A Novel 1-Glycosyl-1*H*-triazole-Based *P,N* Ligand for Rhodium-Catalyzed Asymmetric Hydrosilylation of Ketones

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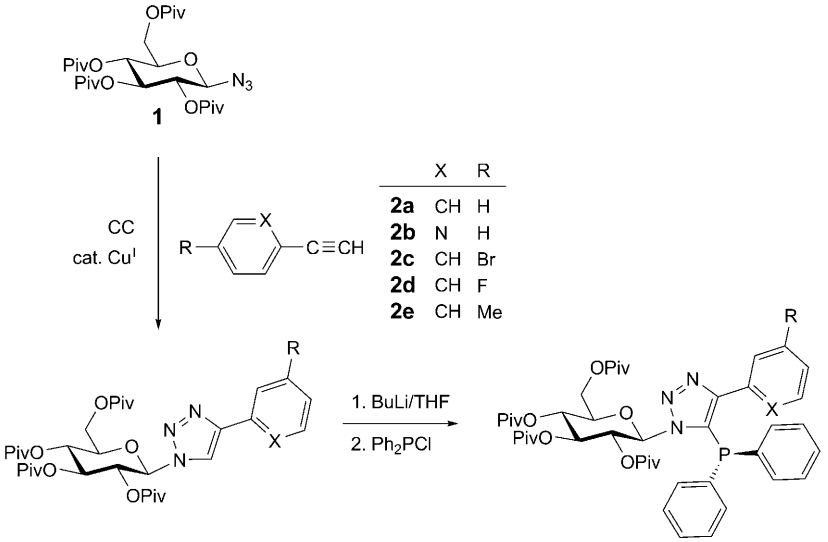
A novel class of chiral glycosyl-triazole-based *P,N* ligands were synthesized by 'click chemistry' and were applied to the Rh-catalyzed asymmetric hydrosilylation of a range of substituted acetophenones. Enantioselective hydrosilylation of acetophenone gave (*S*)-1-phenylethanol in moderate enantioselectivity (72% ee) and in good conversion (93%).

1. Introduction. – Over the last few decades, the asymmetric Rh-catalyzed hydrosilylation of ketones has been recognized as a versatile method for the synthesis of enantiomerically enriched alcohols and amines [1]. The chiral catalysts for asymmetric hydrosilylation were based on neutral cationic Rh precursors in combination with chiral bidentate diphosphines and amines to mixed donor-atom moieties [2], such as phosphino ethers [3], phosphino thioethers [4], and aminophosphines [5]. These catalytic systems have been applied to asymmetric hydroformylation, hydrogenation, hydrosilylation, and allylic alkylation reactions. Numerous configurations of phosphorus,nitrogen (*P,N*) ligands have been reported [6]. The *P,N* ligands can be generically divided into two categories, namely those based on structurally rigid sp^2-N-centers, unsaturated pyridine or imine groups [7], and the other are sp^3-N-centers, which constitute saturated amine functionalities [8]. 'Click chemistry' has recently attracted considerable attention as a powerful and efficient way to synthesize desired compounds in high yields by using a simple and benign procedure [9]. Recently, we were interested in the Cu^I-catalyzed 1,3-dipolar 'click' azide–alkyne cycloaddition [10], since the resulting 1,4-disubstituted 1,2,3-triazoles can be a part of bidentate *P,N*-type ligands that have been applied in various catalytic transformations [11][12]. ClickFerrophos, ferrocenyl, and *P,P* and *P,N* ligands have been prepared by *Fukuzawa et al.* by 'click chemistry', and their Rh complexes have been demonstrated to work effectively in asymmetric hydrogenation and allylic alkylation reactions [13]. Carbohydrates are readily available and highly functionalized compounds with several stereogenic centers. This allows a systematic regio- and stereoselective introduction of different functionalities in the course of the synthesis of a series of chiral ligands that can be screened in the search for high activities and enantioselectivities [14]. Prompted by our interest in carbohydrates as an inexpensive and highly modular chiral sources for

the glucose-mediated asymmetric *Strecker* reaction [15], we herein report the preparation of triazole-based *P,N* ligands (sp^3 type), which are derived from (+)-D-glucose for Rh-catalyzed asymmetric hydrosilylation. To the best of our knowledge, triazole-based *P,N* ligands have not been tested in this process.

