

Communication

# Sugar-Annulated Oxazoline Ligands: A Novel Pd(II) Complex and Its Application in Allylic Substitution

Jochen Kraft, Katharina Mill and Thomas Ziegler \*

Institute of Organic Chemistry, University of Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany; jochen.kraft@uni-tuebingen.de (J.K.); katharina.mill@student.uni-tuebingen.de (K.M.)

\* Correspondence: thomas.ziegler@uni-tuebingen.de; Tel.: +49-(0)7071-29-78763; Fax: +49-(0)7071-29-5244

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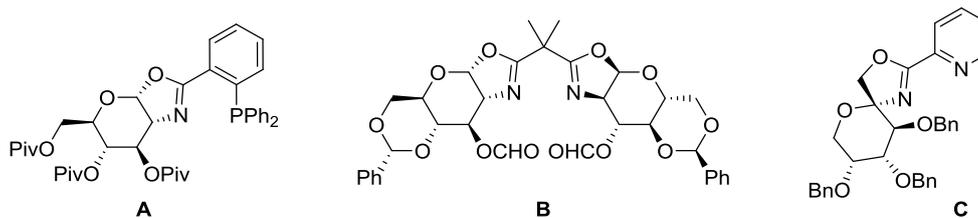
**Abstract:** Two novel carbohydrate-derived pyridyl (PYOX)- and cyclopropyl (CYBOX)-substituted oxazoline ligands were prepared from D-glucosamine hydrochloride and 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy- $\beta$ -D-glucopyranose hydrochloride in two steps, respectively. The sugar-annulated PYOX ligand formed a stable metal complex with Pd(II), which was fully characterized by NMR spectroscopy and X-ray crystallography. NMR and X-ray analysis revealed a change of the conformation in the sugar moiety upon complexation with the palladium(II) species. Both glycosylated ligands resulted in high asymmetric induction (up to 98% *ee*) upon application as chiral ligands in the Pd-catalyzed allylic alkylation of *rac*-1,3-diphenylallyl acetate with dimethyl malonate (Tsuji-Trost reaction). Both ligands provided mainly the (*R*)-enantiomer of the alkylation product.

**Keywords:** asymmetric catalysis; carbohydrates; oxazolines; palladium complexes; pyridines; Tsuji-Trost

## 1. Introduction

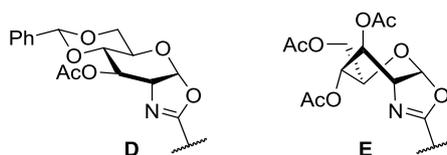
During the past decades, the use of carbohydrates as chiral auxiliaries, chiral reagents, organocatalysts and, most notably, as chiral ligands for metal-catalyzed stereoselective reactions has become a powerful tool for organic chemists [1,2]. This is in part due to the fact that carbohydrates are one of the most abundant chiral natural products on earth and, therefore, in many cases are easily isolable from natural sources in high enantiomeric purity and large quantities. As a matter of fact, several highly efficient privileged ligands for asymmetric syntheses have been obtained from carbohydrates [3–7]. However, the enantioselective construction of C-C bonds, in particular the synthesis of tertiary carbon stereocenters, remains an ongoing challenge for organic chemists. Over the last years, however, transition metal-catalyzed allylic alkylation (Tsuji-Trost reaction) has evolved into one of the most potent methods for synthesizing such tertiary stereocenters [8,9].

In 1998, Kunz and Gläser introduced a *glucoPHOX* ligand (Figure 1A) derived from D-glucosamine, which was used in the Pd(II)-catalyzed allylic substitution of various symmetrically and non-symmetrically 1,3-disubstituted 2-propenyl acetates with dimethyl malonate [10]. The in situ generated Pd-catalyst showed a high asymmetric induction of up to 98% *ee* for the addition of dimethyl malonate to *rac*-1,3-diphenylallyl acetate.



**Figure 1.** Examples of literature-known *glucoPHOX* (A); *glucoBOX* (B) and *spiroPYOX* (C) ligands.

Recently, Boysen et al. described the synthesis of several *D-gluco*- and *D-allo*-configured bisoxazoline (BOX) ligands (Figure 1B) [11–13]. The ligands were applied in the Cu(I)-catalyzed cyclopropanation of olefins with azoesters and in the asymmetric alkynylation of imines with up to 99% *ee*. The authors observed that a cyclic 4,6-*O*-benzylidene acetal-protecting group at the carbohydrate scaffold has a positive influence on the stereo-discrimination properties of the ligands. Boysen et al. attributed this outcome to the  ${}^4H_5$  chair-like conformation of the carbohydrate moiety (Figure 2D) which is fixed by the 4,6-*O*-benzylidene acetal [12,13]. This conformation is in contrast to similar bisoxazoline glycosides lacking a cyclic protecting group, which adopt an  ${}^0S_2$  twist-like conformation (Figure 2E).



**Figure 2.** Carbohydrate conformations of sugar-annulated 1,2-oxazoline ligands in the presence (D) and absence (E) of cyclic protecting groups.

As part of our ongoing research program towards the development of novel carbohydrate ligands for asymmetric syntheses, we previously described the preparation of a series of spiro-fused PYOX ligands (Figure 1C) and Pd(II) complexes thereof which were applied in Pd-catalyzed allylic alkylations [14,15]. X-ray crystallography of the Pd complexes revealed that the orientation of the OBn-protecting group at C-3 in these *spiroPYOX* ligands could have a major impact on the shielded side of the metal center and, thus, could result in a different stereo-discrimination in Pd-catalyzed asymmetric reactions. Indeed, we could further demonstrate that our *D*-fructose-based ligands mainly provided the (*R*)-enantiomer in the Pd-catalyzed allylic alkylation of 1,3-diphenylallyl acetate with dimethyl malonate whereas the *D*-psicose-derived ligands gave the (*S*)-enantiomer of the alkylation product instead [15].

