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Organocatalyzed Direct Glycosylation of Unprotected and Unactivated Carbohydrates

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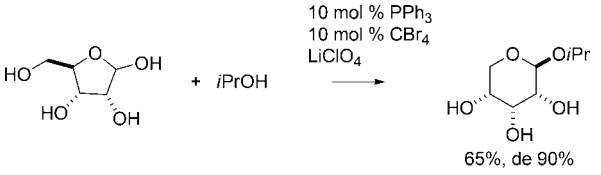
ABSTRACT



Organocatalyzed direct glycosylation of unprotected and unactivated carbohydrates is reported. This process is catalyzed by triphenylphosphine and tetrabromomethane at room temperature under neutral conditions. With this operationally simple protocol thermodynamically favored, glycosides were obtained in a very straightforward reaction.

Polysaccharides, glycoconjugates, or glycosides are mostly linked by O-glycosidic bonds. Hence, the synthesis of O-glycosidic bonds is of great interest. There exist a great many methods to synthesize glycosides of defined configuration in high yield.[1] These are mostly based on the following protocol. To differentiate the reactivities of the different hydroxyl groups, the carbohydrate is usually completely protected. Afterward a leaving group is installed at the anomeric center of the carbohydrate. After successful glycosylation a final deprotection step releases the newly made glycoside. To avoid this multistep methodology, several efforts have been made to increase the reactivity of the hydroxy group at the anomeric center and thus to exploit this difference for a direct glycosylation.[2] Also, direct glycosylations of unprotected and unactivated carbohydrates that are based on the Fischer glycosylation[3] conditions have been developed. These reactions are carried out in strongly acidic media and mostly at high temperature.[4] For more current examples of this methodology see ref 5. Also, Lewis acids have been deployed in glycosylation reactions of unprotected carbohydrates.[6] But for quantitative performance an excess of Lewis acid is necessary in such reactions. Recently, Auge and Sizun reported the catalytic deployment of Lewis acids in a glycosylation reaction (10 mol %). These reactions were performed at 80−100 °C for 24 h in ionic

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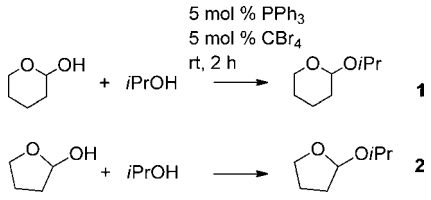
liquids.[7] Catalytic glycosylation of unprotected and unactivated carbohydrates remains a challenge.[8] Recently, we have reported a direct glycosylation methodology that is performed in the presence of catalytic amounts of titanium(IV) alkoxides and mandelic acid. The reaction proceeds under near-neutral conditions.[9]

During our ongoing studies in the field of organocatalysis we observed a rapid and quantitative formation of acetals of enolizable aldehydes or cyclic hemiacetals in the presence of catalytic amounts of triphenylphosphine and substituted trihalomethanes. After optimizing the process, we obtained the best results for yield and reaction time by deployment of catalytic amounts of tetrabromomethane and triphenylphosphine.

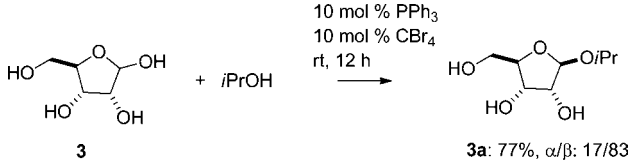
Scheme 1. Acetalization of Cyclic Hemiacetals



These reactions were carried out at room temperature in the presence of 5 mol % of triphenylphosphine and tetrabromomethane in propanol. After 2 h the propyl acetals **1** and **2** of hydroxytetrahydropyrans and hydroxytetrahydrofurans were isolated in quantitative yield (Scheme 1). Similar results have been reported for acetalisation of aromatic aldehydes.[10] Cleavage of acetals was not detected under these conditions, as is known under Appel conditions.[11]