2. Results and Discussion. – 2.1. *Ligand Design.* On the basis of the efficient formation of the disubstituted triazoles, a straightforward two-step synthesis of the several ligands has been developed (*Scheme 1*). 1-Azido-2,3,4,6-tetra-*O*-pivaloyl-*β*-D-glucopyranose (**1**) was subjected to click chemistry under *Sharpless* conditions to give the corresponding 1,2,3-triazoles **3a**–**3e** in good yields. Then, reaction of carbohydrate-derived triazoles **3a**–**3e** with 1 mol-equiv. of BuLi in THF at −78°, followed by trapping with 1.1 mol-equiv. of Ph_2PCl, gave the desired ligand **4b** only. The presence of other groups in the carbohydrate-derived triazoles did not allow the synthesis of corresponding chiral *P,N* ligands, even upon exposure to a large excess of BuLi. The ligand **4b** was stable during purification on neutral alumina under an Ar atmosphere and isolated as white solid. The ^{1}H-, ^{31}P-, and ^{13}C-NMR spectra were as expected for this type of ligands (see *Exper. Part*).

Scheme 1. *Preparation of 1-Glycosyl-triazole-Based Chiral Ligand* **4**



	X	R
2a	CH	H
2b	N	H
2c	CH	Br
2d	CH	F
2e	CH	Me

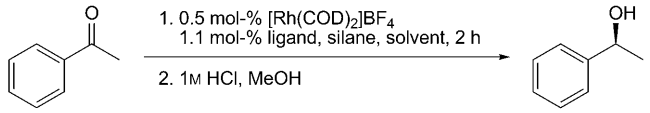
	X	R
3a	CH	H
3b	N	H
3c	CH	Br
3d	CH	F
3e	CH	Me

	X	R
4a	CH	H
4b	N	H
4c	CH	Br
4d	CH	F
4e	CH	Me

2.2. *Asymmetric Hydrosilylation of Ketones.* We first investigated the Rh-catalyzed hydrosilylation of acetophenone, which is widely used as a model substrate. The catalysts were generated *in situ* by adding the corresponding ligand to the catalyst

precursor. The effect of the solvent, temperature, and catalyst precursor was investigated. The results are summarized in *Table 1*.

Table 1. *Hydrosilylation of Acetophenone* (**5a**) *Using Chiral Ligand* **4b** *under Various Conditions*[a])



5a **6a**

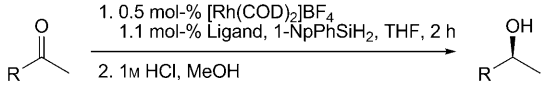
Entry	Silane	*T* [°]	Solvent	Time [h]	Conv. [%][b])	ee [%][c])
1	$PhSiH_3$	– 20	CH_2Cl_2	2	45	11 (*S*)
2	$PhSiH_3$	– 20	THF	5	52	15 (*S*)
3	Ph_2SiH_2	– 20	Et_2O	2	87	23 (*S*)
4	Ph_2SiH_2	– 20	THF	2	87	40 (*S*)
5	(1-Np)$PhSiH_2$[d])	r.t.	THF	2	87	52 (*S*)
6	(1-Np)$PhSiH_2$	– 20	THF	2	78	66 (*S*)
7	(1-Np)$PhSiH_2$	– 20	THF	5	89	68 (*S*)

[a]) Reaction conditions: **5a** (1 mmol), silane (1.1 mmol), ligand **4b** (0.011 mmol), **4b**/Rh = 1.1, solvent (2 ml). [b]) Conversion after 2 h determined by GC using undecane as internal standard. [c]) Enantiomeric excess determined by GC. [d]) 1-Np = Naphthalen-1-yl.

