

A New Pyridyl Bis(oxazoline) Ligand Prepared from D-Glucosamine for Asymmetric Alkynylation of Imines

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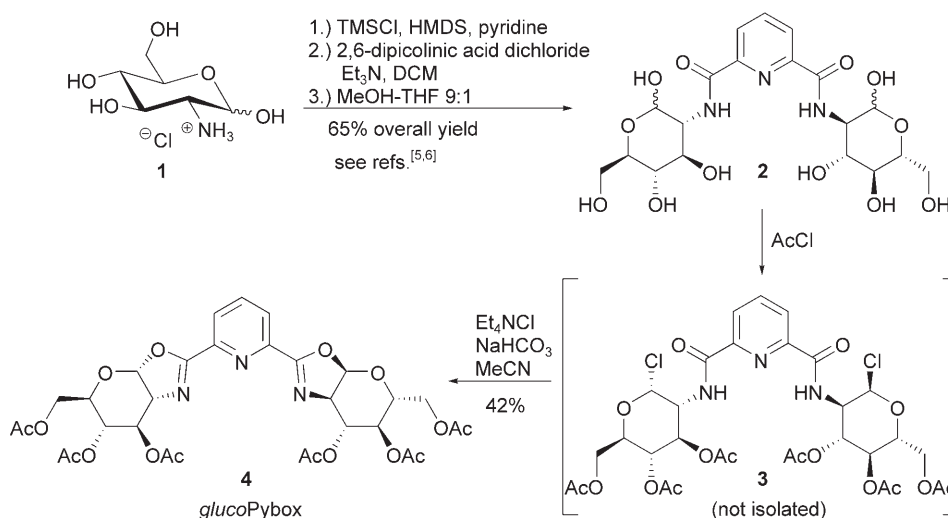
Abstract: A new carbohydrate-based pyridyl bis(oxazoline) has been prepared from D-glucosamine *via* simple steps. With this ligand enantioselectivities up to 99% were achieved in copper(I)-catalysed alkynylations of imines.

Keywords: alkynylation; asymmetric catalysis; carbohydrates; copper; ligand design; oxazolines

Asymmetric induction in stereoselective reactions is often effected by compounds derived from the *chiral pool*. Unlike amino acids, terpenes and alkaloids, carbohydrates are not commonly employed in asymmetric synthesis. Nevertheless, an increasing number of efficient auxiliaries, reagents, complex ligands and even organocatalysts based on saccharides has been reported over the past two decades.^[1,2] With the aim to develop new carbohydrate ligands for metal cataly-

sis, we became interested in bidentate bis(oxazolines)^[3] (box) and tridentate pyridyl bis(oxazolines)^[3b,c,4] (pybox). These ligands, which are very useful in a wide range of reactions, are usually not obtainable from naturally occurring precursors. Recently we introduced a new box ligand based on D-glucosamine (*glucoBox*), leading to good enantioselectivities in asymmetric cyclopropanation.^[5] In continuation of this work, we prepared a pyridyl bis(thiazoline)^[6] and now report a new carbohydrate pybox ligand and its evaluation in an asymmetric transformation.

Preparation of the new ligand started from bis-(amide) **2**, which was obtained from D-glucosamine hydrochloride (**1**) by a procedure described earlier by us.^[5,6] Treatment of **2** with neat acetyl chloride and subsequently with solid sodium hydrogen carbonate in the presence of tetraethylammonium chloride in a one-pot reaction^[5,7] yielded ligand *glucoPybox* (**4**) which, starting from D-glucosamine, was obtained in an overall yield of 27% in four simple steps (Scheme 1).



Scheme 1. Preparation of *glucoPybox* ligand **4**.

Table 1. Enantioselective alkynylation of imines^[a] with *glucoPybox* **4**.

