available optically pure reactive compounds possessing multiple stereogenic centers and modifiable functional groups.

Earlier, we developed methods for the synthesis of optically pure nitrogen and phosphorus derivatives of diterpene resin acids and employed the resultant mono- and bidentate N, P-ligands in catalytic asymmetric reactions.[17,18] Here we present a high yield procedure for an optically pure diterpene derived *trans*-1,2-diamine and its further use as a key compound for obtaining a series of secondary amines with different substituents. These novel diamine ligands were employed in the Cu(II)-catalyzed Henry reaction. The asymmetric nitroaldol reaction (Henry reaction) is an important method in organic synthesis, used for the creation of C–C bonds via condensation of carbonyl compounds with saturated nitroalkanes.[19–22] The Henry reaction is efficiently catalyzed by complexes of copper(I) and copper(II) with nitrogen containing ligands, including oxazoline (bisoxazoline),[23–27] amines,[28–31] amine oxides,[32] aminoalcohols,[33–36] sulfonylamides,[37] Schiff bases[38] and salans.[39–43] Most of the chiral amine ligands used contain *trans*-diamine fragments from 1,2-diaminocyclehexane[29,42–47] or 1,2-diphenylethanediamine.[39,41,48,49] The essential advantage of the Cu(II) complexes over those of Cu(I) is that they do not require inert atmosphere for catalysis performance.[32,50,51] With this regard herein we report the employment of a new *trans*-1,2-diamine scaffold type in chiral Cu(II) complex catalysts for nitroaldol condensation.

2. Results and discussion

2.1. Synthesis of 1,2-diamine derivatives of levopimaric acid

After considering the properties of levopimaric acid **1** and the other constituents in the starting plant feedstock[52,53] we designed an

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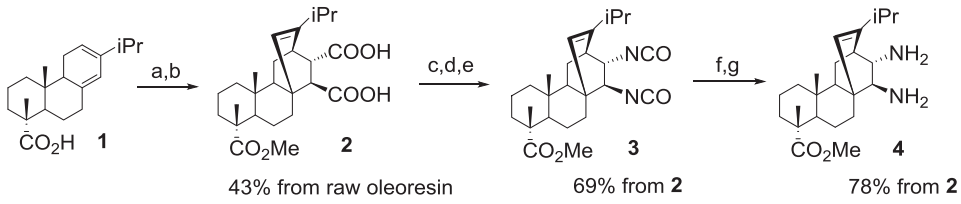


Scheme 1. Synthesis of diamine **4** from pine oleoresin, containing levopimaric acid **1**. Reagents and conditions: (a) CH_3I, K_2CO_3, acetone, 6 h; (b) fumaric acid, 180 °C, Ar, 6 h; (c) $SOCl_2$, DMF, 110 °C, 3 h; (d) NaN_3, $PhCH_3$, +5 °C, 2 h; (e) 110 °C, 2 h; (f) HCl (35%), 110 °C, 2 h; (g) aqueous $NaHCO_3$.

optimum sequence for the synthesis of the 1,2-diamine (Scheme 1). Pine oleoresin is mainly composed (75–95%) of mixed abietic-type resin acids,[54–59] i.e. tricyclic diterpenes with a single carboxyl group and a conjugated double bond system. The four abietic-type acids (abietic, neoabietic, palustric and levopimaric) undergo interconversion under heat or acidic conditions,[60–62] and in the fresh pine resin levopimaric acid **1** amounts to 30–50%.[52,61] Owing to its *cis*-diene structure, levopimaric acid easily reacts with activated dienophiles at 20–30 °C forming the Diels-Alder adducts.[52,63] Other abietic-type acids form the same adducts at 150 °C after *in situ* isomerization into levopimaric acid.[63–66] Cycloaddition proceeds with a high stereoselectivity[66] and the target product is easily separated by crystallization from both minor isomers and non-reacted feedstock components due to a difference in the solubility of the diastereoisomers. The obtained optically pure cycloaddition adduct **2** contains *trans*-1,2-carboxyl groups, which can be used to introduce amino groups through Curtius rearrangement.

The raw pine oleoresin with high content of abietic-type acids was used as the starting material for the synthesis of 1,2-diamine **4** without any purification or isolation of the resin acids. In order to avoid undesired triamine formation the oleoresin was methylated before the diene synthesis. Cycloaddition of fumaric acid to the methyl levopimarate was performed without a solvent at 180 °C under argon using the crude mixture of the methylated products obtained at the previous stage. Unreacted oleoresin components were removed from the resultant reaction mixture by extraction with diethyl ether. The residual crude solid was crystallized from methanol yielding individual product **2** at 50 g per 100 g of the raw oleoresin used. The obtained monomethyl ester of fumaropimaric acid **2** is stereochemically pure, which is confirmed by the single set of signals in ^1H and ^{13}C NMR spectra.