A preliminary optimization was carried out by studying the effect of various solvents and temperature on both conversion and enantioselectivity. According to *Table 1*, THF gave the best results regarding both conversion and enantiomeric excess, as well as short reaction time. We had applied the monosubstituted silane, *i.e.*, $PhSiH_3$ (*Entry 1*), and obtained the product with an enantioselectivity lower than when ligand **4b** was used. Previous studies by *Fu* have shown that the size of the aromatic group on the silane has a significant effect on enantioselectivity [5]. Therefore, we prepared more sterically demanding silanes than Ph_2SiH_2 and applied (naphthalen-1-yl)phenylsilane with ligand **4b**. The (1-Np)$PhSiH_2$ was found to give lower conversion (78%) than Ph_2SiH_2, although a slight increase in enantioselectivity to 66% was observed (*Table 1*, *Entry 4 vs. 6*). We next studied how the steric and electronic properties of the ketone affected the outcome of the reaction. For this purpose, a series of substituted benchmark aryl ketones **6a**–**6f** were tested. The results are summarized in *Table 2*. We found that *para*-substitution (substrate **6f**) resulted in higher selectivities in the hydrosilylation, while *ortho*-substitution (substrate **6d**) gave lower selectivities.

2.3. *Mechanism*. Here, we propose the catalytic mechanism for this reaction. For the Piv_4Glc skeleton, which played a primary impact in controlling the diastereoselectivity, influencing the metal coordination according to *Scheme 2*, in which Rh is coordinated to one of the O-atoms of the 2′-PivO group and the P-atoms of the Ph_2P group. However, the 1,2,3-triazole moiety could also interact with the catalytic metal and trigger non-enantioselective reaction pathways, whereas formation of chelates like *B*- or *C*-type would decrease the coordination between N-atom of the triazole and P-atoms and lead to low enantiomeric excess. From the experimental results, we found that *A*-type chelates are favored over the *B*- and *C*-type chelates, and are facilitating

Table 2. *Asymmetric Hydrosilylation of Various Prochiral Ketones in the Presence of Chiral Ligand* **4b**[a])

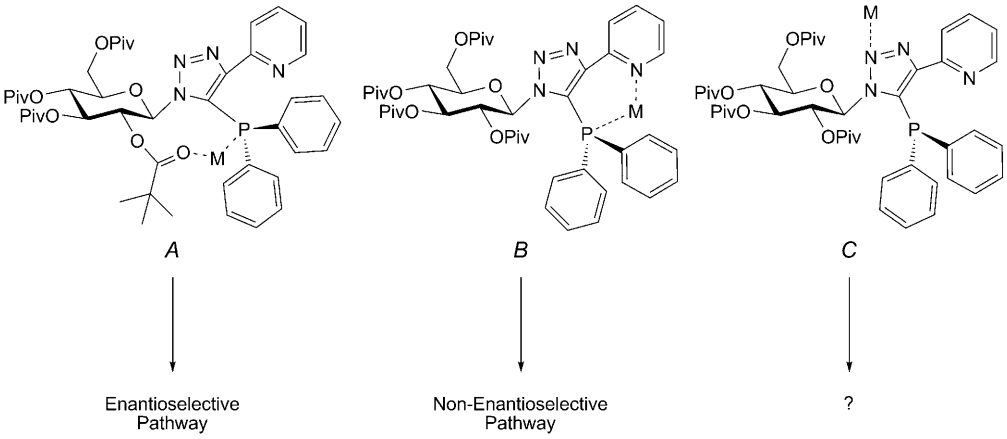


5 **6**

Entry	Ketone	R	Conv. [%][b])	ee [%][c])
1	**5a**	Ph	78	66 (*S*)
2	**5b**	4-MeO–C_6H_4	72	50 (*S*)
3	**5c**	4-Me–C_6H_4	60	52 (*S*)
4	**5d**	3-Me–C_6H_4	75	55 (*S*)
5	**5e**	4-Br–C_6H_4	83	69 (*S*)
6	**5f**	4-NO_2–C_6H_4	82	72 (*S*)

[a]) Reaction conditions: ketones **5a**–**5f** (1 mmol), (1-Np)$PhSiH_2$ (1.1 mmol), ligand **4b** (0.011 mmol), **4b**/Rh = 1.1, solvent (2 ml). [b]) Conversion after 2 h determined by GC using undecane as internal standard. [c]) Enantiomeric excess determined by GC.