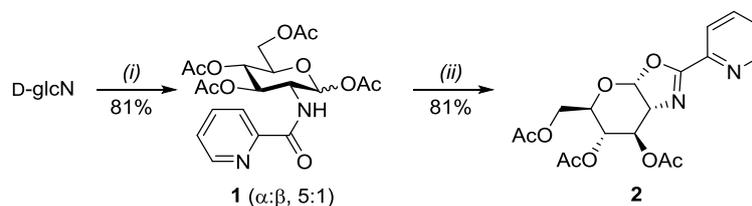
These results on the spiro-fused carbohydrate-oxazoline ligands encouraged us to take a closer look into sugar-annulated oxazoline ligands and their metal complexes. Herein we report a straightforward synthesis of a novel *D*-glucosamine-derived PYOX ligand and its Pd(II) complex. Furthermore, we report on a new sugar-annulated cyclopropane-based CYBOX ligand as well as preliminary findings in the application of these ligands in the Tsuji-Trost reaction.

## 2. Results and Discussion

### 2.1. Synthesis of Oxazoline Ligands

Our synthesis route to the PYOX ligand (Scheme 1) proceeded via amide coupling of *D*-glucosamine hydrochloride with picolinic acid to afford the corresponding picolinamide **1**. Subsequent cyclization of **1** under modified Lemieux conditions [11,16] gave 1,2-oxazoline **2** in 81% yield. The regioselective condensation of *D*-glucosamine with picolinic acid was best accomplished with the HBTU/HOBt reagent, followed by exhaustive acetylation with  $\text{Ac}_2\text{O}$  in pyridine. Previously,

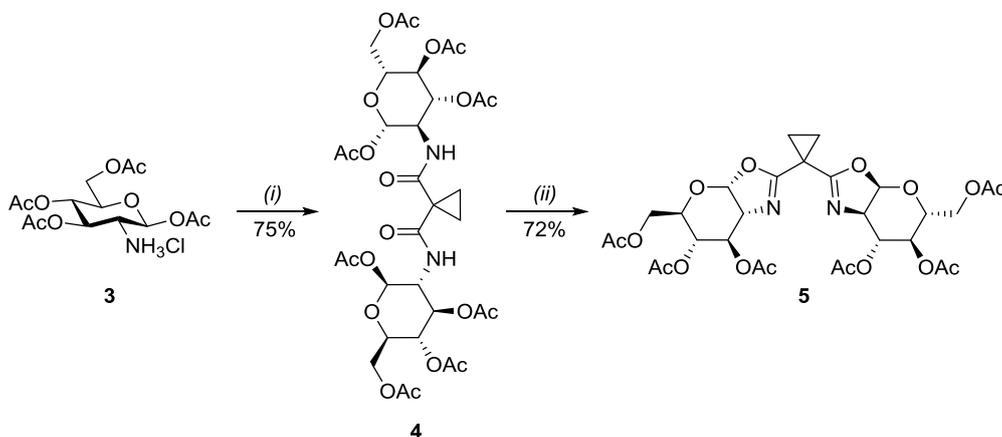
glucose derivative **1** was prepared via a Pd-catalyzed aminocarbonylation of 2-pyridyl tosylate in 48% yield [17].



**Scheme 1.** Synthesis of sugar-annulated PYOX ligand **2**. Reagents and conditions: (i) (a) HBTU/HOBt, picolinic acid, DIPEA, DMF, 0 °C-rt, 14 h; (b) Ac<sub>2</sub>O, pyridine, 0 °C-rt, 12 h, 81% ( $\alpha:\beta$ , 5:1; determined by <sup>1</sup>H-NMR); (ii) (a) HBr in AcOH, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C-rt, 2 h; (b) Bu<sub>4</sub>NBr, NaHCO<sub>3</sub>, MeCN, rt, 12 h, 81%.

Although compound **1** was obtained as a 5:1 mixture of its anomers, favoring the  $\alpha$ -anomer, the two anomers were not separated for the next synthetic step since treatment with HBr in the next step gave solely the corresponding  $\alpha$ -glycosyl bromide intermediate from both anomers. Subsequent cyclization of the intermediate with Bu<sub>4</sub>NBr and NaHCO<sub>3</sub> gave the annulated oxazoline ligand **2** in 81% yield.

For the synthesis of the cyclopropane-based CYBOX ligand **5** (Scheme 2) we started from readily available 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy- $\beta$ -D-glucopyranose hydrochloride **3** [18] which was condensed with cyclopropane-1,1-dicarboxylic acid under mediation of HBTU/HOBt to afford the corresponding bis-amide **4**. Cyclization to **5** was again achieved by sequential substitution of the anomeric acetate in **4** with HBr in AcOH, followed by treatment of the intermediate glycosyl bromide with Bu<sub>4</sub>NBr and NaHCO<sub>3</sub> (Scheme 2). Yields for both steps were medium due to the formation of unidentified by-products which had to be removed by column chromatography.

