*gluco*Box—a new carbohydrate-based bis(oxazoline) ligand. Synthesis and first application†

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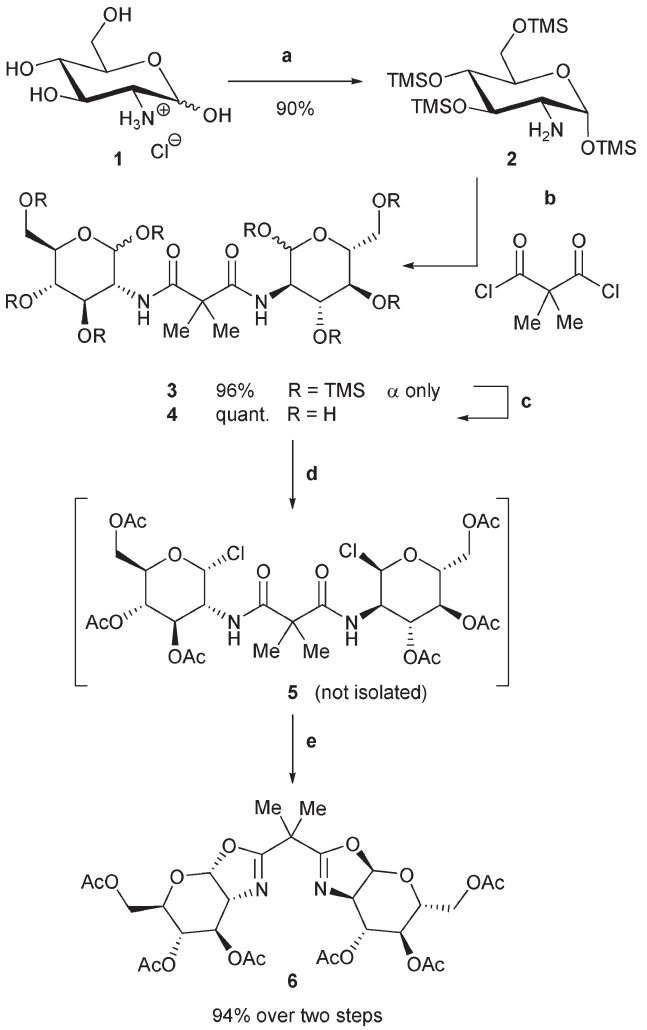
The synthesis of a new bis(oxazoline) ligand from D-glucosamine and its application in enantioselective copper(I) catalysed cyclopropanations of olefins is described.

Over the last two decades bis(oxazolines) have emerged as one of the most versatile ligand classes for metal catalysed asymmetric transformations.[1] They are prepared from chiral β-amino alcohols and dicarboxylic acid derivatives by condensation[1c] and are applied in several important and synthetically valuable enantioselective reactions. Among them the cyclopropanation of olefins with diazoesters first reported independently by Pfaltz *et al.*,[2a] Masamune and co-workers[2b,2c] and Evans *et al.*[2d] is a prominent example and also a kind of "sharpening stone" for new ligand structures.

Even though D-glucosamine, an inexpensive amino sugar from the *chiral pool*, contains a β-amino alcohol substructure and its *N*-acylated derivatives form oxazolines quite easily, this carbohydrate has rarely been employed for the synthesis of chiral oxazoline ligands. To date only a handful of examples of such structures have appeared. The groups of Kunz and Gläser[3], Uemura and co-workers[4] as well as Diéguez and colleagues[5] reported on bidentate phosphorus-containing mono(oxazolines) based on glucosamine and their application in palladium catalysed reactions. The only contribution so far concerning carbohydrate bis(oxazolines) was published by Hartinger *et al.*[6] in 2005 describing two ferrocene-bridged structures also derived from glucosamine. The publication included MS studies of palladium complexes of these ligands but no data on application have been reported so far.

In this communication we disclose a facile synthesis of a new carbohydrate bis(oxazoline) ligand with a dimethylmethylene bridge (*gluco*Box) from glucosamine hydrochloride. Further, the first results obtained for its application in the copper(I) catalysed cyclopropanation of olefins with ethyl diazoacetates are presented.

For ligand synthesis we selected a route *via* the bis(amide) of glucosamine with dimethylmalonyl dichloride and subsequent cyclisation to yield the bis(oxazoline). All attempts to form the bis(amide) directly from unprotected glucosamine and malonyl dichloride under mildly basic conditions (sodium methoxide in methanol, triethylamine in DMF) only led to decomposition of the acid chloride component. Therefore glucosamine hydrochloride (**1**) was first treated with trimethylsilylchloride (TMSCl) and hexamethyl disilazane (HMDS) in pyridine[7a] to exclusively yield per-*O*-silyl protected derivative **2** as a crystalline solid. Under these conditions the amino function remains unprotected.[7b] Reaction of **2** with dimethylmalonyl dichloride in the presence of triethyl amine as base, conditions originally employed for preparation of bis(amides) from cyclohexyl amine derivatives,[8] yielded bis(amide) **3**. After *O*-silyl deprotection with trifluoroacetic acid in methanol, the unprotected bis(amide) **4** was obtained and directly used for further transformations (Scheme 1).



