Applied Catalysis A: General 425–426 (2012) 28–34

Contents lists available at SciVerse ScienceDirect

Applied Catalysis A: General

journal homepage: www.elsevier.com/locate/apcata

Recyclable copper catalysts based on ionic-tagged C_2-symmetric Indabox ligands and their application in asymmetric Henry reactions

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ARTICLE INFO

Article history:
Received 22 December 2011
Received in revised form 22 February 2012
Accepted 24 February 2012
Available online 5 March 2012

Keywords:
Catalyst recycled
Imidazolium/pyrrolidinium-tagged
Indabox
Asymmetric Henry reaction
Theoretical mechanistic study

ABSTRACT

New imidazolium/pyrrolidinium-tagged Indabox ligands were designed and prepared. Catalysts based on these ligands with $Cu(OAc)_2 \cdot H_2O$ were applied to the asymmetric Henry reaction using various aldehydes and CH_3NO_2, the products were obtained in high enantioselectivity. Specifically, (*R*)-1-(2-methoxylphenyl)-2-nitroethanol was obtained in 94% *ee* in MeOH. Furthermore, the catalyst based on **7** could be recycled at least 12 times by simple wash without an obvious loss of activity or enantioselectivity. This catalytic procedure demonstrated the potential for catalyst recyclability in the asymmetric Henry reaction. Additionally, a theoretical mechanistic study was conducted to explain the origin of the enantioselectivity.

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1. Introduction

Enantioenriched 2-nitro-1-arylalkanols, which are key intermediates and building blocks for the synthesis of β-adrenergic drugs and natural products such as polyamino alcohols and polyhydroxylated amides, are generally prepared via the Henry (nitroaldol) reaction [1–6]. Since the first asymmetric Henry reaction was reported by Shibasaki and co-workers, who used a series of heterobimetallic catalysts [7], a large number of effective asymmetric metal-based catalytic systems have been developed [8–10], and they [11–14] have all demonstrated their ability to promote the asymmetric Henry reaction in high yields with high enantioselectivities. Among these protocols, copper-based asymmetric catalytic systems have been employed with various ligands [15–18]. Moreover, bis(oxazoline) complexes derived from $Cu(OAc)_2 \cdot H_2O$, like those employed by Evans et al., were found to be promising catalysts for the Henry reaction under mild reaction conditions [17].

Chiral bis(oxazoline) (box) ligands have proven to be very effective in generating high levels of activity and enantioselectivity in many reactions [19–29]. The recyclability of box ligands has now emerged as a priority. However, to date, there are only a handful of reports describing the immobilization and recycling of a catalyst in asymmetric Henry reactions [3,30–37]. Lee [3] immobilized a box ligand onto a magnetically separable, hierarchically ordered mesocellular mesoporous silica (M-HMMS), and this new catalytic system was examined in the asymmetric Henry reaction between various aldehydes and CH_3NO_2. This catalyst was separated magnetically and reused 5 times with little loss of reactivity or enantioselectivity. Khan [31] reported catalysts derived from C_2-symmetric chiral secondary bis-amines based on the 1,2-diaminocyclohexane structure. Partnered with copper acetate, its application was investigated in the asymmetric Henry reaction in the presence of different ionic liquids, with a focus on [Emim] BF_4. In this context, the catalyst could be reused 5 times with retention of the enantioselectivity. More recently, Didier [32] reported that an anthracenyl-modified chiral bis(oxazoline) copper complex was recovered through the formation of a charge transfer complex between the chiral ligand and trinitrofluorenone and its subsequent precipitation with pentane. In recent years, the use of ionic liquids as biphasic systems and the use of catalysts based on ionic-tagged ligands are promising recycling methods [33]. However, to the best of our knowledge, only a few of the ionic-tagged box compounds have been used as ligands in the asymmetric Henry reaction (Scheme 1).

Following our previous work on imidazolium-tagged box ligands and their good performance and recyclability in asymmetric reactions [37], we designed and prepared new ionic-tagged Indabox ligands and investigated their performance in asymmetric

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doi:10.1016/j.apcata.2012.02.044