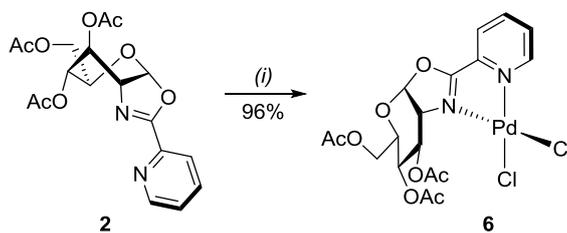


**Scheme 2.** Synthesis of sugar-annulated CYBOX ligand **5**. Reagents and conditions: (i) HBTU/HOBt, cyclopropane-1,1-dicarboxylic acid, DIPEA, DMF 0 °C-rt, 15 h, 75%; (ii) (a) HBr in AcOH, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C-rt, 2 h; (b) Bu<sub>4</sub>NBr, NaHCO<sub>3</sub>, MeCN, rt, 17 h, 72%.

## 2.2. Palladium(II) Complex of Ligand 2

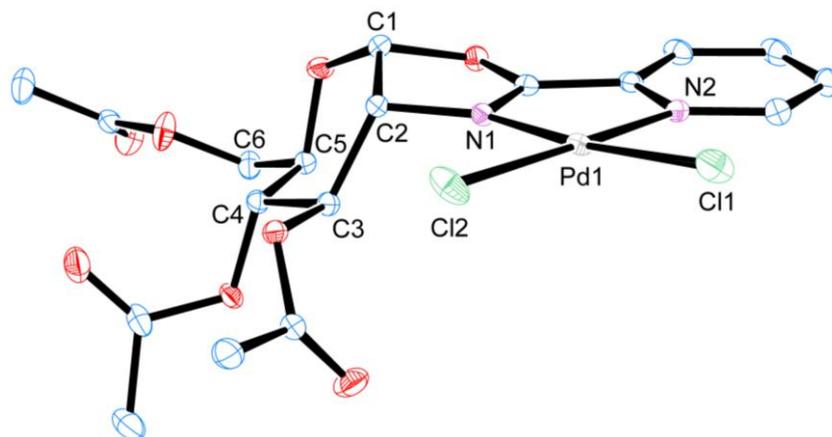
The Pd(II) complex **6** was prepared by the reaction of a slight molar excess of the sugar-annulated ligand **2** with dichloro-(1,5-cyclooctadiene)palladium(II) in 1,2-dichloroethane (Scheme 3). Pd complex **6** was obtained as an orange, microcrystalline solid which was air- and moisture-stable in solution as well as in the solid state. Unfortunately, complexation of CYBOX ligand **5** with Pd(II) under identical conditions did not yield suitable crystals. Complex **6** was soluble in polar organic solvents such as

MeCN, but insoluble in  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$  and non-polar organic solvents such as *n*-pentane, *n*-hexane and  $\text{Et}_2\text{O}$ .



**Scheme 3.** Complexation of PYOX ligand **2** with Pd(II). Reagents and conditions: (i)  $\text{PdCl}_2(\text{cod})$ , DCE, rt, 72 h, 96%. cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane.

Crystals suitable for X-ray analysis of complex **6** were obtained by slow diffusion of  $\text{Et}_2\text{O}$  into a saturated solution of **6** in MeCN. Crystal data and structure refinements of the X-ray analysis are given in the Supplementary Material. Figure 3 illustrates the molecular structure of **6** along with selected interatomic distances and bond angles. Pd complex **6** crystallizes in the orthorhombic space group  $P2_12_12_1$  and showed the expected square-planar molecular geometry of the  $d^8$ -configured palladium. The bite angle of  $80.7^\circ$ , which is formed by oxazoline-*N* (N1) and pyridine-*N* (N2), is in accordance with previously published similar PYOX-Pd complexes [14,19–21].



**Figure 3.** ORTEP plot of the molecular structure of the Pd complex **6**. Hydrogen atoms have been omitted for clarity; ellipsoids are given at the 50% probability level. Blue = carbon; red = oxygen; pink = nitrogen; grey = palladium; green = chlorine. Selected bond-distances (Å) and -angles ( $^\circ$ ): Pd1-N1 2.0284(14), Pd1-N2 2.0439(15), Pd-Cl1 2.2779(5), Pd-Cl2 2.2692(5); N1-Pd-N2  $80.70(6)$ .

The carbohydrate scaffold in the palladium complex **6** adopts a slightly distorted  ${}^4H_5$  conformation in the solid state. This is contrary to the conformation of similar literature-known uncomplexed 1,2-annulated sugar-oxazolines such as compound **2** which adopt a  ${}^0S_2$  conformation [22,23]. We therefore suggested a conformational change of the carbohydrate moiety upon complexation of **2** with the palladium salt. This assumption was supported by  ${}^1\text{H-NMR}$  analysis of ligand **2** and Pd complex **6** and a comparison of the relevant chemical shifts and vicinal coupling constants (Table 1). All NMR spectra were recorded in trideuteroacetonitrile in order to avoid possible solvent effects on the chemical shifts and the coupling constants.

The vicinal coupling constant  $J_{3,4}$  in ligand **2** changed upon complexation with  $\text{PdCl}_2(\text{cod})$  by 0.7 Hz, whereas  $J_{4,5}$  alternated by 2.0 Hz, respectively. This is in accordance with the present change of the vicinal-proton torsion angles from the modified skew ( ${}^0S_2$ ) to the distorted half-chair ( ${}^4H_5$ ) conformation.



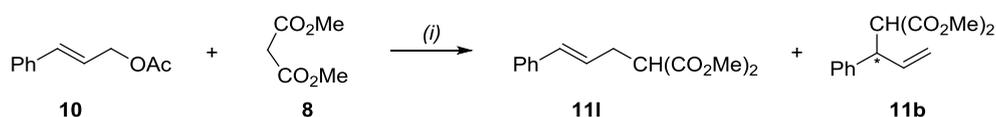
**Table 2.** Pd-catalyzed allylic alkylation of *rac*-7 using ligands 2 and 5.

