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Recyclable Cu(II)-macrocyclic salen complexes catalyzed nitroaldol reaction of aldehydes: A practical strategy in the preparation of (*R*)-phenylephrine

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ABSTRACT

Chiral macrocyclic salen ligands **1′–3′** derived from 1*R*,2*R*-(−)-1,2-diaminocyclohexane, 1*R*,2*R*-(+)-1,2-diphenyl-1,2-diaminoethane and (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine with trigol bis aldehyde were prepared and characterized by microanalysis, ^{1}H NMR, UV/Vis. spectroscopy, optical rotation and mass spectroscopy. Highly enantioselective nitroaldol reaction of various aromatic and aliphatic aldehydes with nitromethane in presence of several bases were carried out in the presence of in situ generated Cu(I)/Cu(II) complexes with chiral macrocyclic salen ligands **1′–3′** at RT. Excellent yields (up to 92% with respect to the aldehyde) of β-nitroalcohols with high enantioselectivity (ee, ~95%) was achieved in case of 3-methoxy- and 4-nitrobenzaldehyde in ca. 30 h with the use of chiral macrocyclic salen ligands **3′** with $CuCl_2{\cdot}2H_2O$ in presence of 2,6-lutidine as a base. Chiral macrocyclic salen catalyst **3** mediated nitroaldol process is recyclable (up to 8 cycles with no significant loss in its performance). This protocol is also used for the synthesis of enantiomerically pure (*R*)-phenylephrine (α1-adrenergic receptor agonist) via asymmetric nitroaldol reaction of 3-methoxybenzaldehyde in three steps.

1. Introduction

The ever-increasing demand for enantiopure β-hydroxy nitroalkanes as valuable precursors for β-amino alcohols, α-hydroxy carboxylic acids, other natural products and pharmaceuticals including (*R*)-denopamine and (*R*)-arbutamine [1a] led the development of chiral catalysts for enantioselective nitroaldol condensation reaction [1–3]. As a fallout of the most impressive work based on rare-earth-lithium-BINOL [4] as enantioselective catalyst for nitroaldol reaction, there were numerous reports on the development of various types of chiral metal complexes of sulfonyl diamine [5], Schiff bases [3f,6], bi-piperidine [7], BINOL [4,8], amino alcohols [9], bis-oxazolines [3d,10], bis-thiazoline [1e,11], bis-imidazolines [3e], thiols [12], thiophenes [13] and amino-pyridines [14]. In addition to chiral metal complexes, efforts were also made to develop organocatalysts for enantioselective itroaldol reaction [15]. Among chiral metal complexes, the Cu-catalyzed asymmetric nitroaldol reaction with bidentate and polydentate chiral ligands at room temperature has received much attention in recent years [4c,6c,7]. Although, Co(III) [16] and Cr(III) [5d,16b] salen complexes were also developed for the asymmetric nitroaldol reaction of aldehydes which required extremely low temperatures (−78 to −40 °C), long reaction time (40–144 h) and the presence of diisopropylethylamine as an additive to show reasonably high enantioselectivity. Mechanistically speaking, nitroaldol reaction requires both acidic (to activate aldehyde) and a basic center (to abstract proton from nitroalkane). Building upon these understanding and our own desire of developing recyclable catalysts [8g,9a,17], we previously reported a facile enantioselective nitroaldol reaction catalyzed by in situ formed copper complexes of monomeric and dimeric macrocyclic [H_4] salen ligands having 1*R*,2*R*-(−)-1,2-diaminocyclohexane and 1*R*,2*R*-(+)-1,2-diphenyl-1,2-diaminoethane collar [17]. Here, we report, the preparation of chiral macrocyclic salen ligands **1′–3′** derived from 1*R*,2*R*-(−)-1,2-diaminocyclohexane, 1*R*,2*R*-(+)-1, 2-diphenyl-1,2-diaminoethane and (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine of different bulkiness with trigol bis aldehyde. In situ generated Cu(II)/Cu(I) complexes with different counter ions and the above chiral macrocyclic ligands were used for nitroaldol reaction of various aldehydes in presence of 2,6-lutidine as base at RT in order to understand some structure–activity-relationship. Excellent yields (up to 92% with respect to the aldehyde) of β-nitroalcohols with high enantioselectivity (ee, ~95%) was achieved in case of 3-methoxy- and 4-nitrobenzaldehyde in ca. 30 h with the use of chiral macrocyclic salen ligands **3′** with $CuCl_2{\cdot}2H_2O$ in presence of 2,6-lutidine as a base.

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