Tetrahedron 67 (2011) 4640–4648

Contents lists available at ScienceDirect

Tetrahedron

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

Chiral monooxazolines as modular copper(I)-heterocomplex building blocks: investigations on the catalytic asymmetric cyclopropanation of alkenes

Elisabete P. Carreiro [a,b], J.P. Prates Ramalho [a,b], Anthony J. Burke [a,b,*]

[a] Centro de Química de Évora, Universidade de Évora, Rua Romão Ramalho, 59, 7000 Evora, Portugal
[b] Departamento de Química, Universidade de Évora, Rua Romão Ramalho, 59, 7000 Evora, Portugal

ARTICLE INFO

Article history:
Received 22 February 2011
Received in revised form 10 April 2011
Accepted 15 April 2011
Available online 21 April 2011

Keywords:
Mono(oxazoline)
Arylid-OX
Asymmetric catalysis
Cyclopropanation
Homocomplex
Heterocomplex
π–π interactions

ABSTRACT

Novel chiral monodentate oxazoline ligands have been synthesized in good yields. The catalytic activity of these monodentate oxazoline/Cu catalysts was evaluated in the catalytic asymmetric cyclopropanation of styrene and α-methylstyrene, giving moderate to good enantioselectivities (up to 74% ee for the *trans*-cyclopropane product) and full conversions (up to 100%). In an attempt to enhance the enantioselectivities of the cyclopropanations, heterocombinations of these ligands were used. Unfortunately, with the data set that was used in this study, no improvements were observed. However, to gain an insight into the nature of the active catalyst present under these circumstances, NMR, mass spectrometric and computational studies were carried out and indicated the presence of bidentate heterocomplexes in the equilibrium mixture. Analysis of the stereoselectivities (ees and des) did not prove very useful in pinpointing the identity of the active chiral catalyst and only afforded a very weak conclusion. In order to ascertain the importance of the π–π interactions, the monodentate oxazoline ligands **3a** and **3b** were synthesized and screened in these reactions, and the resulting stereoselectivities were compared to the results obtained using ligands **1a** and **1b**. There seemed to be very weak π–π interactions at work.

1. Introdution

Over the last number of years chiral monodentate ligands have proven their potential in numerous transition-metal-catalyzed asymmetric transformations. Although there is enormous application of bidentate chiral ligands in catalytic asymmetric synthesis, monodentate versions have rarely had the same impact, for the main reason that they fail to form compact catalytic manifolds, which are pivotal for high asymmetric induction during the reaction. Monodentate ligands offer the advantage that they are in general less structurally complex than di- and multi-dentate ligands, thus the synthesis in principle is less demanding. For example, Binol-based modular mono-phosphonites,[1] mono-phosphites[2] and mono-phosphoramidites[3] so far have been the principle monodentate ligand to be investigated, often leading to medium or high enantioselectivities in diverse asymmetric catalytic reactions when metals like Rh or Cu were used. Oxazoline ligands are superior to phosphine ligands in that they are stable to both hydrolysis and oxidative conditions, a considerable advantage when compared to the latter family, which are easily converted into phosphine oxides.[4] Monodentade oxazolines were applied successfully in catalytic asymmetric cyclopropanations,[5,6] in catalytic enantioselective [2+2+2] cycloadditions with Ni[7] and in enantioselective Diels–Alder reactions.[8,9] All of these reactions showed moderate stereoselectivity.

Chiral olefinic ligands have been shown to be useful in catalytic asymmetric synthesis and have been the subject of various reviews.[10a–c] In fact, recently, Glorius et al. introduced a new family of modular oxazolines, which are olefin/oxazolines (abreviated OlefOX).[10d] They were tested in Rh catalyzed conjugate additions of phenylboronic acid to cyclohexenone, and gave very good enantioselectivities. However, theses ligands are true bidentate ligands as the coordination to the Rh is via the oxazoline nitrogen and the olefinic bond. Monodentate ligands are very empowering as they allow for the creation of a large diversity of chiral catalysts, and are very amenable for application in combinatorial enantioselective catalysis using mixtures of such ligands. The first combinatorial homogeneous asymmetric catalysis using the concept of mixing chiral monodentate ligands was reported simultaneously by Reetz[11] and Feringa.[12] Using this concept in some catalytic asymmetric hydrogenations[11,12a] and in the conjugated addition of arylboronic acids[12b] it was possible to enhance the enantioselectivities, as well as the reaction rate, by simply mixing two known monodentate ligands. The heterocomplex formed was assumed to be the active catalyst.

In this paper, we introduce two families of olefinated monodentate oxazolines, designated Arylid-OX **2** and Propen-OX **3**, (Fig. 1). The design and synthesis of the Arylid-OX **1** family (Arylid-

* Corresponding author. Tel.: +351266745310; fax: +351266745303; e-mail address: ajb@dquim.uevora.pt (A.J. Burke).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.04.066

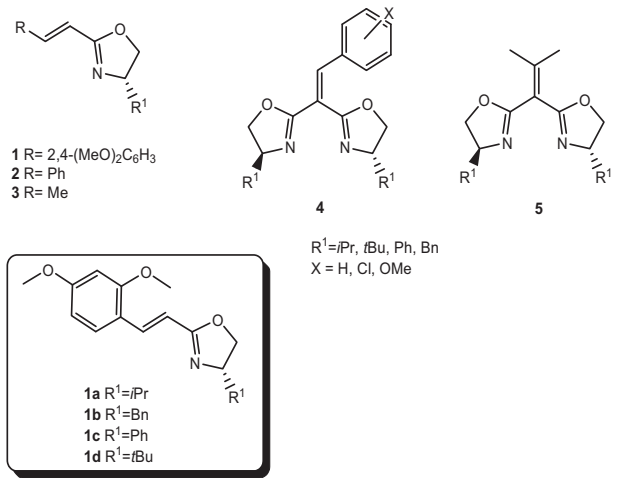
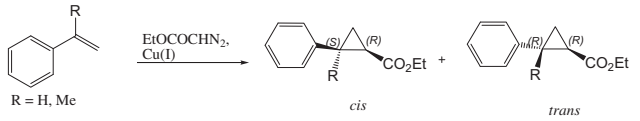


Fig. 1. Structures of monodentate oxazolines (**1**–**3**) and bis(oxazolines) (**4**,**5**).