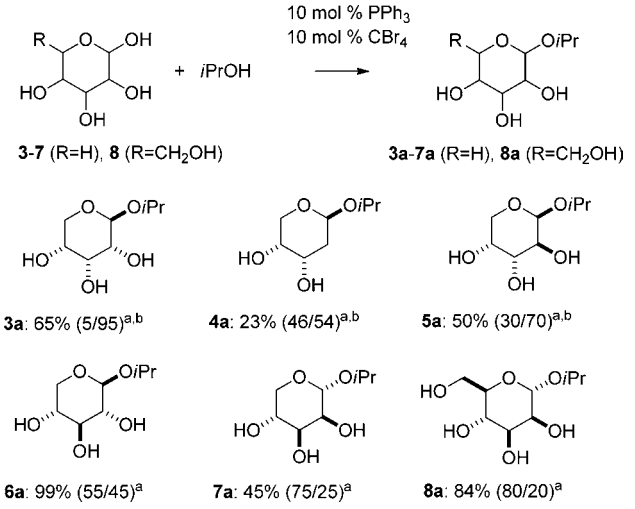
Encouraged by these findings we tested these conditions for the glycosylation of ribose **3** with isopropanol. We obtained the corresponding isopropylriboside **3a** in high yield and with high β-selectivity (Scheme 2). The reactions were carried out directly in isopropanol in the presence of catalytic amounts of triphenylphosphine/tetrabromomethane (10 mol %) at room temperature. A clean and rapid reaction was observed. Side products were not detected. The reaction proceeds under genuinely catalytic and neutral reaction conditions.

Scheme 2. Catalytic Glycosidation of D-Ribose with Isopropanol



By extending these initial results to the glycosylation of other pentoses, unexpected and differing results were obtained. Clean reactions were detected when ribose **3** and deoxyribose **4** were used under the described conditions (**3a**: 77% and **4a**: 75% in *iso*PrOH, 10 mol % PPh_3/10 mol % CBr_4, rt, procedure A). In contrast, only low reaction rates and yields were observed when arabinose (**5**), xylose (**6**), and lyxose (**7**) were employed.[12] During optimization, several different solvents and additives were tested in these reactions. Nitromethane, acetonitrile, or propylene carbonate proved to be optimal solvents for the direct glycosidation of these pentoses. To increase the yields of this direct glycosylation, several lithium salts were analyzed as additives. Lithium perchlorate is known to promote glycosylation processes,[13] and as a consequence, its effects were examined under these conditions, and a direct catalytic glycosylation of unprotected carbohydrates was achieved. Again, a very clean reaction was observed where byproducts were not detected. The best results were obtained in acetonitrile in the presence of 2 equiv of lithium perchlorate as an additive (procedure C). The isopropyl glycosides **4a**, **5a**, **6a**, and **7a** were obtained mostly in the pyranoid form, indicating thermodynamic control of these transformations. Support for this is provided by the glycosidation of D-mannose **8**. In direct glycosylation reactions of mannose **8**, the α-configured isopropyl glycoside **8a** was isolated as the main product, which is known to be the thermodynamically favored anomer in the mannose series[14] (Scheme 3).

Scheme 3. Yields and Anomeric Ratio of Isopropyl Glycosides



Reaction conditions: 2 equiv of *iso*PrOH, 2 mL of MeCN, 2 equiv of $LiClO_4$, rt, 12 h (procedure C). [b] α/β ratio. [c] Corresponding isopropyl furanosides were detected as minor products (yields < 10%); see Table 1 in Supporting Information.

(8) With the exception of an enzymatic glycosylation. For recent reviews in this field, see: (a) Bojarova, P.; Rosencrantz, R. R.; Elling, L.; Kren, V. *Chem. Soc. Rev.* **2013**, *42*, 4774. (b) Flitsch, S. L. In *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H., Eds.; Elsevier: 2012; Vol. 7, p 454.