Entry	R ¹ –CHO	R ² –NH ₂	R ³ –C≡CH	Solvent	Yield [%] ^[b]	ee [%] ^[c]
1	Ph	Ph	Ph	toluene	75	78
2	Ph	Ph	Ph	CHCl ₃	29	80
3	Ph	Ph	Ph	CH ₂ Cl ₂	69	99
4	Ph	4-MeOC ₆ H ₄	Ph	CH ₂ Cl ₂	38	90 ^[d]
5	Ph	Ph	TMS	CH ₂ Cl ₂	21	90
6	Ph	4-MeOC ₆ H ₄	TMS	CH ₂ Cl ₂	29	<i>rac.</i>
7	4-MeOC ₆ H ₄	Ph	Ph	CH ₂ Cl ₂	33	80
8	4- <i>i</i> -PrC ₆ H ₄	Ph	Ph	CH ₂ Cl ₂	57	75
9	4-ClC ₆ H ₄	Ph	Ph	CH ₂ Cl ₂	46	74
10	2-MeOC ₆ H ₄	Ph	Ph	CH ₂ Cl ₂	92	70

^[a] Absolute configurations of the products shown in general structure **9** were assigned by analogy according to literature data.^[9b,10]

^[b] Isolated yields after chromatography.

^[c] Determined by ¹H NMR with Rh₂[R-(+)-MTPA]₄ as chiral complexing reagent (dirhodium method).^[18]

^[d] Determined by GC on a chiral stationary phase.

For evaluation of new ligand **4** we selected the enantioselective copper(I)-catalysed addition of alkynes to imines.^[8] This reaction, leading to propargylamines, was first reported in 2002 by Li^[9] using a pybox ligand. Excellent enantiomeric excesses were achieved for the alkynylation of imines derived from aromatic aldehydes and anilines with phenylacetylene. Later, Singh^[10] developed a one-pot procedure for similar substrates and Chan^[11] reported the addition of aliphatic and aromatic alkynes to α -imino esters, both authors using pybox ligands. Highly efficient procedures for other substrates using different ligands and/or metals have been reported by Knochel,^[12] Carreira,^[13] Benaglia,^[14] Hoveyda,^[15] and Bolm.^[16]

We first explored the reaction of the imine from benzaldehyde and aniline with phenylacetylene using ligand **4** (8 mol%) and copper(I) triflate (5 mol%) in toluene, chloroform and dichloromethane (Table 1, entries 1–3). Of these solvents the latter proved to be the most efficient, giving the propargylamine product in 69% isolated yield and excellent 99% *ee*. Encouraged by this result, which is on par with the selectivities achieved by Li and Singh with pybox ligands from non-natural precursors, we explored other substrates. For a broad application of the reaction, employing 4-methoxyaniline as the amine component is desirable, as the *p*-methoxyphenyl (PMP) residue can be oxidatively cleaved^[17] to access free propargylamines. Regarding the alkyne component, silylacetylenes are attractive substrates as the silyl groups can be removed as well yielding a product with a terminal alkyne moiety for further elaboration. When ligand **4**

was used for the reaction with 4-methoxyaniline (entry 4) and trimethylsilylacetylene (entry 5), respectively, 90% *ee* were obtained for both substrates, but the product yields dropped severely. While the modest yields are certainly disappointing, the enantiomeric excess achieved for the silylacetylene is among the best reported for a copper(I)/pybox catalyst system (60% *ee* by Li^[9b] and 48% *ee* by Chan,^[11a] respectively). The combination of 4-methoxyaniline and trimethylsilylacetylene in one experiment (entry 6) led to only modest yields and surprisingly to a racemic product. Next, we tested ligand **4** with various substituted benzaldehyde substrates along with aniline and phenylacetylene (entries 7–10). The respective products were obtained in modest to good yields and in selectivities of 70–80% *ee*, results that are encouraging, yet will have to be improved for general applicability of ligand **4** in the synthesis of aromatic propargylamines.