Scheme 2. *Possible Pathways in Metal Catalysis with the Chiral Ligand* **4b**



enantiomerically selective pathways which gave (*S*)-1-phenylethanol in moderate enantioselectivity (72% ee).

A novel triazole-based *P,N* ligand has been developed and tested in the Rh-catalyzed asymmetric hydrosilylation of aryl ketones. High activities and moderate enantiomeric excesses (ee up to 72%) were obtained. Although the enantioselectivities remain still modest for the reduction of various ketones, this study shows that new family of chiral ligands can be effectively used for the enantioselective hydrosilylation of prochiral ketones. Further applications of the 1-glycosyl-triazole-based *P,N* ligand approach to other transformations catalyzed by organometallic reagents, including asymmetric allylic alkylation reaction, are currently underway.

Experimental Part

General. 1-Azido-2,3,4,6-tetrakis-*O*-pivaloyl-β-D-glucopyranose (**1**) was prepared according to [15]. Other chemicals and solvents were either purchased or purified by standard techniques. Anal. TLC: *Merck* precoated TLC (silica gel *60 F254*) plates. GC: *Varian 3900* gas chromatograph with an *octakis(6-o-methyl-2,3-di-o-pentyl)-r-CD* column of *Chrompack CP-9000* (*CP-Sil-8*, 30 m × 0.32 mm; 75 kPa of H_2) under the condition given. M.p.: *X_4-Data* microscopic melting-point apparatus; uncorrected. Optical rotations: *ADP 440* polarimeter in CH_2Cl_2. IR Spectra: *Nicolet 380* FT-IR spectrophotometer; KBr discs. ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra: *Bruker Avance 400* spectrometer in $CDCl_3$ with TMS or H_3PO_4 as internal standard. ESI-MS: *Bruker Esquire 3000* plus spectrometer. Elemental analyses: *Carlo-Erba 1106* instrument.

*General Procedure for the Preparation of the 1*H-*[1,2,3]Triazole* **3**. To a mixture of **1** (541 mg, 1.0 mmol) and alkynes **2** (1.0 mmol) in *t*-BuOH (1 ml), 0.5 ml of an aq. soln. of $CuSO_4$ (50 mg, 0.2 mmol) and 0.5 ml of an aq. soln. of sodium ascorbate (79.2 mg, 0.4 mmol) were added. The mixture was stirred vigorously for 24 h. The suspended product was filtered and washed with H_2O. The crude product was purified by column chromatography (CC; SiO_2; hexane/AcOEt mixtures of increasing polarity) to afford the triazole products.

4-Phenyl-1-[2,3,4,6-tetrakis-O-*(2,2-dimethylpropanoyl)*-D-*glucopyranosyl]-1*H-*[1,2,3]triazole* (**3a**). Yellow solid. Yield: 92.3%. M.p. 216–220°. IR: 2970, 2077, 1744, 1637, 1481, 1400, 1368, 1280, 1140, 1037. ^{1}H-NMR: 8.05 (*s*, 1 H); 7.85 (*d*, *J* = 7.6, 2 H); 7.46 (*d*, *J* = 7.6, 2 H); 7.38 (*t*, *J* = 7.2, 1 H); 5.87 (*d*, *J* = 4.0, 1 H); 5.55 (*t*, *J* = 4.4, 1 H); 5.36 (*t*, *J* = 5.6, 1 H); 4.71–4.74 (*m*, 1 H); 4.55–4.59 (*m*, 1 H); 4.31–4.35 (*m*, 1 H); 0.92–1.25 (*m*, 12 Me). ^{13}C-NMR: 177.8; 176.5; 147.4; 144.6; 129.0; 127.9; 127.6; 125.0; 85.1; 74.6; 71.1; 69.2; 66.2; 60.4; 37.8; 25.8; 26.1. ESI-MS: 643.2 ($[M+H]^+$). Anal. calc. for $C_{34}H_{49}N_3O_9$: C 63.43, H 7.67, N 6.53; found: C 63.44, H 7.66, N 6.55.

