Catalytic Glycosylation with Rhodium(III)-Triphos Catalysts

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In memory of Professor Raymond Urgel Lemieux. We dedicate this paper to Ray Lemieux in recognition of his pathbraking contributions to the carbohydrate area.

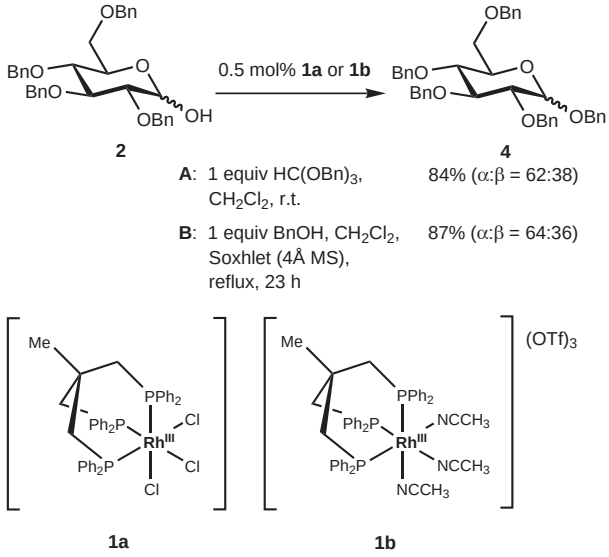
Abstract: The formation of glycosides in high yield from 1-hydroxy sugars using catalytic amounts (0.5mol%) of $Rh(III)Cl_3$(triphos) (**1a**) or [Rh(III)$(MeCN)_3$(triphos)]$(TfO)_3$ (**1b**) is described. High stereocontrol at the anomeric center is achieved by neighboring group participation. In addition, an application of this new glycosylation procedure for the synthesis of a derivative of the oviposition-deterring pheromone of the cherry fruit fly *Rhagoletis cerasi* is presented.

Key words: catalytic glycosylation, Rh(III)triphos catalysts, 1-hydroxy sugars, *O*-glycosides, oviposition-deterring pheromone

Numerous methods for the formation of the biologically important *O*-glycosidic linkage[1] have been developed since the classical Koenigs–Knorr[2] and Fischer[3] glycosylation procedures. Comprehensive reviews of glycosylation methodologies have recently been published.[4] The development of efficient glycosylation procedures is, however, still a most challenging topic in organic synthesis.

A glycosidic bond is generally constructed with a glycosyl donor, which contains a particular leaving group. Direct formation of a glycosidic bond from a 1-hydroxy sugar has obvious advantages, since the reaction step for the introduction of an activating group is not required and the hydrolysis of the donor, which is a major side reaction in glycosylation reactions, can be avoided in principal. Surprisingly, rather little has been reported on dehydrative glycosylation.[5] In this communication we present a novel catalytic glycosylation procedure starting from hemiacetals using Rh(III)-complexes of the terdentate triphos ligand: $Rh(III)Cl_3$(triphos) (**1a**) and [Rh(III)$(MeCN)_3$-(triphos)]$(TfO)_3$ (**1b**).

Venanzi et al.[6] demonstrated the acetalization of ketones and aldehydes using an alcohol, the corresponding trialkyl orthoformate as a desiccant and a catalytic amount of Rh(III) complex **1a** or **1b**. When we applied these conditions to tetra-*O*-benzyl-D-glucopyranose (**2**), an α/β-mixture of the corresponding benzyl glycosides (**4**) was formed in high yield within minutes (see Scheme 1, condition **A**).



Scheme 1 Catalytic glycosylation with 1-hydroxy sugars.

To avoid the disadvantage of the preparation of the orthoformate with three equivalents of the respective glycosyl acceptor, a modified procedure was developed. For the removal of the water formed in the glycosylation reaction, the reaction flask was equipped with a Soxhlet extractor containing activated molecular sieves (4 Å). Under these conditions for the azeotropic removal of water, an excellent yield of the corresponding glycoside was obtained with both catalysts **1a** and **1b** (see Scheme 1, condition **B**).

To study the scope of this catalytic glycosylation procedure, various alcohols and glycosyl donors have been investigated (see Table 1). Using **2** as glycosyl donor, primary (entries 1 and 2) and secondary alcohols (entry 3) or phenols (entry 4) gave good to excellent yields. In addition, glycosylation of the 6-hydroxyl group of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**11**) yielded 81% of the corresponding disaccharide (entry 5). Acceptable yields were obtained with the corresponding galactose donor **13** (entry 6), whereas the glycosylation of the cellobiose derivative **15** gave the glycoside **16** only in moderate yield (entry 7).

