Tetrahedron Letters 51 (2010) 374–377

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Carbohydrate-based spiro bis(isoxazolines): synthesis and evaluation in asymmetric catalysis

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ARTICLE INFO

Article history:
Received 15 September 2009
Revised 2 November 2009
Accepted 9 November 2009
Available online 12 November 2009

ABSTRACT

Two carbohydrate-based spiro bis(isoxazolines) were synthesized via 1,3-dipolar cycloaddition from peracetylated methylene *exo*-glucal and the corresponding bis(arylnitrile oxide). The bis(cycloadducts) were then evaluated as ligands for enantioselective catalytic reactions. The Pd-catalyzed Tsuji–Trost reaction between a malonate and an allylic acetate did not provide good results. The poor conversion observed can be attributed to the rearrangement of the ligand in the reaction mixture to afford the corresponding ring-opened isoxazole which has been characterized. Both ligands were also evaluated in Cu(I)-catalyzed asymmetric imine alkynylation and afforded the product in good yield and modest enantioselectivity.

Asymmetric synthesis is an important area of synthetic chemistry, which has many industrial applications, including the production of pharmaceuticals, agrochemicals, or polymers. One of the most direct ways for accessing enantiomerically pure compounds is through the exploitation of either chiral reagents or catalysts prepared from metal salts and chiral ligands. Over the last decades, oxazolines have emerged as a very successful class of chiral ligands for asymmetric catalysis.[1–4] Especially the C_2-symmetric chiral bis(oxazolines) **1–3** (Fig. 1) have found wide application in various asymmetric reactions.

In the context of stereoselective synthesis, carbohydrates represent excellent starting materials for the preparation of chiral auxiliaries,[5–10] reagents,[5–10] organocatalysts[5], and ligands.[5,6,11–14] Carbohydrate-based ligands have been mainly prepared from saccharides such as D-xylose, D-glucose, D-galactose, D-mannitol, and trehalose backbones.[5,7,10] During the last decade, ligands derived from D-glucosamine have become more and more popular. Some prominent examples are shown in Figure 2, among them many are oxazoline ligands (**4–6**).[15–23]

Recently, the Boysen group prepared glucosamine-based bis(oxazoline) and pyridyl bis(oxazoline) ligands **9a** and **9b** as well as bis(thiazoline) **10** (Fig. 3).[24–27] These ligands have been used in

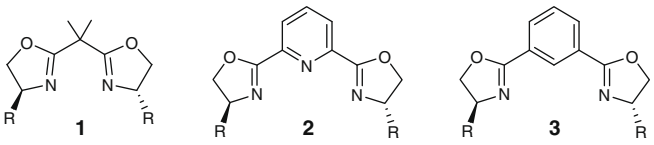

Figure 1. Typical bis(isoxazoline) ligands.

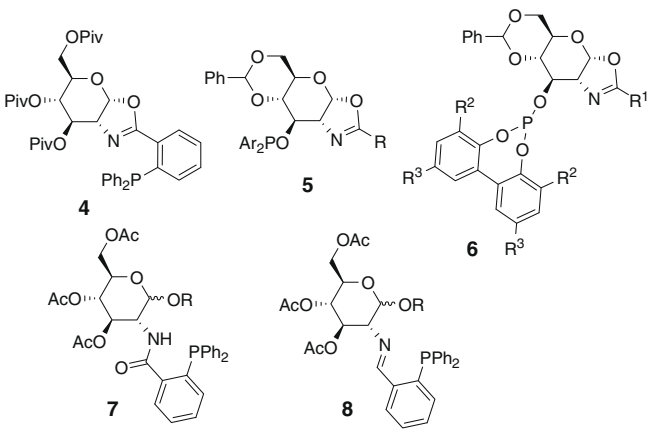

Figure 2. Examples of D-glucosamine-based ligands.

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doi:10.1016/j.tetlet.2009.11.028

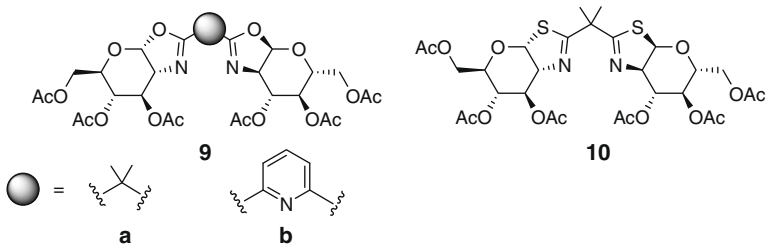


Figure 3. Structure of bis(oxazoline) or bis(thiazoline) ligands.

