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First synthesis of a carbohydrate-derived pyridyl bis(thiazoline) ligand

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Abstract—The first synthesis of a carbohydrate-based pyridyl bis(thiazoline) ligand starting from D-glucosamine and its application in asymmetric cyclopropanation reactions are reported.

As asymmetric metal catalysed reactions have become an invaluable tool in organic synthesis, the development of new chiral ligands is an important scientific task. Bis(oxazolines)[1] represent one important ligand family that has witnessed a rapid evolution. They are nowadays employed in reactions as different as cyclopropanations, pericyclic and Michael reactions as well as aldol type additions. Thiazolines, the sulfur congeners of oxazolines have been rarely used for this purpose, even though the first application of a chiral bis(thiazoline) ligand was reported in one of the first publications on bis(oxazolines) by Helmchen[2] in 1991.

Recently bis(thiazolines) have received renewed attention after Masson and Gulea prepared several methylene bridged bis(thiazolines) and pyridyl bis(thiazolines).[3a] Both types were tested in the Tsuji–Trost reaction,[3a,b] the former led to good selectivities while the pyridyl bis(thiazoline) provided only low stereoinduction in this reaction. This ligand was also tried out in ruthenium catalysed cyclopropanations,[3c] and yielded products with moderate to good selectivity. Further examples of methylene bridged bis(thiazolines) prepared by Du and co-workers[4] led to moderate selectivities in the Tsuji–Trost reaction. Molina and Tárraga[5] prepared ferrocene bridged bis(thiazolines) albeit without reporting on their application. Recently a number of sterically congested bis(thiazolines) and their testing results in copper catalysed Diels–Alder reactions were described by the group of Kunieda,[6] followed shortly afterwards by a report from Nishio and co-workers,[7] using a ligand with an ethylene bridge for the same reaction. Both ligand types led to quite promising results. These reports show that bis(thiazolines) have certainly potential as a new class of ligands in enantioselective synthesis. In this Letter, we report the first preparation of a carbohydrate-derived pyridyl bis(thiazoline) ligand from glucosamine hydrochloride.

With the aim to develop new synthetic tools based on carbohydrates as inexpensive and versatile starting materials from the *chiral pool*[8] we recently prepared a new bis(oxazoline) ligand (*gluco*Box)[9] starting from D-glucosamine. After this bis(oxazoline) had led to good enantioselectivities in copper catalysed cyclopropanations, we became interested in the corresponding thiazoline derivative.

N-Acetyl glucosamine can be easily converted into the corresponding thiazoline by treating the peracetylated compound with Lawesson's reagent[10] following a procedure reported by Withers et al.[11] Therefore we decided to prepare our target molecules via peracetylated bis(amide) precursors. This approach appeared particularly attractive, for a bis(amide) of glucosamine and dimethyl malonic acid is an intermediate in the synthesis of the new bis(oxazoline) ligand.[9]

For the preparation of the desired acetyl-protected bis(amide), amino sugar **1** was per-*O*-TMS protected and the resulting derivative **2** was subsequently coupled with dimethylmalonyl dichloride to yield bis(amide) **3a**,