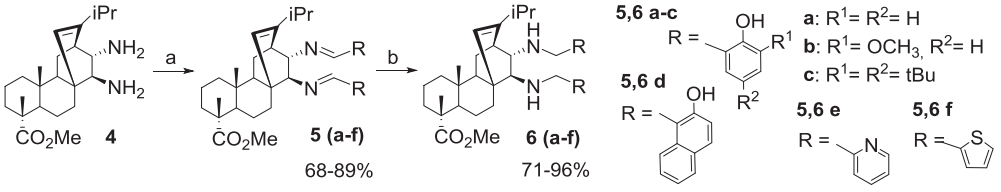
The four stage conversion of monomethyl ester of fumaropimaric acid **2** into *trans*-1,2-diamine **4** via Curtius rearrangement was performed as a one pot procedure without any separation of intermediates (acid dichloride, diazide and diisocyanate). The overall yield was 78%. Intermediate diisocyanate **3** was also synthesized from dicarboxylic acid **2** and isolated in a yield of 69%. Synthesis of the target diamine **4** proceeds stereospecifically, giving an optically pure product which is then used to obtain chiral Schiff bases and secondary amines (Scheme 2).

New Schiff bases **5a-f** were obtained in good yields (68–89%) via *trans*-1,2-diamine **4** condensation with several aromatic aldehydes. Reduction of compounds **5a-f** by sodium borohydride afforded amines **6a-f** isolated in yields of 71–96% after chromatography or crystallization. Therefore, we have synthesized new levopimaric acid derived optically pure secondary amines **6a-f** containing various substituents at the nitrogen atoms.

2.2. New chiral diterpene derived 1,2-diamine ligands in enantioselective Cu(II)-catalyzed Henry reaction

The enantioselectivity and catalytic activity of Cu(II) complexes with ligands **6a-f** were estimated in nitroaldol reactions using 4-nitrobenzaldehyde **7a** and nitromethane **8** as model substrates. Reactions were carried out in tetrahydrofuran solution at room temperature in the presence of a 5 mol% *in situ* catalyst prepared from copper(II) acetate monohydrate (5 mol%) and ligands **6a-f** (5 mol%) just before the Henry reaction. The results of the reactions are shown in Table 1. High chemical and moderate % ees were obtained in nitroaldol condensation in the presence of copper complexes with aminophenols (Table 1, entries 1–2) and aminonaphthol (Table 1, entry 4). As the substituent at the *o*-position of ligand phenol ring increases in volume, the reaction rate and % ee decrease (Table 1, entries 1–3). At the same time, volume of substituents at *m*- or *p*-positions have a lesser effect on catalyst performance (Table 1, entry 4). Obviously, the presence of phenol donor oxygen atoms in the non-chiral substituents at ligand amino groups is necessary for catalyst enantioselectivity. Thus, when the phenol substituents are replaced by heterocyclic ones, the derived metal complexes show moderate or high catalytic activity but negligible stereodifferentiating ability (Table 1, entries 5, 6). Therefore, in further experiments we studied catalyst performance of copper(II) complex with only chiral ligand **6a**.

The results of model reactions carried out in different solvents are shown in Table S1 (see Supporting Information). Since the precursors and catalyst itself well dissolve in all tested solvents, the solvent polarity and specific interactions with metal complex appear to be the main factors determining catalyst efficiency. Reactions in non-polar solvents (Table S1, entries 1–2) afforded product in moderate yields (53–63%) with low *ee* (24%). Similar results are also obtained in chlorinated hydrocarbons (Table S1, entries 3–4). Protic solvent MeOH (Table S1, entry 5) decreases the enantioselectivity even more (to 15% *ee*) most likely due to alcohol coordination to copper providing a mixture of metal complexes. In acetonitrile and dimethylformamide (Table S1, entries 6, 7) nitroaldol condensation resulted in high yield, but near racemic products are attained. Apparently, copper(II) forms non-chiral complexes with these solvents, which hinder formation of



Scheme 2. Synthesis of levopimaric acid derived Schiff bases and diamines. Reagents and conditions: (a) RCHO; (b) $NaBH_4$.