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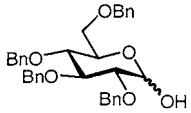
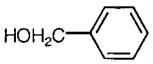
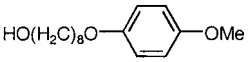
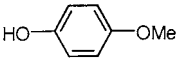
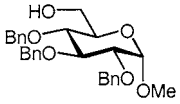
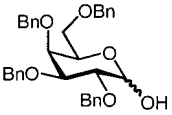
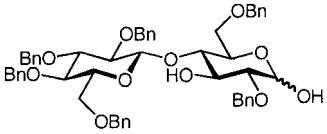
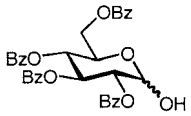
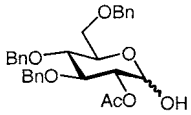
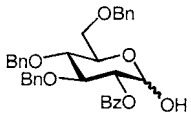
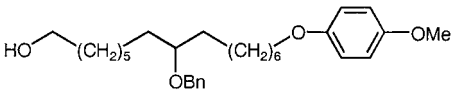
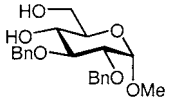
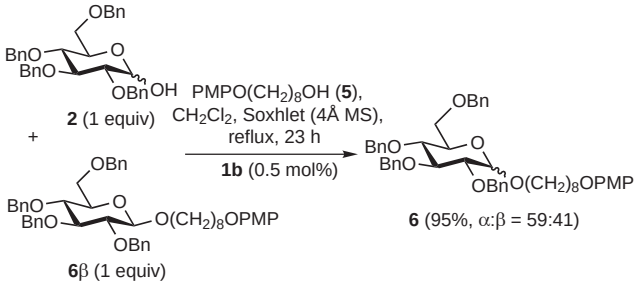
Table 1 Glycosylation with 0.5 mol% Rh(III)-Catalyst **1b** in Refluxing CH_2Cl_2 with Azeotropic Removal of Water

Entry	Glycosyl donors	Glycosyl acceptors	Reaction time	Prod.	Yield	α:β
1	 **2**[7]	 **3**	23 h	**4**	87%	64:36
2		 **5**	20 h	**6**	94%	59:41
3		3β-cholestanol **7**	17 h	**8**	67%	66:34
4		 **9**	23 h	**10**	64%	64:36
5		 **11**[8]	27 h	**12**	81%	74:26
6	 **13**[7]	**5**	21 h	**14**	71%	60:40
7	 **15**[9]	**5**	20 h	**16**[a]	46%	50:50
8	 **17**[10]	**5**	96 h	**18**[b]	29%	67:33
9	 **19**[11]	**5**	21 h	**20**	53%	>2:98
10		**11**	16 h	**21**	41%	>2:98
11	 **22**[12]	**5**	16 h	**23**	96%	>2:98
12		 **24**	16 h	**25**	92%	>2:98
13		**11**	16 h	**26**	75%	>2:98
14		 **27**[13]	26 h	**28**[c]	78%	>2:98

[a] 30% glycosyl donor could be reisolated. [b] The major side reaction is the decomposition of **18**; no product was formed within 96 h using 1.5 mol% TfOH. [c] Only the β(1-6)-disaccharide was formed.

In all these examples, α/β-mixtures corresponding to the thermodynamic ratio were obtained. When the reaction of entry 2 was carried out in the presence of one equivalent of the **6β**-anomer, the thermodynamic control could clearly be demonstrated (see Scheme 2). The product ratio **6α/β** was again 59:41, whereas a kinetic control would have yielded an α/β-ratio of 30:70.



Scheme 2 Thermodynamic vs. kinetic control.

To achieve stereocontrol in respect to the anomeric center, neighboring group assistance proved to be necessary. Since the reaction time with fully acylated glycosyl donors (e.g. **17**) was enormously elongated and did not give the expected stereocontrol (entry 8), donors selectively acylated at the 2-position were used. With 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-glucopranose (**19**) and 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-glucopyranose (**22**) excellent yields as well as β-stereocontrol were realized (entries 9–14).