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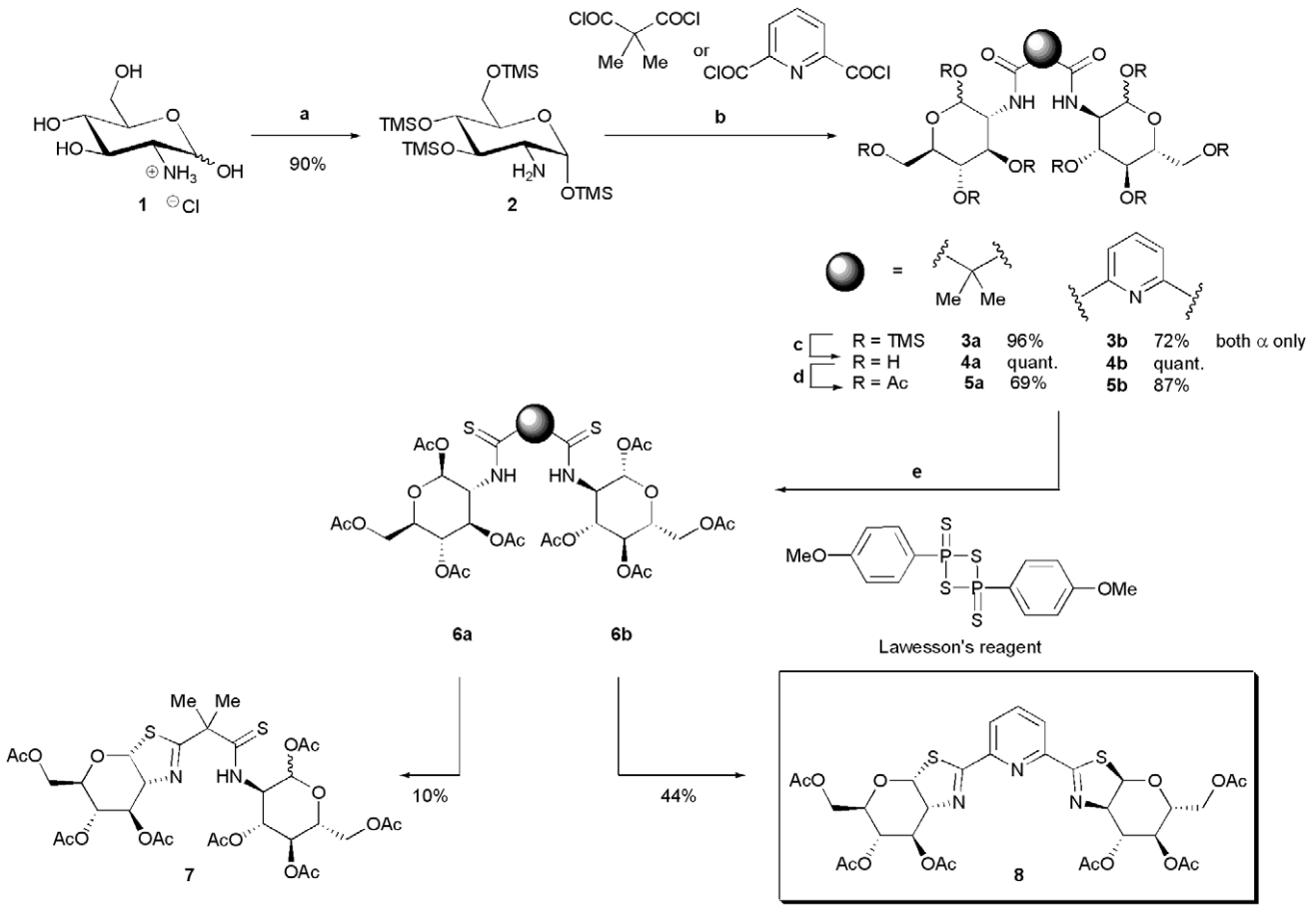
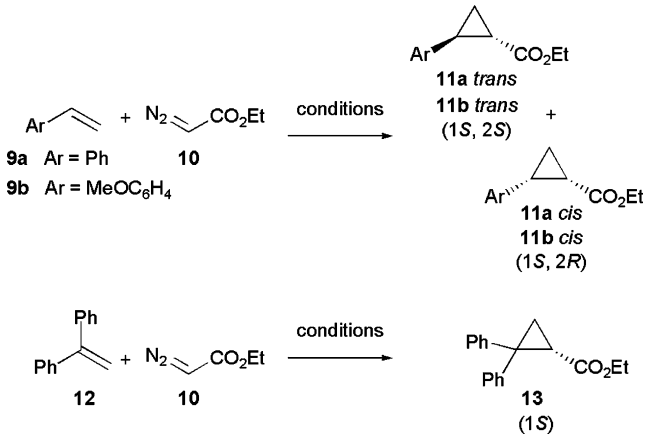


Scheme 1. Synthesis of bis(thiazolines). Reagents and conditions: (a) TMSCl, HMDS, pyridine, rt; (b) Et_3N, CH_2Cl_2, 0 °C to rt; (c) TFA/MeOH 1:9, rt; (d) Ac_2O, pyridine, rt; (e) toluene, reflux.

which was then deprotected. Acetylation of deprotected compound **4a** under standard conditions with acetic anhydride in pyridine gave **5a**, the precursor for the cyclisation reaction. Treatment of **5a** with Lawesson's reagent in refluxing toluene according to the literature procedure[11] led to selective formation of bis(thioamide) **6a**[12] but no cyclisation occurred. Longer reaction time and variation of the reaction conditions as changing the number of equivalents for Lawesson's reagent, microwave conditions or addition of Lewis acids as e.g. TMSOTf did not effect the desired double cyclisation either. Instead mono(thiazoline) **7** was identified as the major product of this reaction (Scheme 1).