2-{1-[2,3,4,6-Tetrakis-O-*(2,2-dimethylpropanoyl)*-D-*glucopyranosyl]-1*H-*[1,2,3]triazol-4-yl}pyridine* (**3b**). Yellow solid. Yield: 95.3%. M.p. 179–181°. ^{1}H-NMR: 8.60 (*s*, 1 H); 8.37 (*d*, *J* = 3.6, 1 H); 8.11 (*t*, *J* = 6.8, 1 H); 7.78 (*t*, *J* = 6.0, 1 H); 7.27 (*d*, *J* = 12.2, 1 H); 5.97 (*d*, *J* = 8.2, 1 H); 5.54–5.56 (*m*, 2 H); 5.32–5.37 (*m*, 1 H); 4.19–4.21 (*m*, 2 H); 4.05 (*d*, *J* = 2.4, 1 H); 1.87–1.89 (*m*, 1 H); 0.94–1.21 (*m*, 12 Me). ^{13}C-NMR: 177.7; 177.1; 177.1; 155.3; 149.2; 137.2; 131.4; 129.5; 123.6; 97.6; 78.2; 73.7; 69.2; 69.8; 62.4; 36.8; 25.79; 26.12. IR: 3431, 2974, 1742, 1601, 1479, 1400, 1281, 1141, 1034. Anal. calc. for $C_{33}H_{48}N_4O_9$: C 61.55, H 7.82, N 8.78; found: C 61.58, H 7.80, N 8.75.

4-(4-Bromophenyl)-1-[2,3,4,6-tetrakis-O-*(2,2-dimethylpropanoyl)*-D-*glucopyranosyl]-1*H-*[1,2,3]triazole* (**3c**). Yellow solid. Yield: 88.1%. M.p. 220–222°. IR: 3422, 2974, 1742, 1637, 1481, 1403, 1368, 1140, 1040. ^{1}H-NMR: 7.97 (*s*, 1 H); 7.70 (*d*, *J* = 5.6, 2 H); 7.56 (*t*, *J* = 7.2, 2 H); 5.99 (*d*, *J* = 7.6, 1 H); 5.52–5.55 (*m*, 2 H); 5.36 (*d*, *J* = 4.2, 1 H); 4.18–4.21 (*m*, 2 H); 4.06–4.09 (*m*, 1 H); 0.92–1.25 (*m*, 12 Me). ^{13}C-NMR: 177.7; 176.7; 131.9; 129.7; 127.2; 122.4; 85.9; 77.2; 71.8; 69.9; 66.9; 61.1; 38.8; 25.53; 26.92. Anal. calc. for $C_{34}H_{48}BrN_3O_9$: C 56.62, H 6.73, N 5.93; found: C 56.65, H 6.70, N 5.91.

4-(4-Fluorophenyl)-1-[2,3,4,6-tetrakis-O-*(2,2-dimethylpropanoyl)*-D-*glucopyranosyl]-1*H-*[1,2,3]triazole* (**3d**). White solid. Yield: 89.1%. M.p. 190–192°. IR: 3436, 2976, 1740, 1641, 1485, 1406, 1360, 1141, 1039. ^{1}H-NMR: 8.02 (*s*, 1 H); 7.82 (*d*, *J* = 7.2, 2 H); 7.82 (*t*, *J* = 6.0, 2 H); 5.96 (*d*, *J* = 6.6, 1 H); 5.54–5.58 (*m*, 2 H); 5.38 (*d*, *J* = 2.4, 1 H); 4.11–4.20 (*m*, 2 H); 4.11 (*d*, *J* = 12.4, 1 H); 0.95–1.26 (*m*, 12 Me). ^{13}C-NMR: 178.7; 176.9; 132.1; 129.7; 127.2; 122.4; 85.9; 77.2; 71.9; 69.9; 66.9; 61.2; 38.7; 25.5; 26.9. Anal. calc. for $C_{34}H_{48}FN_3O_9$: C 61.76, H 7.22, N 6.43; found: C 61.73, H 7.20, N 6.45.