Entry	Ligand	Solvent	Yield <sup>b</sup>	<i>ee</i> <sup>c</sup>
1 <sup>a</sup>	A	CH <sub>2</sub> Cl <sub>2</sub>	94%	98% ( <i>R</i> )
2	2	CH <sub>2</sub> Cl <sub>2</sub>	92%	47% ( <i>R</i> )
3	2	THF	53%	56% ( <i>R</i> )
4	2	MeCN	71%	56% ( <i>R</i> )
5	2	PhCH <sub>3</sub>	traces	n.d.
6 <sup>d</sup>	2	MeCN	9%	66% ( <i>R</i> )
7 <sup>e,f</sup>	2	MeCN	38%	47% ( <i>R</i> )
8	5	CH <sub>2</sub> Cl <sub>2</sub>	48%	98% ( <i>R</i> )
9	5	THF	traces	n.d.
10	5	PhCH <sub>3</sub>	traces	n.d.
11	5	MeCN	35%	97% ( <i>R</i> )

<sup>a</sup> Taken from Reference [10]. <sup>b</sup> Isolated yield after chromatographic purification. <sup>c</sup> Enantiomeric excess was determined by chiral HPLC analysis. The absolute configuration was determined by comparison of the optical rotation with literature values [27]. <sup>d</sup> T = 0 °C. <sup>e</sup> Preformed Pd complex 6 was used. <sup>f</sup> 10 mol % AgSbF<sub>6</sub>. n.d. = not determined.

To our delight, C<sub>2</sub>-symmetrical CYBOX ligand 5 showed a high asymmetric induction of up to 98% *ee* when used as a pre-catalyst in the allylic alkylation of *rac*-7 (Table 2, entry 8). Unfortunately, by switching the solvent to THF or toluene, the reaction was found to be completely blocked (Table 2, entries 9 and 10). Running the reaction in acetonitrile slightly decreased the conversion (35%), although the enantioselectivity remained excellent (97% *ee*, Table 2, entry 11).

Encouraged by these results we decided to investigate the regioselectivity and enantioselectivity of the allylic substitution of non-symmetrical substituted cinnamyl acetate 10 with dimethyl malonate 8 (Scheme 5). This catalytic system was previously studied in great detail by Pfaltz and coworkers [29]. Generally, monosubstituted allylic substrates such as 10 react predominantly at the unsubstituted allyl terminus to give the achiral, linear product 111 rather than the chiral, branched regioisomer 11b [30].



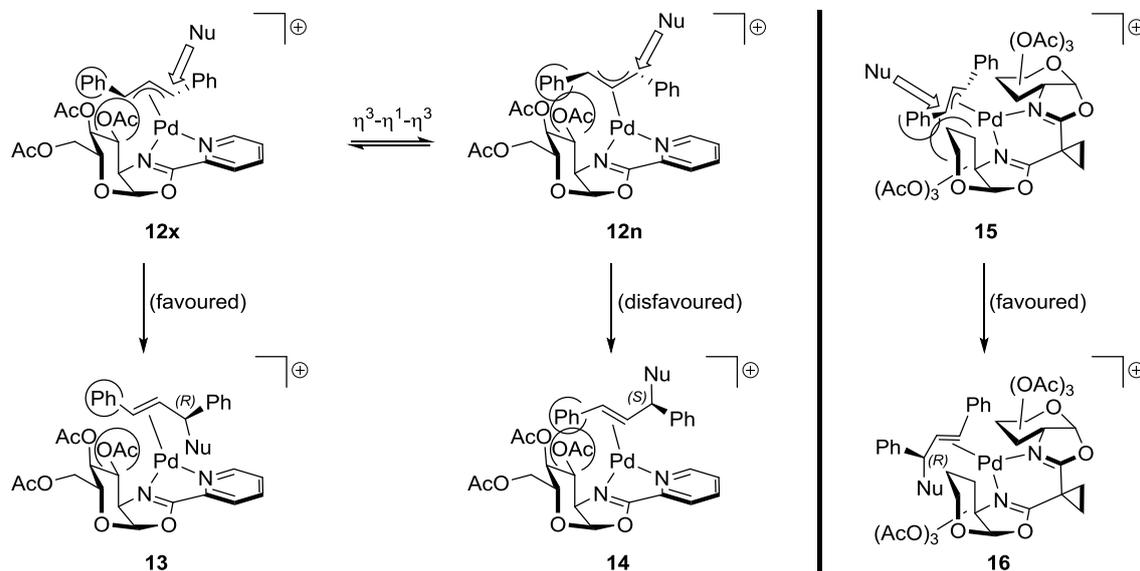
**Scheme 5.** Palladium-catalyzed allylic alkylation of cinnamyl acetate (10). Reagents and conditions: (i) CYBOX ligand 5, [PdCl(C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>], KOAc/BSA, MeCN, rt, 24 h, 100% conv., 111:11b  $\geq$  99:1. BSA = *N,O*-Bis(trimethylsilyl)acetamide.

As very low conversions (5%–7%) were found within 24 h of reaction time with 5 mol % of [PdCl(C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>] and 11 mol % of PYOX ligand 2, we decided to conduct further studies with CYBOX ligand 5. However, cyclopropane-based ligand 5 led to full conversions in 24 h and afforded nearly exclusively linear substituted product 111 (111:11b  $\geq$  99:1).