Scheme 1 Preparation of *gluco*Box ligand **6**. Conditions: (a) TMSCl, HMDS, pyridine, rt; (b) Et_3N, DCM, 0 °C to rt; (c) MeOH–TFA 9 : 1, rt; (d) AcCl, rt; (e) $NaHCO_3$, NEt_4Cl, MeCN, rt.

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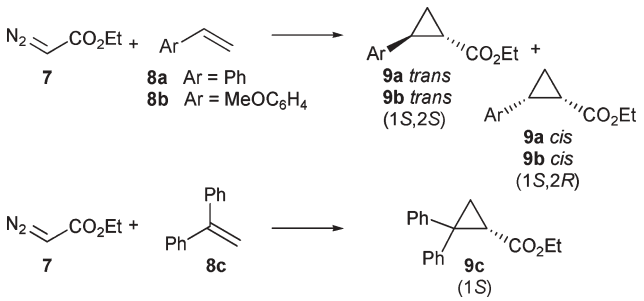

Scheme 2 Asymmetric cyclopropanations performed with copper(I)-*gluco*Box. Absolute configurations of the products were assigned by optical rotation and comparison with literature values (*cf.* electronic supplementary information†).

Most syntheses of carbohydrate oxazolines from *N*-acyl glucosamines use 1-*O*-acylated compounds as starting materials that are cyclised under Brønsted acid or Lewis acid catalysis. We therefore attempted to activate the anomeric position of peracetylated or perbenzoylated derivatives of **4** with different Lewis acids such trimethylsilyl triflate,[9a,9b] stannic chloride[9c] or ferric chloride.[9d] We also treated the acylated derivatives with hydrogen bromide[9e,9f] to subsequently activate the resulting anomeric bromide with tetraalkyl ammonium bromide *via in situ* anomerisation.[9g] However, all these methods were not successful with our acylated precursors, leading either to incomplete transformation or extensive decomposition of the starting material. Therefore we were extremely pleased to find that the desired bis(oxazoline) **6** could be obtained directly from unprotected bis(amide) **4** by simple stirring in acetyl chloride and subsequently treating the resulting bis(glucosyl chloride) **5** with sodium hydrogen carbonate and triethylammonium chloride in a one-pot reaction. These conditions were originally described for oxazoline synthesis from *N*-acetyl glucosamine.[10] Thus *gluco*Box ligand **6**‡ was prepared from **1** in four steps in an excellent overall yield of 81% (Scheme 1).

With *gluco*Box ligand **6** in hand we began our evaluation studies regarding its efficiency in metal catalysed asymmetric transformations. As a first model reaction we chose the enantioselective copper(I) catalysed cyclopropanation of alkenes with diazoacetates. Styrene (**8a**), *para*-methoxy styrene (**8b**) and 1,1-diphenyl ethene (**8c**) as alkene components were reacted with ethyl diazoacetate in the presence of the preformed complex of ligand **6** with copper(I) triflate (Scheme 2).§ The results are summarised in Table 1.

The cyclopropanation of all alkenes proceeded in good yields with *trans* : *cis* ratios for **9a** and **9b** comparable to those reported in the literature.[2] We were pleased to find that enantiomeric excesses for all *trans* as well as for all *cis* products are well above 70%.

Table 1 Asymmetric cyclopropanation of alkenes with ethyl diazoacetate (**7**) catalysed by copper(I) triflate with *gluco*Box ligand **6**

Entry	Alkene	Product	Yield[a] (%)	*trans* : *cis*	ee *trans* (%)	ee *cis* (%)
1	**8a**	**9a**	60	70 : 30[b]	82[c]	82[c]
2	**8b**	**9b**	72	65 : 35[b]	77[d]	80[c]
3	**8c**	**9c**	85	—	75[d]	

[a] Based on **7**, isolated yields after chromatography. [b] Determined after separation of the isomers. [c] Determined by GC. [d] Determined by ^{1}H NMR with Rh_2[*R*-(+)-MTPA]$_4$ as chiral complexing reagent (dirhodium method).[11]

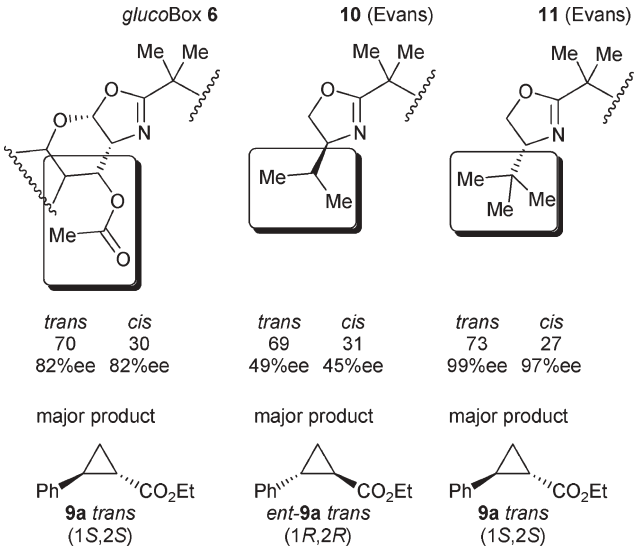

Fig. 1 Comparison of *gluco*Box ligand **6** to known bis(oxazolines).[2d] All values given refer to the cyclopropanation of styrene (**8a**) with ethyl diazoacetate (**7**), configurations for the major *trans* products are given.