4-(4-Methylphenyl)-1-[2,3,4,6-tetrakis-O-*(2,2-dimethylpropanoyl)*-D-*glucopyranosyl]-1*H-*[1,2,3]triazole* (**3e**). White solid. Yield: 92.6%. M.p. 208–210°. IR: 3443, 2352, 2118, 1746, 1649, 1540, 1398, 1280, 1146. ^{1}H-NMR: 8.00 (*s*, 1 H); 7.74 (*d*, *J* = 5.6, 2 H); 7.25 (*t*, *J* = 6.8, 2 H); 5.86 (*d*, *J* = 11.6, 1 H); 5.55 (*d*, *J* = 4.2, 1 H); 5.31–5.34 (*m*, 1 H); 4.71 (*m*, 2 H); 4.45 (*d*, *J* = 2.2, 1 H); 4.30 (*d*, *J* = 6.2, 1 H); 2.39 (*s*, 1 H); 0.92–1.25 (*m*, 12 Me). ^{13}C-NMR: 177.4; 176.2; 176.2; 144.3; 137.9; 129.1; 126.5; 126.2; 115.9; 86.2; 76.8; 76.2; 66.0; 65.9; 60.0; 38.4; 29.19; 26.47. Anal. calc. for $C_{35}H_{51}N_3O_9$: C 63.86, H 7.74, N 6.50; found: C 63.86, H 7.74, N 6.50.

General Procedure for the Preparation of the Ligand **4b** (*=2-{5-(Diphenylphosphanyl)-1-[2,3,4,6-tetrakis*-O-*(2,2-dimethylpropanoyl)-β*-D-*glucopyranosyl]-1*H-*[1,2,3]triazol-4-yl}pyridine*). In a 20-ml *Schlenk* tube containing a magnetic stirring bar were charged triazole **3b** 1.28 g (2.0 mmol) and dry

THF (5 ml) under a slight pressure of N_2. The flask was cooled to $-78°$, and a hexane soln. of BuLi (1 ml, 2.0 mmol, 2M) was then added using a syringe through the septum with magnetic stirring. After 10 min, Ph_2PCl (460 µl, 2.5 mmol) was injected into the mixture at $-78°$, and stirred for 1 h. When the addition was completed, the mixture was allowed to warm to r.t. and then stirred for an additional 2 h. The reaction was quenched with sat. NH_4Cl, and the soln. was then extracted with Et_2O (3×30 ml). The combined extracts were washed (brine), dried (Na_2SO_4), filtered, and the solvent was removed on a rotary evaporator to leave a yellow solid. The crude product was purified by recrystallization from hexane/CH_2Cl_2: 1.16 g (69.8%). White solid. M.p. 189–192°. ^{1}H-NMR: 8.47 (*s*, 1 H); 7.88 (*d*, $J = 5.6$, 1 H); 7.74 (*t*, $J = 7.2$, 1 H); 7.78 (*t*, $J = 4.0$, 1 H); 7.17–7.46 (*m*, 10 H); 5.59–5.62 (*m*, 1 H); 5.35–5.36 (*m*, 2 H); 5.28–5.32 (*m*, 1 H); 4.17–4.19 (*m*, 2 H); 3.90–3.95 (*m*, 1 H); 0.94–1.21 (*m*, 12 Me). ^{13}C-NMR: 205.6; 177.9; 176.9; 176.2; 149.1; 148.7; 145.2; 142.0; 136.8; 134.4; 131.6; 130.3; 128.8; 128.4; 128.3; 127.7; 122.7; 84.9; 78.3; 76.7; 74.4; 67.5; 45.5; 38.7; 27.2; 26.49. ^{31}P-NMR: −11.70. ESI-MS: 828.9 ($[M+H]^+$). Anal. calc. for $C_{45}H_{57}N_4O_9P$: C 62.50, H 6.93, N 6.76; found: C 62.52, H 6.95, N 674.

General Procedure for Asymmetric Hydrosilylation Reactions. To a soln. of the desired catalyst precursor (0.01 mmol Rh) in the corresponding solvent (2 ml), the ligand (0.011 mmol) was added. The mixture was stirred for 30 min. Ketone (1 mmol), Ph_2SiH_2 (1.1 mmol), and undecane as the GC internal standard (0.1 ml) were then added. After the desired reaction time, the reaction was quenched with MeOH (7 ml) and 2.5M aq. NaOH (5 ml). The mixture was extracted with Et_2O (3×5 ml), and the combined Et_2O phases were dried (Na_2SO_4) and filtered. The conversion percentages and ee values were determined by GC.

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