After this first unsuccessful attempt we tried the reaction with Lawesson's reagent on bis(amide) derived from dipicolinic acid (Scheme 1). This was prepared analogously to malonyl bis(amide). First *O*-TMS-protected **2** was reacted with dipicolinic acid chloride to yield compound **3b**,[13] which was de-silylated and subsequently acetylated to give bis(amide) **5b**. All these steps proceeded smoothly and in good to excellent yields. The reaction with Lawesson's reagent in refluxing toluene under the conditions described in the literature[11] gave bis(thioamide) **6b**.[14] Belleau's reagent[15] and phosphorus pentasulfide[16] were also tried as thionation agents, but from these tests the starting material was recovered unchanged. The desired double cyclisation could finally be effected with Lawesson's reagent by prolonging the reaction time. After flash chromatography on silica gel with petroleum ether/ethyl acetate 1:3 only 18% of the target compound were obtained, but after eluting the column residue with pure ethyl acetate, we were pleased to find that this last fraction contained another batch of the product. Thus target compound **8** was obtained in an overall yield of 44% directly from starting material



Scheme 2. Cyclopropanation experiments with ligand **8**.

Table 1. Cyclopropanation reactions of styrene with ligand **8**

Entry	Alkene	Metal salt	Conditions[a]	Yield[b] (%)	trans:cis[c]	ee trans (%)	ee cis[c] (%)
1	Styrene (**9a**)	$[RuCl_2(p\text{-cymene})]_2$	CH_2Cl_2, 0 °C	44	55:45	Racemic[d]	
2	Styrene (**9a**)	Cu(OTf)·0.5Ph·H	CH_2Cl_2, 0 °C	65	58:42	28[d]	18[d]
3	Styrene (**9a**)	Cu(OTf)·0.5Ph·H	CH_2Cl_2, −20 °C	No reaction	—	—	—
4	Styrene (**9a**)	Cu(OTf)·0.5Ph·H	CH_2Cl_2, 35 °C	70	63:37	22[d]	20[d]
5	Styrene (**9a**)	Cu(OTf)·0.5Ph·H	Toluene, 0 °C	64	54:46	22[d]	24[d]
6	Styrene (**9a**)	Cu(OTf)·0.5Ph·H	Et_2O, 0 °C	44	61:39	18[d]	16[d]
7	4-Methoxy styrene (**9b**)	Cu(OTf)·0.5Ph·H	CH_2Cl_2, 0 °C	19	70:30	24[e]	10[e]
8	1,1-Diphenyl ethylene (**12**)	$[RuCl_2(p\text{-cymene})]_2$	CH_2Cl_2, 0 °C	5	—	Racemic[e]	
9	1,1-Diphenyl ethylene (**12**)	Cu(OTf)·0.5Ph·H	CH_2Cl_2, 0 °C	6	—	Racemic[e]	

[a] Ligand **8** (1.1 mol %), metal salt (1 mol %).
[b] Isolated yields after chromatography.
[c] Determined after separation of isomers.
[d] Determined by GC on a chiral stationary phase.
[e] Determined by ^1H NMR with $Rh_2[R\text{-}(+)\text{-MTPA}]_4$ as chiral complexing reagent (dirhodium method).[21]

5b.[17] The different behaviour of bis(amides) **5a** and **5b** in the double cyclisation reaction may be explained by invoking steric aspects. While in bis(amide) **5b** the glucosamine moieties are connected via a planar pyridyl bridge, those in **5a** are connected by a dimethyl methylene spacer. This bridge is a bulky unit as well as a lot shorter than the pyridyl spacer. While the first part of the cyclisation reaction with Lawesson's reagent, formation of bis(thioamides) **6a** and **6b** works for both compounds, the double cyclisation is only observed for **6b** with the longer, flat bridging unit, while **6a** only gives monocyclisation product **7**. Therefore it seems likely that steric congestion prevents a second cyclisation step in compound **7**. For this reaction the sulfur atom of the remaining thioamide has to attack the anomeric centre as a nucleophile, which in this case is formidably bulky.