According to mechanistic studies for the Rh(III)-catalyzed acetalization reaction,[6] it appears that two free *cis* coordination sites are required in the catalyst precursor. Applied to the glycosylation procedure, both substrates, hemiacetal and alcohol, can then be coordinated adjacent to each other to the metal center before coupling. The strong *trans*-effect of the facial chelating tripodal phosphine activates all three *cis*-positions equivalently. Thus, catalyst activity can be attributed to the Lewis acidity of the complex cation and to its ability to act as a template for the simultaneous activation of the hemiacetal and the alcohol. However, e.g. the catalyst **1b** could also react with alcohols by β-H abstraction and formation of $[Rh(III)H(MeCN)_2(triphos)]^{2+}$ leading to the liberation of a proton. To clarify a possible contribution by acid catalysis, the glycosylation reaction of entry 8 was conducted in the presence of 1.5 mol% TfOH. However, under these reaction conditions, the formation of **18** could not be observed within 96 h.

Finally, glycoside **25** (entry 12) proved to be an excellent building block for the synthesis of the derivative **30** of the oviposition deterring pheromone of the cherry fruit fly *Rhagoletis cerasi*[14] (Scheme 3). We have shown[15] that the natural pheromone **29** is a diastereomeric mixture in respect to the stereocenter at C-8. In addition, we could demonstrate that the 15-demethyl-ODP **30** shows comparable biological activity than the natural product.[16]

Starting from the C_7 building block **32** and the C_8 aldehyde **34**, which was obtained from suberic acid (**33**) in 5 steps,[15] the backbone of the pheromone derivative was synthesized by a Grignard reaction. After benzylation of the hydroxyl group in C-8 followed by removal of the terminal silyl protection (→**24**), the Rh(III)-catalyzed glycosylation yielded the corresponding glucoside **25**[17] in excellent chemical yield and stereoselectivity. Oxidative cleavage of the PMP ether followed by Jones oxidation at C-1 gave the carboxylic acid **35** in 69% overall yield. The activated ester of **35**, obtained with *N*-hydroxysuccinimide and DCC, was transformed into the taurin amide. In a final step, all benzyl protective groups were removed by hydrogenolysis yielding 15-demethyl-ODP **30**.[18]

The presented results clearly demonstrate the synthetic potential of this new catalytic glycosylation procedure leading to glycosides with excellent yields and stereoselectivity. The rather long reaction time is a consequence of the inefficient removal of water formed in the glycosylation. We are therefore currently investigating more efficient reaction conditions, which would allow a significant reduction of the reaction time.

General Procedure

To a 50 mL round-bottom flask equipped with a Soxhlet extractor containing activated 4 Å molecular sieves glycosyl donor (2 mmol), glycosyl acceptor (2 mmol), rhodium(III)-catalyst **1a** or **1b** (0.5 mol%) and solvent (CH_2Cl_2, 1,2-dichloroethane, chloroform, benzene, toluene) were added. The reaction mixture was heated to reflux and followed by TLC. When the reaction was shown to be complete, the reaction mixture was filtered through a short pad of silica gel and the solvent was removed in vacuo. The residue was then chromatographed on silica gel.

Acknowledgement

$Rh^{III}Cl_3$(triphos) and $[Rh^{III}(MeCN)_3(triphos)](TfO)_3$ were supplied by the research group of late Prof. Dr. L. M. Venanzi, Laboratory of Inorganic Chemistry, ETH Zürich, Switzerland.