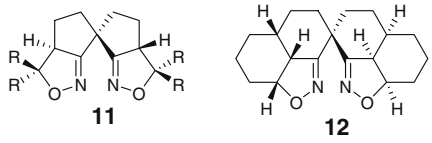
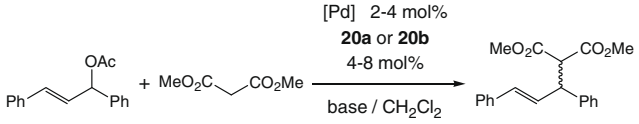
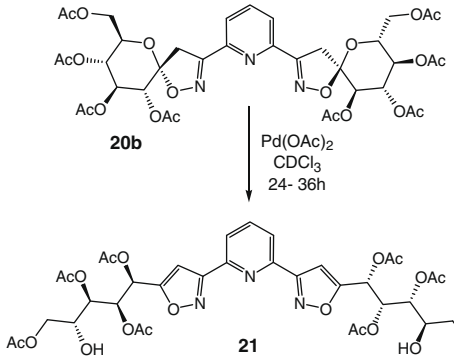


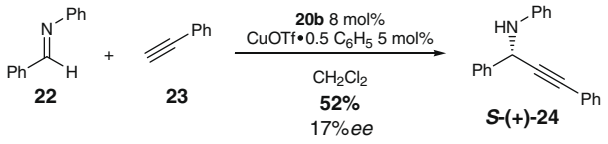
Figure 4. Spiro bis(isoxazolines) ligands developed by Sasai et al.



Scheme 2. Tsuji–Trost allylic alkylation.



Scheme 3. Ring-opening of ligand **20b** upon treatment with $Pd(OAc)_2$.



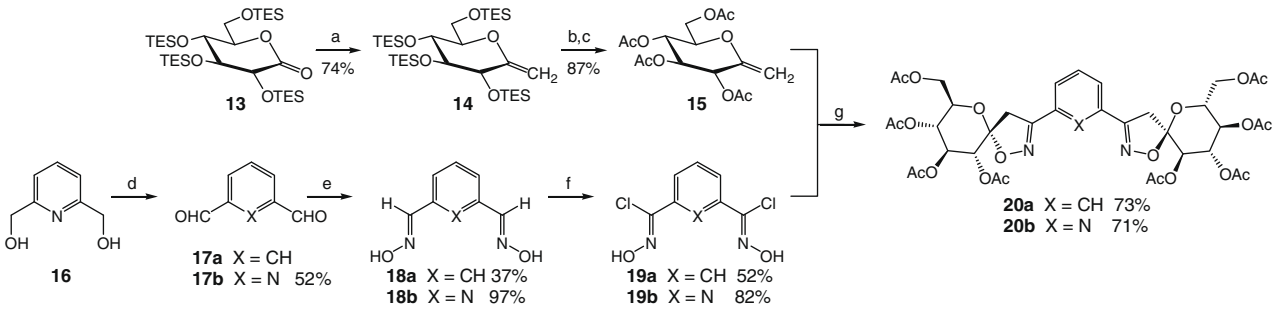
Scheme 4. Cu(I)-catalyzed addition of phenylacetylene **23** to imine **22**.

the preparation of copper(I) complexes for asymmetric cyclopropanation (**9a** and **10**) and imine alkynylation (**9b**). The yields are generally good with medium to excellent regio- and enantioselectivities.

Isoxazolines are rigid five-membered ring systems with two heteroatoms acting as Lewis bases. Spiro bis(isoxazolines) have been previously developed as chiral ligands by Sasai and co-workers[28] (Fig. 4) promoting Pd-catalyzed asymmetric Wacker-type cyclization of alkenyl alcohols,[28] intramolecular amino-carbonylation of alkenyl amines and tosylamides,[29] intramolecular cyclization of 2-alkynoates[30], and glyoxylate-ene reaction.[31] Nevertheless, the synthesis of this type of spiro bis(isoxazolines) requires several steps including a Trost asymmetric allylic alkylation to introduce chirality, which is a disadvantage for a broader application of these ligands.