These results are very promising, as the carbohydrate scaffold of **6** offers many opportunities for structural modifications. By optimising the ligand structure through modification, it should be possible to further increase the optical yields and thus to obtain tailor-made ligands for the cyclopropanation reaction.

Fig. 1 shows a comparison of the results achieved in the cyclopropanation of styrene (**8a**) with ethyl diazoacetate (**7**) with new ligand **6** to those reported for known bis(oxazolines)[2d] derived from biogenic amino acid (*S*)-valine (**10**) and non-biogenic (*R*)-*tert*-leucine (**11**). The absolute stereochemistry of the major *trans* products is displayed as well. While all three ligands lead to essentially the same *trans* : *cis* ratios, the enantomeric excesses differ substantially. While *gluco*Box **6** is inferior to *tert*-butyl substituted ligand **11**, it gives substantially better results than valine derived ligand **10**. This can be explained by the steric demand of the substituent at the stereocenter adjacent to the coordinating nitrogen atom: exchanging the isopropyl residue of **10** for a bulkier *tert*-butyl group in **11** results in increased enantioselectivity. The steric demand of the "substituent" in ligand **6** (the sugar moiety) appears to be somewhere between that of the isopropyl and the *tert*-butyl group, as is reflected by the results obtained for the cyclopropanations.

It is important to note that ligand **6** is prepared in a few simple steps from inexpensive glucosamine whereas ligand **11** requires the rather costly *tert*-leucine as a starting material. Thus, by improving the efficiency of ligand **6** by modification, it might be possible to obtain a low-price alternative to **11**.

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Notes and references

‡ Spectroscopic data for *gluco*Box ligand **6**: $[\alpha]_D^{25}$ + 53 (*c* 1.9 in chloroform); δ_H (400 MHz; $CDCl_3$) 1.58 (6H, s, $(CH_3)_2C$), 1.98, 2.05, 2.16, (each 6H, each s, CH_3CO), 3.86 (2H, ddd, $J_{4,5}$ 9.2, $J_{5,6}$ 4.8, H-5), 4.13

(2H, dd, $J_{5,6'}$ 2.7, $J_{6,6'}$ 12.3, H-6′), 4.18 (2H, ddd, $J_{1,2}$ 7.5, $J_{2,3}$ 2.4, $J_{2,4}$ 1.3, H-2), 4.22 (2H, dd, $J_{5,6}$ 4.8, $J_{6,6'}$ 12.3, H-6), 4.94 (2H, ddd, $J_{3,4}$ 2.4, $J_{2,4}$ 1.3, $J_{4,5}$ 9.2, H-4), 5.31 (2H, dd ≈ t, $J_{2,3}$ $J_{3,4}$ 2.4, H-3), 6.05 (2H, d, $J_{1,2}$ 7.5, H-1); δ_C (100 MHz, $CDCl_3$) 20.7, 20.8, 20.9 (each 2 × t, CH_3CO), 23.8 (2 × t, $(CH_3)_2C$), 39.2 (q, $(CH_3)_2C$), 62.8 (2 × s, C-6), 64.8 (2 × t, C-2), 67.8 (2 × t, C-5), 68.3, (2 × t, C-4), 70.1, (2 × t, C-3), 100.0 (2 × t, C-1), 170.6, 170.2, 169.5, 169.2 (each 2 × q, CH_3CO, CN).; HRMS (ESI) $C_{29}H_{39}O_{16}N_2$ $[M + H]^+$ calcd. 671.2300, found 671.2298, $C_{29}H_{38}O_{16}N_2Na$ $[M + Na]^+$ calcd. 693.2119, found 693.2036.

§ General conditions for cyclopropanation: in a dry box CuOTf·0.5C_6H_6 (1.8 mg, 7.2 μmol, 1 mol%) and *gluco*Box ligand **6** (5.2 mg, 8 μmol, 1.1 mol%) were placed into a flame-dried flask. Under nitrogen dichloromethane (2 cm^3) was added and the resulting mixture was stirred for 2 h at room temperature. To this preformed catalyst solution the alkene component (5 mmol) was added. The mixture was cooled to 0 °C and ethyl diazoacetate (0.7 mmol) dissolved in dichloromethane (1 cm^3) was slowly added over a period of 2.5 h with a syringe pump at the same temperature. The mixture was allowed to warm to room temperature and was stirred for another 16 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel.

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