With pyridyl bis(thiazoline) **8** in hand we tried the new ligand in the metal catalysed cyclopropanation of styrene (**9a**) with ethyl diazoacetate (**10**), which is often used as a benchmark reaction for new ligand structures (Scheme 2, Table 1). The first experiments were performed with ruthenium(II) as the metal centre according to the protocol reported by Nishiyama[18] and also employed by Masson.[3c] Bicyclic ligand **8** gave only racemic products in rather poor yield, while the monocyclic bis(thiazoline) ligands reported by Masson et al. led to enantiomeric excesses above 85%. Therefore bicyclic ligand **8** appears as not well suited for the ruthenium catalysed reaction. While copper(I) catalysed cyclopropanations with bis(oxazoline) ligands yield products with good to excellent enantioselectivities,[19] pyridyl bis(oxazolines) have rarely been used as ligands in this reaction and optical yields of cyclopropanes are low.[20] Using ligand **8** and copper(I) triflate at 0 °C in dichloromethane as the solvent, cyclopropanation products **11a** trans and **11a** cis were obtained in improved yields and with improved but still low enantioselectivities. Next we performed several cyclopropanation experiments under varying conditions to increase the enantioselectivity (cf. Table 1). Running the reaction at lower temperature (entry 3) did not give any product, while elevated temperatures led to a small increase in product yield but predictably to slightly lower enantioselectivities (entry 4). Keeping the temperature at 0 °C but switching the solvent from dichloromethane to toluene or diethyl ether (entries 5 and 6) lowered the enantioselectivities compared to those achieved in dichloromethane under the same conditions (entry 2). Finally two other alkenes, 4-methoxy styrene (**9b**) and 1,1-diphenyl ethylene (**12**) were tried in the reaction (Scheme 2). These gave the corresponding products only in severely decreased yield and with low or no selectivity. All results of the cyclopropanation experiments are summarised in Table 1.

In conclusion we have prepared a new carbohydrate-derived pyridyl bis(thiazoline) ligand in five simple steps and employed it in asymmetric cyclopropanation as a trial reaction. Although the first trials did not lead to high enantioselectivities, we think that the new ligand structure may be of more value in other metal catalysed transformations. Investigations to this end are currently underway.