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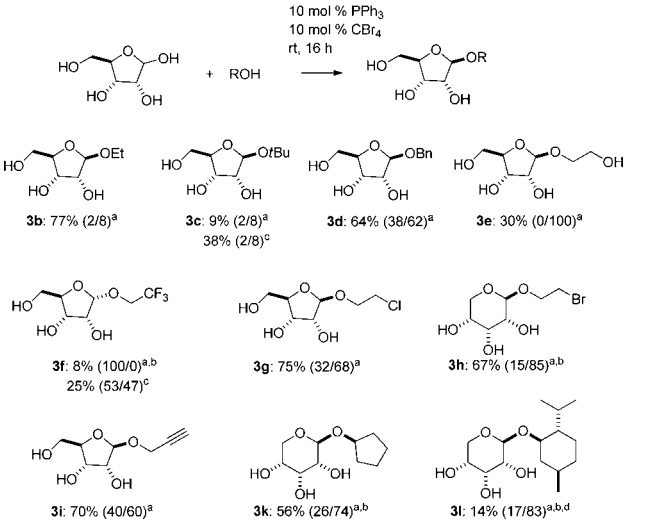
We have explored the scope and limitations of this new glycosylation methodology, reacting several different aglycones with D-ribose **3** under the standard conditions (Scheme 4).

The glycosylation reactions were performed in the presence of catalytic system PPh_3/CBr_4 (10 mol % of each) at room temperature without additional solvent (procedure A). The corresponding ribosides **3b**−**3k** were isolated in moderate-to-high yield except for the reactions of ribose with *tert*-butanol (**3c**) and trifluoroethanol (**3f**). These results indicate extreme influences of the deployed aglycons on the glycosylation: both an electronic effect (**3f**) and a steric effect (**3c**). These yield-minimizing effects can be overcome by the additional application of lithium salts, especially lithium perchlorate.[15] Furthermore, a moderate-to-high β-selectivity was noticed in these glycosylation reactions. Excellent diastereoselectivities were obtained with aglycones containing oxygen (**3e**: de > 99%). When used with solid aglycones (e.g., menthol) propylene carbonate was deployed as solvent (procedure B).

The application of triphenylphosphine and tetrabromomethane in glycosylation processes has been described in the literature.[16] These conditions were deployed for glycosylation of fully protected 1-hydroxy carbohydrates. In these reactions triphenylphosphine and tetrabromomethane were used in excess (up to 9 equiv) under inert and dry reaction conditions to generate the protected 1-bromo glycosyl derivative. The following glycosylation was achieved by the addition of amines or DMF.

The present conditions cannot be compared with those described in literature. Water generated during the reaction is tolerated. Also, alterations to the yields and selectivities were not noticed by adding 1 or 2 equiv of water. The formation of 1-bromoglycosyl intermediates was not observed. Additional bases or DMF are not necessary for this glycosylation. These results are in contrast with reactions carried out in the presence of an excess of triphenylphosphine and tetrabromomethane. Also, the formation

Scheme 4. Catalytic Glycosidation of D-Ribose with Different Aglycones

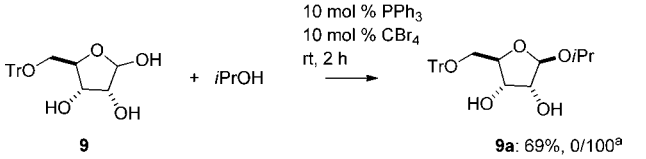


[a] α/β ratio. [b] Corresponding isopropyl furanosides were detected as minor products (yields < 10%), see Supporting Information. [c] 2 equiv of $LiClO_4$ were added. [d] Reactions were carried out in propylen carbonate.

of triphenylphosphine oxide cannot be the driving force of this catalytic procedure.[16] This consideration is not consistent with the high yields of compounds **6a** (99%) or **8a** (84%) by deployment of a 10 mol % catalyst system.