#### 2.4. Proposed Mechanism

The stereoselective outcome of the Tsuji-Trost reaction can be explained by a model for the proposed transition state (Scheme 6). Due to the C<sub>1</sub>-symmetry of PYOX ligand 2, *exo* (12x) and *endo* (12n) diastereomers of the intermediate allyl-palladium complexes can be distinguished. These *exo/endo* diastereomers exist in a dynamic equilibrium and can isomerize via a fast  $\eta^3$ - $\eta^1$ - $\eta^3$  mechanism. The *exo/endo* isomerization is approximately 10 to 100 times faster than the nucleophilic addition to the allyl-palladium complex. Thus, it is reasonable to assume that the *exo/endo* ratios have a major impact on the observed stereoselectivities [9,26]. The attack of the nucleophile is therefore possible in four different ways: at the allyl terminus which is *cis* or *trans* to the oxazoline ring in each of the *exo* or *endo* diastereomers, respectively. In accordance with previously published reports of PYOX ligands in

allylic substitutions, we assume that the attack of the nucleophile occurs at the allyl terminus which is *trans* to the oxazoline [31,32]. If the nucleophile attacks *trans* to the oxazoline ring in the *endo* complex **12n**, the formed  $\eta^2$  complex **14** must have the (*S*) configuration which, however, is contrary to our observed stereoselectivity. Hence, we suggest that the nucleophilic attack occurs predominantly to the *exo* isomer **12x**, leading to the  $\eta^2$  complex **13** which exhibits the (*R*) configuration.



**Scheme 6.** Proposed transition state and origin of enantio-discrimination in allylic substitution. Nu = CH(CO<sub>2</sub>Me).

In the case of the C<sub>2</sub>-symmetrical CYBOX ligand **5**, there is no distinction between *exo* and *endo* diastereomers in the allyl-palladium intermediate **15**. Therefore, there are only two possible reaction pathways. The origin of the enantio-discrimination arises here from repulsive interactions between one of the carbohydrate moieties and a phenyl group in the allyl substrate [33]. If the nucleophilic attack occurs at the allyl terminus at which the repulsion between the carbohydrate scaffold and the phenyl group is present, the steric strain in **15** will be reduced. The so-formed  $\eta^2$  complex **16** exhibits an (*R*) configuration, which is in accordance with our observed stereoselectivity.

### 3. Materials and Methods

#### 3.1. General Remarks

All solvents were dried according to standard methods, distilled and stored over molecular sieves 3 Å under an atmosphere of nitrogen prior to their use. Petroleum ether (PE) refers to the fraction boiling in the 60–90 °C range. All non-aqueous reactions were performed in oven-dried glassware under an atmosphere of N<sub>2</sub> unless stated otherwise. NMR spectra were recorded on a Bruker Avance 400 spectrometer (Bruker Biospin GmbH, Rheinstetten, Germany) and were calibrated for the solvent signal (<sup>1</sup>H-CDCl<sub>3</sub>: 7.26 ppm; <sup>13</sup>C-CDCl<sub>3</sub>: 77.16 ppm. <sup>1</sup>H-CD<sub>3</sub>CN: 1.94 ppm; <sup>13</sup>C-CD<sub>3</sub>CN: 1.32 ppm). NMR signals were numbered in accordance with carbohydrate nomenclature. ESI-HRMS data were measured on a Bruker Daltonics MAXIS 4G spectrometer (Bruker Daltonics GmbH, Bremen, Germany). MALDI-TOF spectra were recorded on a Bruker Autoflex II (Bruker Daltonics GmbH) using *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propylidene]malonodinitril (DCTB) as the matrix. Elemental analyses were performed on a HEKAtech Euro 3000 CHN (HEKAtech GmbH, Wegberg, Germany) analyzer. Optical rotations were measured with a Perkin-Elmer Polarimeter 341 (Perkin Elmer Inc., Waltham, MA, USA) in a 10 cm cuvette at 20 °C. Melting points were determined with a Büchi Melting Point M-560 apparatus (BÜCHI Labortechnik GmbH, Essen, Germany). Reactions were monitored

by TLC on Polygram Sil G/UV silica gel plates from Machery & Nagel (Machery & Nagel GmbH & Co. KG, Düren, Germany). Detection of spots was effected by charring with H<sub>2</sub>SO<sub>4</sub> (5% in EtOH), staining by spraying the plates with an alkaline aqueous solution of potassium permanganate or by inspection of the TLC plates under UV light. Preparative chromatography was performed on silica gel (0.032–0.063 mm) from Machery & Nagel (Machery & Nagel GmbH & Co. KG) with different mixtures of solvents as eluent. Racemic samples of **9** and **11** were synthesized according to the general procedure described in Section 3.4. by using 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) as ligand. The enantiomeric excess of compound **9** was determined by chiral HPLC analysis on a Sykam S 1121 chromatograph (SYKAM Chromatographie Vertriebs GmbH, Fürstenfeldbruck, Germany) equipped with a Reprosil Chiral-NR column (*n*-hexane:*i*PrOH, 90:10; flow 1.6 mL/min): *t*<sub>R</sub> = 6.8 min for (*R*)-**9**, *t*<sub>R</sub> = 8.6 min for (*S*)-**9**. All yields given below are isolated yields determined after purification of the product either by silica gel column chromatography or crystallization and were not optimized unless noted otherwise.