Acknowledgements

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12. *Analytical data for compound* **6a**: ^{1}H NMR (400 MHz; $CDCl_3$, rt): 7.81 (2H, d, $J = 8.5$ Hz, NH), 6.37 (2H, d, $J = 9.4$ Hz, H-1), 5.39 (2H, dd ≈ t, $J = 9.5$ Hz, H-3), 5.20 (2H, dd ≈ t, $J = 9.5$ Hz, H-4), 5.21 (2H, ddd, $J = 3.8$, 8.5, 10.9 Hz, H-2), 4.26 (2H, dd, $J = 4.8$, 12.9 Hz, H-6), 4.07–3.99 (4H, m, H-6′, H-5), 2.17, 2.07, 2.03, 2.01 (each s, each 6H, OAc) ppm; HR ESI MS (positive): $[M+Na]^+$ found *m*/*z* 845.1854, $C_{33}H_{46}O_{18}N_2S_2$ requires *m*/*z* 845.2085.
13. *Analytical data for compound* **3b**: ^{1}H NMR (400 MHz; $CDCl_3$, rt): 8.43 (1H, d, $J = 7.8$ Hz, pyridine H), 8.05 (2H, t, $J = 7.9$ Hz, pyridine H), 7.38 (2H, d, $J = 10.4$ Hz, NH), 5.19 (2H, d, $J = 3.8$ Hz, H-1), 4.41 (2H, m, H-2), 3.65–3.90 (10H, m, H-3, H-4, H-5, H-6, H-6′), 0.25, 0.22, 0.19, 0.10 (each 18H, each s, TMS) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, rt): 163.9 (C, C=O), 149.5 (C, pyridine), 139.5 (CH, pyridine), 128.1 (CH, pyridine), 92.4 (CH, C-1), 74.2, 72.3, 72.2 (CH, C-3, C-4, C-5), 61.9 (CH_2, C-6), 55.0 (CH, C-2), 1.4, 0.8, 0.5, 0.2 (CH_3, TMS) ppm; HR ESI MS (positive): $[M+Na]^+$ found *m*/*z* 1088.4624, $C_{43}H_{91}O_{12}N_3Si_8$ requires *m*/*z* 1088.4758; $[\alpha]_D$ +247.4 (*c* 1.8, $CHCl_3$).
14. *Analytical data for compound* **6b**: ^{1}H NMR (400 MHz; $CDCl_3$, rt): 9.98 (2H, d, $J = 10.2$ Hz, NH), 8.58 (2H, d, $J = 7.8$, pyridine H), 7.93 (1H, t, $J = 7.8$ Hz, pyridine H), 6.18 (2H, d, $J = 8.5$ Hz, H-1), 5.74 (2H, dd ≈ t, $J = 9.9$, Hz, H-3), 5.40–5.25 (4H, m, H-4, H-2), 4.28 (2H, dd, $J = 4.8$, 12.6 Hz, H-6), 4.15 (2H, dd, $J = 2.4$, 12.6 Hz, H-6′), 3.90 (2H, ddd, $J = 2.4$, 4.8, 9.9 Hz, H-5), 2.08, 2.07, 2.0, 1.88 (each s, each 6H, OAc) ppm; HR ESI MS (positive): $[M-H]^-$ found *m*/*z* 856.1841, $C_{35}H_{43}O_{18}N_3S_2$ requires *m*/*z* 856.1905.
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17. To a solution of acetylated bisamide **5b** (1.00 g, 1.26 mmol, 1 equiv) in dry toluene (20 cm^3) Lawesson's reagent (1.54 g, 3.84 mmol, 3 equiv) was added. The reaction mixture was first refluxed for 48 h at 140 °C and then for another day at rt. The progress of the reaction was monitored by TLC (petroleum ether/ethyl acetate 1:2). After removal of the solvent by evaporation the raw product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 1:2). Further, the residue was eluted from the column with ethyl acetate and the spectroscopic data proved it to be another batch of pyridyl bis(thiazoline) **8**, which was isolated in an overall yield of 44% (0.41 g, 0.55 mmol) as a brown foam. Analytical data for compound **8**: ^{1}H NMR (400 MHz; $CDCl_3$, rt): 8.19 (2H, d, $J = 7.2$ Hz, pyridine H), 7.92 (1H, t, $J = 7.9$ Hz, pyridine H), 6.32 (2H, d, $J = 7.5$ Hz, H-1), 5.68 (2H, dd, $J = 2.1$, 3.1 Hz, H-3), 5.03 (2H, dd ≈ d, $J = 8.9$ Hz, H-4), 4.82 (2H, m, H-2), 4.18–4.05 (4H, m, H-6, H-6′), 3.62 (2H, ddd ≈ t, $J = 4.8$ Hz, H-5), 2.19, 2.06, 2.04 (each s, each 6H, OAc) ppm; ^{13}C NMR (100 MHz; MeOD, rt): 174.9, 174.8, 173.9 (C, C=O, Ac), 173.7 (C, S–C=N), 153.8 (C, pyridine), 142.2 (CH, pyridine) 127.3 (CH, pyridine), 89.9 (CH, C-1), 81.3 (CH, C-2), 74.3 (CH, C-3), 73.5 (CH, C-4), 72.4 (CH, C-5), 67.2 (CH_2, C-6), 23.4, 23.4, 23.2 (CH_3, Ac–CH_3) ppm; HR ESI MS (positive): $[M+Na]^+$ found *m*/*z* 760.0986, $C_{31}H_{35}O_{14}N_3S_2$ requires *m*/*z* 760.1560; $[\alpha]$ +81.3 (*c* 0.8, $CHCl_3$).
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