In conclusion, we have developed a new pyridyl bis(oxazoline) ligand (*glucoPybox*) based on D-glucosamine. As the new ligand is prepared from an inexpensive carbohydrate precursor in four simple steps, it may be possible to turn it into an interesting alternative to conventional pybox ligands which are not accessible from natural sources. For this purpose, the selectivity and also the activity of the copper(I)/*glucoPybox* (**4**) system has to be improved by modification of the ligand structure. Investigations to this end are currently in progress in our laboratories.

Experimental Section

Procedure for the Preparation of *glucoPybox* (4) from Bis(amide) 2

Bis(amide) **2** (3.60 g, 7.36 mmol), obtained as described previously,^[5,6] was taken up in acetyl chloride (40 mL) and stirred at room temperature. The progress of the reaction was monitored by TLC (petroleum ether/ethyl acetate, 1:3). After 16 h the acetyl chloride was removed under vacuum and the residue was twice co-evaporated with toluene. The raw chloride **3** was then dissolved in dry acetonitrile (40 mL), Et₄NCl (2.63 g, 15.8 mmol) and solid NaHCO₃ (2.63 g, 31.30 mmol) were added. The resulting mixture was stirred for 16 h at room temperature. The reaction was monitored by TLC (petroleum ether/ethyl acetate, 1:3). The solvent was removed under vacuum, the residue was taken up in dichloromethane (50 mL) and washed with water (50 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The raw product was purified by flash chromatography on silica gel (first eluting with petroleum ether/ethyl acetate, 1:2, and finally with pure ethyl acetate) affording *pybox* ligand **4** as a yellow foam; yield: 2.16 g (3.07 mmol, 42%); ¹H NMR (CDCl₃, 400 MHz, ppm): δ = 8.18 (2H, d, *J* = 7.9 Hz, pyridine H), 7.88 (1H, t, *J* = 7.9 Hz, pyridine H), 6.21 (2H, d, *J* = 7.5, H-1), 5.31 (2H, dd ≈ t, *J* = 2.7 Hz, H-3), 4.88 (2H, ddd, *J* = 1.0, 2.7, 7.5 Hz, H-4), 4.35 (2H, ddd, *J* = 1.0, 2.7, 7.5 Hz, H-2), 4.05–4.10 (4H, m, H-6, H-6'), 3.62 (2H, ddd ≈ dt *J* = 3.8, 8.5 Hz, H-5), 2.14, 2.10, 1.97 (each s, each 6H, OAc); ¹³C NMR (CDCl₃, 400 MHz, ppm): δ = 170.5, 169.5, 169.3 (C, C=O, Ac), 163.8 (C, O=C=N), 147.0 (C, pyridine), 139.0 (CH, pyridine), 128.0 (CH, pyridine), 100.3 (CH, C-1), 70.1 (CH, C-5), 68.2 (CH, C-3), 68.0 (CH, C-4), 65.0 (CH, C-2), 62.5 (CH₂, C-6), 20.8, 20.6, 20.5 (CH₃, OAc); HR ESI-MS (positive): *m/z* = 728.1898, calcd. for C₃₁H₃₅N₃O₁₆ [M+Na]⁺: 728.2017; [α]: +92.72 (c 1.87, CHCl₃).

General Procedure for Cu(I)-Catalyzed Asymmetric Alkynylation of Imines

The imines were synthesized by heating a mixture of freshly distilled aldehyde (0.66 mmol) and amine (0.72 mmol) at 60°C for about two hours. Under a nitrogen atmosphere CuOTf·0.5C₆H₆ (5 mol%) and *glucoPybox* **4** (8 mol%) were dissolved in dry dichloromethane (2–3 mL) and the alkyne (0.99 mmol) was added. The preformed imine was slowly added and the mixture was stirred at room temperature for 48 h. After completion of the reaction the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 33:1).

Supporting Information

Full experimental procedures, characterisation data for all compounds are available as Supporting Information.

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