We present herein the preparation of two carbohydrate-based bis spiro(isoxazoline) ligands prepared via 1,3-dipolar cycloaddition of a bis(nitrile oxide) and methylene *exo*-glucal.[32,33] The resulting bis(cycloadducts) were then evaluated in two enantioselective reactions: the Pd-catalyzed Tsuji–Trost allylic alkylation[34] and the Cu-catalyzed imine alkynylation.[35,36]

A convenient approach for the preparation of *exo*-glycals through a modified Julia olefination from the corresponding lactones has recently been reported by Gueyrard et al.[37,38] The silylated methylene *exo*-glucal **14** was therefore prepared from the lactone **13** and then converted into the corresponding acetylated glucal **15** (Scheme 1). 2,6-Pyridinedimethanol **16** was converted to the (bis)aldehyde **17b** by a Swern oxidation.[39] The benzene- and pyridine-based dialdehydes **17a–b** were then converted to the corresponding (bis)oximes **18a–b** and chlorination by NCS in the presence of a catalytic amount of HCl gas afforded the bis(carboximidoyl) chlorides **19a–b**.[40] The 1,3-dipolar cycloaddition was then carried out by generating the bis(nitrile oxides) in situ from **19a–b** and in the presence of dipolarophile **15** to afford the desired spiro bis(isoxazolines) **20a–b**.



Scheme 1. Synthesis of the glucose-based bis(spiroisoxazoline) ligands. Reagents and conditions: (a) $MeSO_2Btz$, LiHMDS, THF, −78 °C, 30 min then DBU, THF, rt, 1 h; (b) TBAF, THF, rt, 4h. (c) Ac_2O, pyridine, rt, 16h; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (e) $NH_2OH{\cdot}HCl$, $EtOH/H_2O$, 3 h; (f) NCS, DMF, HCl(g) cat., rt, 1 h; (g) Et_3N, CH_2Cl_2, rt, 16 h.

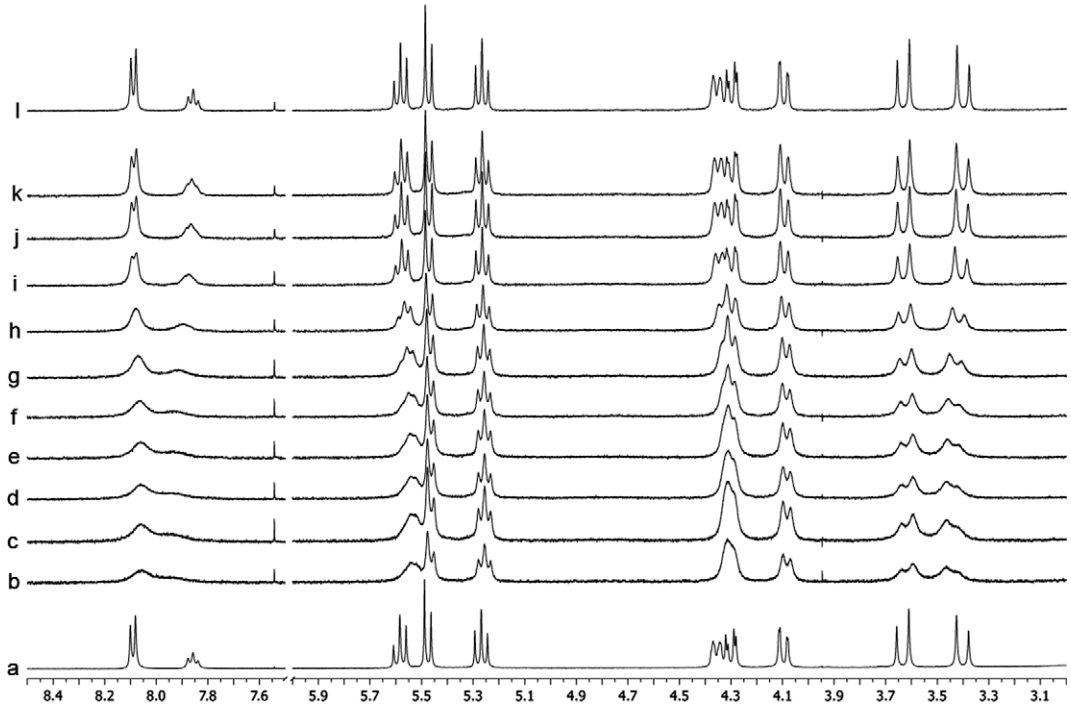


Figure 5. ^{1}H NMR stability study for ligand **20b** in the presence of Cu(I) (400 MHz, 298 K, $CDCl_3$). (a) Without metal salt and with 1 equiv of CuOTf·0.5C_6H_6 after (b) 25 min, (c) 1 h, (d) 2 h, (e) 4 h, (f) 6 h, (g) 12 h, (h) 24 h, (i) 48 h, (j) 72 h, (k) 96 h, (l) 144 h.