### 3.2. Synthesis of Compounds

**1,3,4,6-Tetra-O-acetyl-2-deoxy-2-picolinamido-D-glucopyranose (1)**: To an ice cold solution of D-glucosamine hydrochloride (0.50 g, 2.32 mmol) and Hünig's base (*N,N*-diisopropylamine) (1.20 mL, 6.96 mmol) in dry DMF (15 mL) was added in the following order: HOBT (1-hydroxybenzotriazole) (0.53 g, 3.48 mmol), picolinic acid (0.29 g, 2.32 mmol) and HBTU (2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.32 g, 3.48 mmol). The resulting mixture was stirred for 1 h at 0 °C followed by rt until TLC (CHCl<sub>3</sub>:MeOH, 5:1) showed complete consumption of starting material (14 h). The solution was evaporated in vacuo, re-dissolved in pyridine (10 mL) and treated with Ac<sub>2</sub>O (1.75 mL, 18.6 mmol) at 0 °C. The resulting mixture was stirred at rt until TLC (eluent EtOAc) indicated complete *O*-acetylation (12 h). The solution was poured into ice/water mixture (50 mL) and extracted twice with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The combined organic phases were washed with 0.5 M citric acid, sat. aqueous NaHCO<sub>3</sub>-sol., H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, filtered and concentrated. Chromatography of the residue (PE:EtOAc, 1:1) afforded **1** (0.85 g, 81%) as an amorphous foam (anomeric mixture; α:β, 5:1). Spectroscopic data were in accordance with literature values [17].

**2-(2-Pyridyl)-(3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-glucopyranoso)-[2,1-d]-2-oxazoline (2)**: HBr (33% in AcOH, 4.80 mL, 27.4 mmol) was added dropwise to an icecold solution of **1** (0.73 g, 1.61 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). After complete addition the mixture was allowed to warm to rt and stirring at this temperature was continued for 2 h until all starting material was consumed (TLC; PE:EtOAc, 1:1). The solution was hydrolyzed by addition of ice/water and the phases were separated. The organic layer was washed with sat. aqueous NaHCO<sub>3</sub>-sol., H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was re-dissolved in MeCN (20 mL) and Bu<sub>4</sub>NBr (0.57 g, 1.77 mmol) and NaHCO<sub>3</sub> (0.27 g, 3.23 mmol) were added. After stirring for additional 12 h at rt the suspension was evaporated in vacuo and the yellowish residue re-dissolved in EtOAc (15 mL), washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Chromatography of the residue (PE:EtOAc, 1:3 +2.5% Et<sub>3</sub>N) afforded **2** (0.51 g, 81%) as a colorless foam.  $[\alpha]_D^{20} +50.3$  (c 1.00, CHCl<sub>3</sub>). *R*<sub>f</sub> = 0.43 (PE-EtOAc, 1:3 +2.5% Et<sub>3</sub>N). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.72–8.71 (m, 1H, pyridine-H), 8.04 (d, *J* = 7.9 Hz, 1H, pyridine-H), 7.82–7.80 (td, *J* = 3.9 Hz, *J* = 1.8 Hz, 1H, pyridine-H), 7.44–7.41 (m, 1H, pyridine-H), 6.23 (d, *J*<sub>1,2</sub> = 7.4 Hz, 1H, H-1), 5.41 (t, *J* = 2.5 Hz, 1H, H-3), 4.97–4.94 (m, 1H, H-4), 4.42–4.39 (m, 1H, H-2), 4.15–4.13 (m, 2H, H-6a, H-6b), 3.70–3.66 (m, 1H, H-5), 2.10, 2.03, 1.98 (3s, 9H, CH<sub>3</sub>). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 170.6, 169.6, 169.2 (C=O), 164.2 (OCN), 150.2, 145.4, 136.9, 126.4, 124.3 (pyridine-C), 100.4 (C-1), 70.3 (C-3), 68.4 (C-4), 67.8 (C-5), 65.4 (C-2), 63.2 (C-6), 21.0, 20.8, 20.8 (CH<sub>3</sub>). HRMS-ESI: *m/z* calcd for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>8</sub>Na [M + Na]<sup>+</sup>: 415.111187; found: 415.111056. Anal. calcd for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>8</sub> (392.4): C, 55.10; H, 5.14; N, 7.14; found: C, 55.06; H, 5.45; N, 6.67.

***N,N'*-Bis(1,3,4,6-tetra-O-acetyl-2-deoxy-β-D-glucopyranos-2-yl)-cyclopropane-1,1-dicarboxamide (4)**: To an ice cold solution of 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochloride (**3**) [18]

(1.20 g, 3.12 mmol) and Hünig's base (1.63 mL, 9.38 mmol) in dry DMF (15 mL) was added in the following order: HOBt (0.72 g, 4.69 mmol), cyclopropane-1,1-dicarboxylic acid (0.20 g, 1.56 mmol) and HBTU (1.78 g, 4.69 mmol). The resulting mixture was stirred for 1 h at 0 °C followed by rt for 14 h. The mixture was evaporated to dryness and the residue re-dissolved in EtOAc (15 mL). The organic solution was washed with 0.5 M citric acid, sat. aqueous NaHCO<sub>3</sub>-sol., H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, filtered and concentrated. Chromatography of the residue (PE:EtOAc, 1:3 +1% Et<sub>3</sub>N) afforded **4** (0.93 g, 75%) as a colorless foam.  $[\alpha]_D^{20} +38.8$  (c 1.00, CHCl<sub>3</sub>).  $R_f = 0.29$  (PE:EtOAc, 1:3 +1% Et<sub>3</sub>N). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 6.59 (d,  $J = 9.6$  Hz, 2H, NH), 6.01 (d,  $J_{1,2} = 8.6$  Hz, 2H, H-1), 5.39 (t,  $J = 9.8$  Hz, 2H, H-3), 5.20 (t,  $J = 9.9$  Hz, 2H, H-4), 4.37 (q,  $J_{2,3} = 9.5$  Hz, 2H, H-2), 4.27 (dd,  $J_{6a,6b} = 12.6$  Hz,  $J_{6a,5} = 4.8$  Hz, 2H, H-6a), 4.14 (dd,  $J_{6b,6a} = 12.5$  Hz,  $J_{6b,5} = 2.4$  Hz, 2H, H-6b), 3.86 (ddd,  $J_{5,6a} = 4.7$  Hz,  $J_{5,6b} = 2.2$  Hz,  $J_{5,4} = 10.1$  Hz, 2H, H-5), 2.10, 2.10, 2.08, 2.08 (4s, 24H, CH<sub>3</sub>), 1.54–1.49 (m, 2H, cyclopropane-CH<sub>2</sub>), 1.10–1.05 (m, 2H, cyclopropane-CH<sub>2</sub>). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 173.0, 170.9, 169.8, 169.3 (C=O), 168.9 (CONH), 92.5 (C-1), 74.0 (C-3), 72.9 (C-5), 67.6 (C-4), 61.8 (C-6), 53.8 (C-2), 30.3 (quar. cyclopropane-C), 21.0, 20.9, 20.8 (CH<sub>3</sub>), 17.5 (cyclopropane-CH<sub>2</sub>). HRMS-ESI:  $m/z$  calcd for C<sub>33</sub>H<sub>44</sub>N<sub>2</sub>O<sub>20</sub>Na [M + Na]<sup>+</sup>: 811.23796; found: 811.23806. Anal. calcd for C<sub>33</sub>H<sub>44</sub>N<sub>2</sub>O<sub>20</sub> (788.7): C, 50.25; H, 5.62; N, 3.55; found: C, 50.28; H, 5.72; N, 3.37.