Furthermore, this catalytic reaction proceeds in an essentially neutral medium. To demonstrate the neutral reaction medium, we have reacted 5-tritylated ribose **9** under the described standard reaction conditions (procedure A). A very rapid, clear, and selective glycosylation was observed. Cleavage of the trityl group was not detected as is normal in the presence of the Appel reagent.[17] After 2 h at room temperature 5-protected isopropylriboside **9a** was isolated with high yields as a single stereoisomer (Scheme 5).

Scheme 5. Organocatalyzed Glycosylation of 5-Tritylated Ribose



[a] α/β ratio.

To demonstrate the utility of this operationally simple protocol we have reacted Cbz-protected serine methyl ester with ribose under the reported standard conditions (procedure B, Scheme 6). After 12 h at room temperature the riboside **3m** was isolated in 25% yield. For a

(12) A similar tendency has been observed in glycosylations using a mandelic acid/titanium(IV) alkoxide catalyst. See ref 9.

(13) (a) Worm-Leonhard, K.; Larsen, K.; Jensen, K. J. *J. Carb. Chem.* **2007**, *26*, 349. (b) Babu, B. S.; Balasubramanian, K. K. *Carb. Lett.* **1999**, *3*, 339. (c) Schene, H.; Waldmann, H. *Synthesis* **1999**, 1411. (d) Schene, H.; Waldmann, H. *Chem. Commun. (Cambridge, U.K.)* **1998**, 2759. (e) Schmid, U.; Waldmann, H. *Chem.—Eur. J.* **1998**, *4*, 494. (f) Uchiro, H.; Miyazaki, K.; Mukaiyama, T. *Chem. Lett.* **1997**, 403. (g) Boehm, G.; Waldmann, H. *Tetrahedron Lett.* **1995**, *36*, 3843. (h) Waldmann, H.; Boehm, G.; Schmid, U.; Roettele, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1994. (i) Mukaiyama, T.; Matsubara, K. *Chem. Lett.* **1992**, 1041. (j) Mukaiyama, T.; Shimpuku, T.; Takashima, T.; Kobayashi, S. *Chem. Lett.* **1989**, 145. (k) See also ref 9.

(14) (a) Cumpstey, I. *Org. Biomol. Chem.* **2012**, *10*, 2503 and references cited therein. (b) Taubken, N.; Thiem, J. *Synthesis* **1992**, 517.

(15) Also, quantitative yields are obtained by increasing the catalyst system up to 50 mol %.

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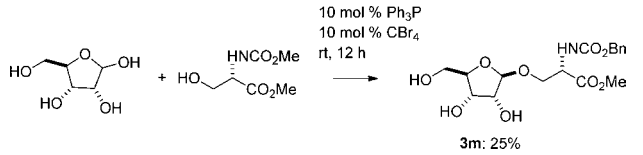
(17) For cleavage of triyl ethers under Appel-conditions see Yadav, J. S.; Reddy, B. V. S. *Carb. Res.* **2000**, *329*, 885.

Scheme 6. Synthesis of Protected Serine Riboside



[a] Reactions were carried out in propylene carbonate. For ratio of α- and β-anomers of pyranoid and furanoid structures see Table 4 in the Supporting Information.

comparison with the classical synthesis of Cbz-protected serine methyl ester glycoside in the xylose series (protection−glycosylation−deprotection) see ref 18.

In summary, we have developed an organocatalyzed method for the direct glycosylation of unprotected and unactivated carbohydrates under mild reaction conditions. This new transformation utilizes catalytic amounts of triphenylphosphine and tetrabromomethane. Also, the use of lithium perchlorate as an additive strongly increases the yields of products observed. Under these reaction conditions, thermodynamic control of the glycosidation is observed. As a consequence, the formation of pyranosides is preferred. Further extension of these findings and investigations into the reaction mechanism are underway.

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Supporting Information Available. NMR data for all of the synthesized compounds, full characterization of novel compounds, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.