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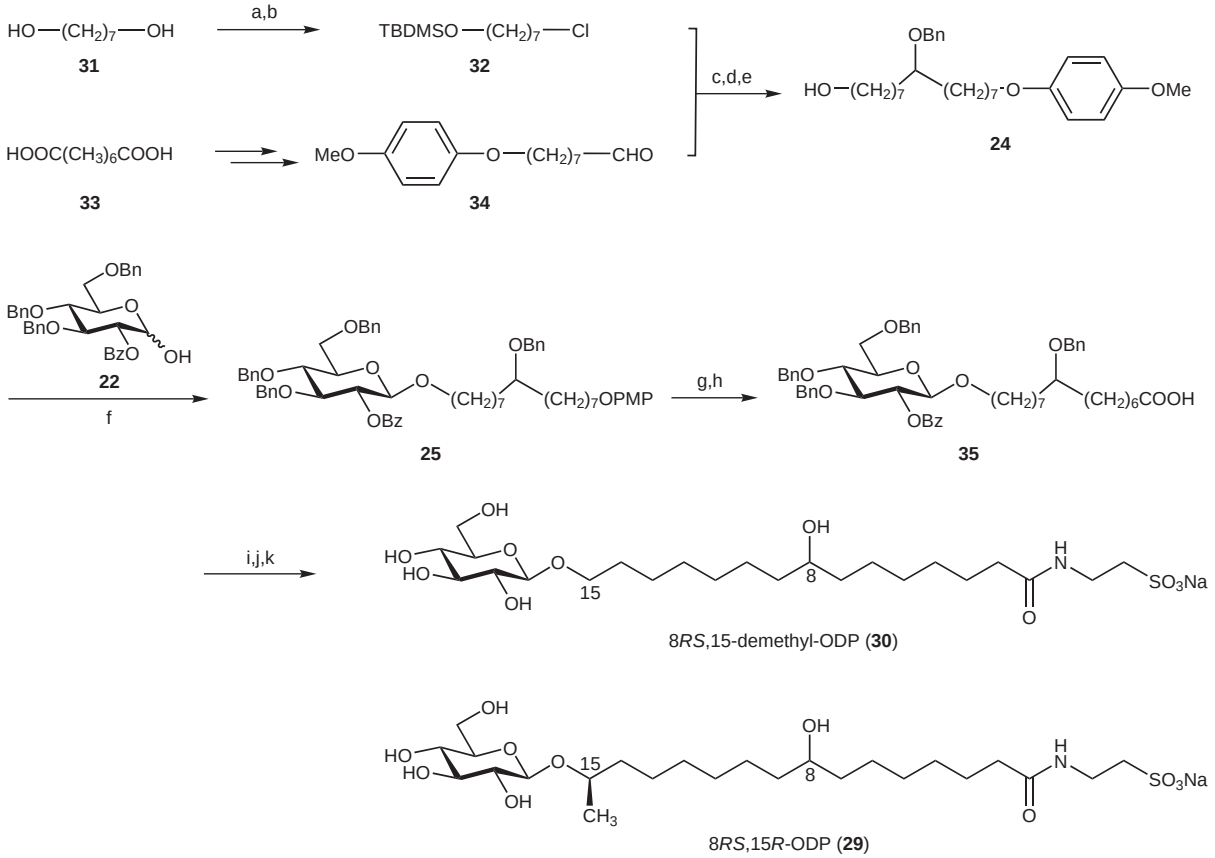

Scheme 3 a) TBDMSCl, imidazole, CH_2Cl_2, r.t. (82%); b) $Me_2C{=}CClNMe_2$,[19] CH_2Cl_2, 0 °C to r.t. (88%); c) Mg, THF, r.t. to 80 °C (61%); d) BnBr, NaH, DMF, 60 °C (72%); e) Bu_4NF, THF, r.t., 1 h (91%); f) 0.5 mol% $[Rh(III)(MeCN)_3(triphos)](TfO)_3$, 1 equiv **22**, CH_2Cl_2, 16 h (92%, β:α >98:2); g) CAN, CH_3CN/H_2O, r.t., 1 h (90%); h) CrO_3, H_2SO_4, acetone, 0 °C, 2 h (84%); i) *N*-hydroxysuccinimide, DCC, DME, r.t., 20 h (92%); j) $H_2NCH_2CH_2SO_3Na$, MeOH, r.t., 5 h (88%); k) H_2, Pd/C (10%), MeOH, r.t., 24 h (78%).

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(17) ^{13}C NMR ($CDCl_3$, 50 MHz) of **26**: 25.2(2t), 25.8 (t), 26.0 (t), 29.2 (t), 29.3(2t), 29.4 (t), 29.6 (t), 29.7 (t), 33.8 (t), 55.6 (q), 68.6 (t), 69.0 (t), 69.7 (t), 70.7 (t), 73.5 (t), 73.9 (d), 74.8(2t), 75.3 (d), 78.1 (d), 79.0 (d), 82.8 (d), 101.2 (d), 114.6–132.8 (29d, aromatic CH), 130.2 (s), 137.9 (s), 138.0 (s), 138.2 (s), 139.2 (s), 153.3 (s), 153.7 (s), 165.0 (s).

(18) ^{13}C NMR (CD_3OD, 50 MHz) of **30**: 26.9–51.8(14t), 63.1 (t, C-6′), 71.2 (d, C-4′), 72.0 (t, C-15), 72.7 (d, C-8), 75.4 (d, C-2′), 78.1, 78.4 (2d, C-3′, C-5′), 104.6 (t, C-1′), 176.5 (s, C-1).

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