2,2'-Cyclopropylidenebis[(3,4,6-tri-O-acetyl-1,2-dideoxy- $\alpha$ -D-glucopyranoso)[2,1-d]-2-oxazoline] (**5**): HBr (33% in AcOH, 6.80 mL, 37.50 mmol) was added dropwise to an icecold solution of **4** (0.87 g, 1.10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL). After complete addition the mixture was allowed to warm to rt and stirring at this temperature was continued for 2 h (TLC; PE:EtOAc, 1:1). The solution was hydrolyzed with ice/water mixture and the phases were separated. The organic layer was washed with sat. aqueous NaHCO<sub>3</sub>-sol., H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was re-dissolved in MeCN (15 mL) and Bu<sub>4</sub>NBr (0.39 g, 1.21 mmol) and NaHCO<sub>3</sub> (0.19 g, 2.21 mmol) were added. After stirring for additional 17 h at rt the suspension was evaporated *in vacuo* and the yellowish residue was re-dissolved in EtOAc (20 mL). The organic solution was then washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Chromatography of the residue (PE:EtOAc, 1:3 +2.5% Et<sub>3</sub>N) afforded **5** (0.53 g, 72%) as a colorless foam.  $[\alpha]_D^{20} +47.4$  (c 1.00, CHCl<sub>3</sub>).  $R_f = 0.38$  (PE:EtOAc, 1:3 +2.5% Et<sub>3</sub>N). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 6.01 (d,  $J_{1,2} = 7.3$  Hz, 2H, H-1), 5.27–5.24 (m, 2H, H-3), 4.92 (dd,  $J = 0.8$  Hz,  $J = 9.4$  Hz, 2H, H-4), 4.21–4.12 (m, 6H, H-2, H-6a, H-6b), 3.92–3.87 (m, 2H, H-5), 2.09, 2.08, 2.07 (3s, 18H, CH<sub>3</sub>), 1.69–1.65 (m, 2H, cyclopropane-CH<sub>2</sub>), 1.42–1.37 (m, 2H, cyclopropane-CH<sub>2</sub>). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 170.8 (OCN), 169.7, 169.3, 167.1 (C=O), 100.1 (C-1), 70.4 (C-3), 68.5 (C-4), 67.8 (C-5), 64.9 (C-2), 63.2 (C-6), 21.0, 20.8 (CH<sub>3</sub>), 18.4 (quar. cyclopropane-C), 15.7 (cyclopropane-CH<sub>2</sub>). HRMS-ESI:  $m/z$  calcd for C<sub>29</sub>H<sub>36</sub>N<sub>2</sub>O<sub>16</sub>Na [M + Na]<sup>+</sup>: 691.19570; found: 691.19644. Anal. calcd for C<sub>29</sub>H<sub>36</sub>N<sub>2</sub>O<sub>16</sub> (668.6): C, 52.10; H, 5.43; N, 4.19; found: C, 52.35; H, 5.66; N, 4.10.