The Tsuji–Trost allylic alkylation was performed using a standard protocol[16,17] using racemic (*E*)-1,3-diphenyl-2-propenyl acetate and dimethyl malonate in CH_2Cl_2 under two experimental conditions (Scheme 2).

The reaction was performed with either 4 mol % of a π-allyl complex of Pd(II) or 2 mol % of a tetrakis phosphine Pd(0) derivative. Even though we could observe a modest conversion of the substrate to the desired product, the amount of material obtained was too small to determine reliable enantiomeric excess values.

When pyridine-based ligand **20b** was placed in solution with 1 equiv of $Pd(OAc)_2$ in $CDCl_3$, we observed by NMR the formation of a new product after only a few minutes. Its proportion kept slowly increasing and the reaction reached to completion within 24–36 h. The structure of the product was assigned to the ring-opened derivative **21** in which the aromatic isoxazole ring is formed as a driving force for the reaction (Scheme 3). We therefore assume that the poor conversion observed under Tsuji–Trost allylic alkylation conditions is mostly due to the gradual decomposition of the ligand in the presence of the Pd catalyst.

Next, the Cu(I)-catalyzed addition of imine alkynylation was investigated using conditions employed previously (Scheme 4).[24] While the catalyst formed with benzene-based ligand **20a** did not promote the conversion of imine **22** and alkyne **23** even after prolonged reaction time, pyridine-based ligand **20b** afforded the desired addition product **24** in good yield albeit with modest enantioselectivity. This shows that new pyridine-based ligand **20b** is capable of forming a catalytically active *N*,*N*,*N*-tridentate complex with the metal. On the other hand, benzene-based ligand **20a**, possibly because of the lack of the pyridine's nitrogen atom, is not suitable for the formation of an efficient copper catalyst, affording poor results in the alkynylation. These results were favorably compared with the data obtained for the Tsuji–Trost reaction, even though the enantioselectivity has to be improved.

The stability of pyridine-based ligand **20b** under the conditions required for the imine alkynylation protocol was verified in a ^{1}H NMR study (Fig. 5). The initial NMR spectrum of **20b** (Fig. 5, spectrum a) displays sharp multiplets for both the pyranose ring and the pyridine system. Upon addition of 1 equiv of CuOTf·0.5C_6H_6, these signals become significantly broader due to the presence of Cu(I) species and their interactions with the ligand in solution (Fig. 5, spectrum b). The peak resolution for the pyranose peaks improves significantly after 24 h (Fig. 5, spectrum h) and after almost 4 days the pyridine signals were also well resolved again (Fig. 5, spectrum k). We can therefore assume that ligand **20b** is stable under the conditions required for the imine alkynylation reaction.

In conclusion, we have designed a short synthetic route to carbohydrate-based spiro bis(isoxazoline) ligands using a 1,3-dipolar cycloaddition of a methylene *exo*-glucal as the key step. These ligands were then evaluated in the Tsuji–Trost allylic alkylation providing only modest conversion. Ring-opening of the carbohydrate isoxazoline moieties upon addition of $Pd(OAc)_2$ could explain the lack of conversion observed. Nevertheless, in Cu(I)-catalyzed imine alkynylation the pyridine-bridged ligand **20b** provided better results in terms of reactivity. This finding is encouraging us in pursuing this research program toward more rigid carbohydrate scaffolds but also furanose derivatives, involving a 2,6-disubstituted pyridine motif as the central core unit for the selective formation of tridentate complexes with Cu(I).

Acknowledgments

The authors wish to thank CNRS and Université Lyon 1 (S.V.), the DFG, and VolkswagenFoundation (M.M.K.B) for financial support.

Supplementary data

Supplementary data (experimental details for all new compounds and enantioselective reaction procedures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.028.

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