OXs **1c** and **1d** have previously been reported for the catalytic asymmetric cyclopropanation reaction, CACP)[6] was inspired by the known Arylid-BOX **4**[13,14] and Isbut-BOX **5**[15] ligands developed by our research group. These ligands were tested in the catalytic asymmetric cyclopropanation of alkenes with ethyl diazoacetate (EDA) using $[Cu(MeCN)_4]PF_6$ and Cu(I)OTf as the pre-catalysts (Scheme 1).



Scheme 1. Asymmetric cyclopropanation of styrenes—the benchmark reaction for this study.

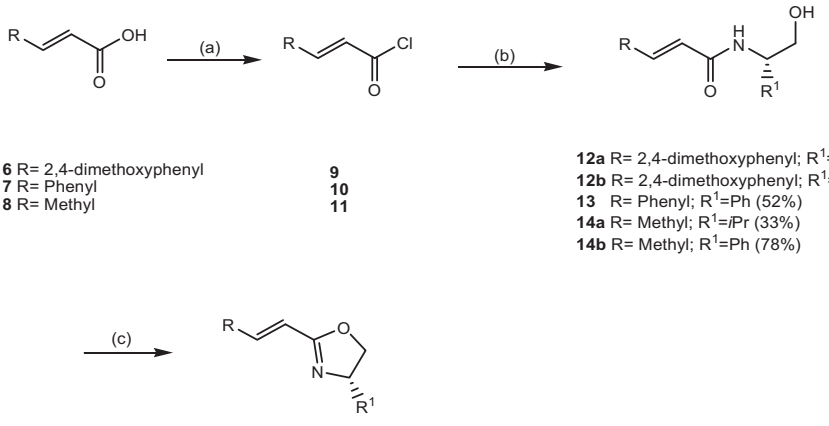
2. Results and discussion

The Arylid-OX families **1** and **2** and Propen-OX **3** were prepared in good yields using the synthetic pathway shown in Scheme 2. The carboxylic acid precursor was obtained via the procedure reported by Neustadt et al.[16] using a simple Knoevenagel condensation with malonic acid and the respective aldehyde. Our standard synthetic procedure was subsequently used to transform the acids to the corresponding ligands.[14,15]

2.1. Asymmetric catalytic cyclopropanation: homo- and heterocombinations of mono(oxazolines)

The novel monodentate mono(oxazolines) were evaluated in the Cu(I)-catalyzed asymmetric cyclopropanation of styrene and α-methylstyrene using ethyl diazoacetate (EDA) (Scheme 1). The catalyst was generated in situ by the addition of the pre-catalyst, $[Cu(MeCN)_4]PF_6$, and the relevant chiral mono(oxazoline) **1**–**3** in catalytic quantities, followed by the addition of excess alkene and then by the slow addition of EDA. This method had previously been established and optimized by our research group for the bisoxazolines **4**–**5**.[13–15] The reactions were conducted in both CH_2Cl_2 and toluene to determine the influence of both polar and apolar solvents. The reactions with toluene required heating for activation, but, unfortunately, heating probably destroyed or deactivated the catalyst, as the yield was poor. Given the distinct possibility of having π–π interactions at play, we focused on three types of Arylid-OX or Alkylid-OX ligands, namely, **1**, **2** and **3** (Scheme 2). The Arylid-OX ligands **1** contained a very electron-rich π-system. In fact, computational studies (vide infra) show that the aryl group is co-planar with the C=C. It was hoped that this extensive π-electron delocalization would promote significant π–π interactions, leading to more compact Cu-catalysts that would promote better asymmetric induction.[17] To test this hypothesis, the two ligand families, type **2**, with only a phenyl group in the back-bone, and thus expected to show less intense π–π interactions with lower reaction enantioselectivities expected, and type **3**, bereft of an aryl-backbone group, and thus expected to manifest even lower reaction enantioselectivities, were prepared and screened.

The homocombinations of Arylid-OXs **1a**/**1a** and **1b**/**1b** were tested in some catalytic asymmetric cyclopropanations with Cu(I) and styrene (Table 1). For comparative purposes, the Cu(I) catalyst was applied at two loading levels: 0.36 and 2 mol %, respectively. Unfortunately, the yields were low for all the reactions studied (6–37%). In the case of **1a**/**1a** the best enantioselectivity obtained was 48% ee for the *cis*-cyclopropane product using 6.3 mol % of ligand, on the other hand, with ligand **1b** the best enantioselectivity obtained was 45% ee for the *cis*-cyclopropane at a loading of only



Scheme 2. Reagents and Conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (b) (*S*)-Phenylglycinol or (*S*)-Valinol or (*S*)-Phenylalaninol, NEt_3, CH_2Cl_2; (c) CH_3SO_2Cl, NEt_3, CH_2Cl_2.