Dichloro[2-(2-Pyridyl)-(3,4,6-tri-O-acetyl-1,2-dideoxy- $\alpha$ -D-glucopyranoso)-[2,1-d]-2-oxazoline]palladium(II) (**6**): PdCl<sub>2</sub>(cod) (dichloro-(1,5-cyclooctadiene)palladium(II)) (57 mg, 0.200 mmol, 98 mol %) was added to a solution of **2** (80 mg, 0.204 mmol) in 4 mL dry Cl(CH<sub>2</sub>)<sub>2</sub>Cl and stirred for 72 h at rt. Evaporation to dryness and re-crystallization of the residue from dry MeCN/Et<sub>2</sub>O afforded the palladium complex **6** (110 mg, 96%) as orange needles. M.p. > 209 °C (decomp, Et<sub>2</sub>O/MeCN).  $[\alpha]_D^{20} -143.4$  (c 1.00, MeCN). <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>CN): δ = 8.97–8.95 (m, 1H, pyridine-H), 8.24 (td,  $J = 3.9$  Hz,  $J = 1.4$  Hz, 1H, pyridine-H), 7.97 (dd,  $J = 7.8$  Hz,  $J = 0.9$  Hz, 1H, pyridine-H), 7.80–7.77 (m, 1H, pyridine-H), 6.71 (d,  $J_{1,2} = 7.6$  Hz, 1H, H-1), 6.09 (t,  $J = 3.0$  Hz, 1H, H-3), 4.95 (ddd,  $J = 7.1$  Hz,  $J = 2.7$  Hz,  $J = 1.3$  Hz, 1H, H-4), 4.67 (ddd,  $J = 7.6$  Hz,  $J = 3.3$  Hz,  $J = 1.3$  Hz, 1H, H-2), 4.26–4.17 (m, 2H, H-6a, H-6b), 3.94–3.90 (m, 1H, H-5), 2.16, 2.07, 2.02 (CH<sub>3</sub>). <sup>13</sup>C-NMR (100 MHz, CD<sub>3</sub>CN): δ = 171.9, 171.3, 170.4, 169.8 (C=O, OCN), 151.7, 145.1, 142.1, 131.2, 128.0 (pyridine-C), 106.3 (C-1), 70.6 (C-5), 67.6 (C-4), 66.9 (C-3), 64.1 (C-6), 60.9 (C-2), 21.6, 21.2, 20.9 (CH<sub>3</sub>). MS (MALDI-TOF):  $m/z = 608.9$  [M + K]<sup>+</sup>. Anal. calcd for C<sub>18</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>8</sub>Pd (569.7): C, 37.95; H, 3.54; N, 4.92; found: C, 37.66; H, 3.45; N, 4.93. Crystal Data for C<sub>18</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>8</sub>Pd (M = 569.66 g/mol): orthorhombic, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (no. 19), a = 8.6185(6) Å, b = 14.6441(10) Å,

$c = 16.5033(11) \text{ \AA}$ ,  $\alpha = \beta = \gamma = 90^\circ$ ,  $V = 2082.9(2) \text{ \AA}^3$ ,  $Z = 4$ ,  $T = 100(2) \text{ K}$ ,  $\mu(\text{MoK}\alpha) = 1.197 \text{ mm}^{-1}$ ,  $D_{\text{calc}} = 1.817 \text{ g/cm}^3$ , 44885 reflections measured ( $2.666^\circ \leq 2\theta \leq 30.526^\circ$ ), 6370 unique ( $R_{\text{int}} = 0.0287$ ) which were used in all calculations. The final  $R_1$  was 0.0144 ( $I > 2\sigma(I)$ ) and  $wR_2$  was 0.0362 (all data).

### 3.3. Crystallography

Crystals of **6** for X-ray analysis were obtained by slow diffusion of Et<sub>2</sub>O into a sat. solution of **6** in MeCN. X-ray data were collected on a Bruker SMART APEX II DUO (Bruker AXS Advanced X-ray Solutions GmbH, Karlsruhe, Germany) diffractometer using a graphite-monochromated Mo K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). Corrections for absorption effects were applied using SADABS [34]. The structure was solved by direct methods using SHELXS and SHELXL for structure solution and refinement [35–38]. Further details of the refinement and crystallographic data are given in the supplementary material.

### 3.4. Asymmetric Allylic Alkylation (Tsuji-Trost Reaction)

General Procedure for the addition of dimethyl malonate (**8**) to allyl acetates (*rac*-**7** or **10**): A solution of chiral ligand **2** or **5** (0.011 mmol, 11 mol % in respect to the allyl acetate) and [PdCl(C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>] (1.8 mg, 0.005 mmol, 5 mol %) in dry CH<sub>2</sub>Cl<sub>2</sub> (1 mL) were stirred for 30 min at rt. To this catalyst solution allyl acetate (0.1 mmol, 25 mg for *rac*-**7**; 17  $\mu\text{L}$  for **10**), dimethyl malonate (**8**) (34  $\mu\text{L}$ , 0.3 mmol), *N,O*-bis(trimethylsilyl)acetamide (73  $\mu\text{L}$ , 0.3 mmol) and KOAc (0.5 mg, 0.005 mmol) were added and stirring was continued for 12 h at rt. The reaction mixture was diluted with Et<sub>2</sub>O (3 mL) and NH<sub>4</sub>Cl (2 mL) and the aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  5 mL). The combined organic phases were washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Chromatography of the residue (PE:EtOAc, 6:1) afforded the alkylated product **9** or **11**, respectively, as a colorless oil. Spectroscopic data were in accordance with literature [39,40].

## 4. Conclusions

In summary, we have synthesized the novel sugar-annulated ligands PYOX (**2**) and CYBOX (**5**) from D-glucosamine hydrochloride and readily available 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy- $\beta$ -D-glucopyranose hydrochloride in two steps, respectively. PYOX ligand **2** formed a stable Pd(II) complex upon reaction with PdCl<sub>2</sub>(cod) and was fully characterized by means of NMR, CHN, MS and crystal structure analysis. NMR and X-ray studies revealed a conformational change of the carbohydrate scaffold in ligand **2** upon complexation with Pd(II). Both ligands were used as pre-catalysts in the Pd-catalyzed allylic substitution of *rac*-1,3-diphenylallyl acetate with dimethyl malonate (Tsuji-Trost reaction). CYBOX ligand **5** provided the (*R*)-enantiomer of the alkylation product with high enantiomeric excess (up to 98% *ee*). Further ligand optimizations and substrate scope evaluations of allylic substitution are currently under investigation and will be published soon.

**Supplementary Materials:** The following are available online at <http://www.mdpi.com/1420-3049/21/12/1704/s1>.

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**Author Contributions:** J.K. and T.Z. conceived and designed the experiments; J.K. and K.M. performed the experiments and analyzed the data; J.K. and T.Z. wrote the paper. T.Z. supervised the whole research.

**Conflicts of Interest:** The authors declare no conflict of interest.

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