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Indium(III) Iodide-Catalyzed Stereoselective Synthesis of β-Glucopyranosides by Using a Glucosyl Fluoride Donor with 2-*O*-Benzoyl-3,4,6-Tri-*O*-Benzyl Protection

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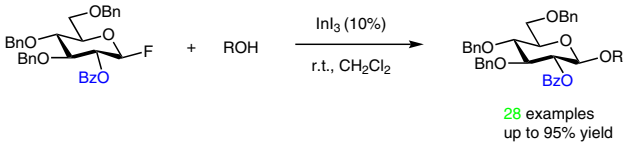

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Abstract We have developed a novel protocol for glucosylation by adopting a glucosyl fluoride donor with 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protection. The protocol is useful for the ready assembly of β-linked functional glycoconjugates, and the reaction accommodates a broad range of substrates. Conveniently, water-tolerant and commercially available InI_3 is used as a catalyst, and no other additional reagent is required. The method involves an interesting process for glucosyl fluoride activation and, in particular, permits the stereoselective construction of partially benzylated glucopyranosides carrying a selectively removable 2-*O*-benzoyl group, which hold great potential as glycosyl receptors for building further 1,2-glycosidic linkages.

Key words indium triiodide, glucopyranosides, glucosyl fluoride, stereoselectivity, benzoylation

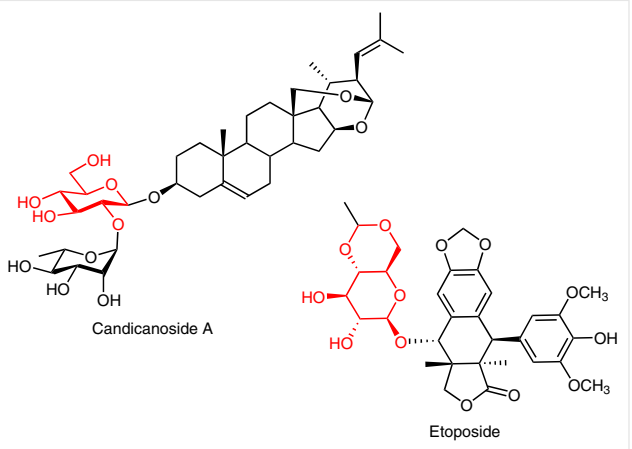


Figure 1 Selected bioactive compounds containing β-glucoside motif

Glucose units with β-glucosidic linkages are an important class of structural motifs in many bioactive natural glycoconjugates, and are present in several drugs currently on the market. Extensive research by medicinal chemists has shown that many molecules carrying β-glucoside residues display promising pharmacological activities, which renders them attractive targets. For instance, candicanoside A, isolated from Dioscoreaceae plants, possesses potent antithrombotic and antiviral activities,[1] whereas etoposide is used to clinically treat the cancer (Figure 1).

Glycosylation is a procedure that is routinely necessary in constructing glycosidic bonds during the total syntheses of valuable β-glucosides. The reaction involves coupling of a glycosyl donor with a fully protected saccharide with a leaving group at the anomeric position. A promoter activates the anomeric leaving group, causing its departure and the concomitant formation of an oxocarbenium ion. The anomeric center of the oxocarbenium ion subsequently undergoes nucleophilic attack by an alcohol to give the glycoside. A topic of current interest in glycochemistry is catalytic activation for glycosylation reactions by using transition metals. In this regard, the use of the gold-activated donor developed by Yu and co-workers has recently become an important niche method for chemical glycosylation.[2,3] Glycosyl fluorides are group of attractive donors for the synthesis of oligosaccharides, due to their enhanced stability, ease of handling, and high stereoselectivity compared with other glycosyl halides.[4] In particular, they can provide attractive levels of atomic efficiency in glycosylation, thereby simplifying the purification process. A legion of Lewis-acid-activated glycosyl fluorides have been well documented.[5] However, these conventional promoters have to be loaded stoichiometrically or in excess, and, what is worse, they often provide products as mixtures of isomers that can be difficult to purify by chromatographic techniques. With this background, the development of new Lewis acids that catalytically activate glycosyl fluorides for glycosylation in a highly selective manner remains highly desirable. So far only a few catalyst systems such as SiF_4,[5a] $Ln(ClO_4)_3$,[6a] and $SnCl_2{\cdot}AgB(C_6F_5)_4$,[6b] have been developed that avoid the use

of stoichiometric promoters. Unfortunately, however, all of these promoters have particular disadvantages. The use of gaseous SiF_4 or its solutions in the laboratory entails problems associated with storage, transportation, handling, and safety regulations. To activate donors successfully, $Ln(ClO_4)_3$ has to be used in combination with a large excess of K_2CO_3 as an additive. $AgB(C_6F_5)_4$ is not an easily accessible reagent. Consequently, there is still room for development of new catalytic systems that can display differences in reactivity, functional-group tolerance, and diversity.

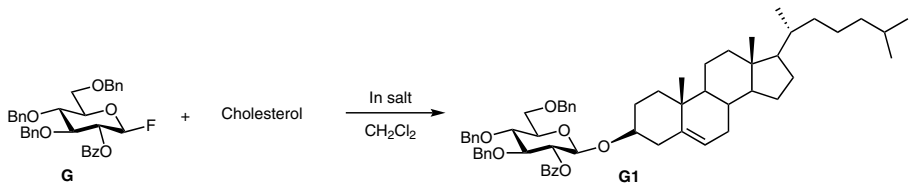
In recent years, indium catalysts have been widely applied in coupling reactions.[7] On the basis of our recent findings that fully acetylated aldoses react with arylthiols in the presence of $InBr_3$ as a catalyst to provide 1,2-*trans*-thioglycosides,[8] we sought to explore the generality of the indium-catalyzed glycosylation reaction. Here, we describe our new discovery that glucosyl fluoride donors with protective groups can be rapidly and cleanly converted into a wide range of glucosides by treatment with alcohols in the presence of catalytic amounts of InI_3.

1,2-Glycosyl ortho esters are valuable synthetic intermediates for the preparation of carbohydrate building blocks. Treatment of 1,2-glycosyl ortho esters with an excess of a nucleophile generates the corresponding 2-*O*-acyl glycosides with exclusively 1,2-*trans*-configurations. On the basis of this consideration, we used a 1,2-glycosyl ortho ester to prepare the β-glucosyl fluoride **G** by using simple 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protection. Additionally, in our recent study indium reagents were found to be excellent catalysts for constructing S-glycosidic bonds. In the context, we also hoped that they would act as effective catalysts in the synthesis of glucosides from **G**.

As part of our continuing interest in glycosylation, we investigated the reactivity of **G** as a donor with cholesterol as an electrophile. Our initial examination focused on the indium-catalyzed coupling of cholesterol with **G** in CH_2Cl_2 (Table 1). Gratifyingly, when the reaction was performed with 10 mol% of $InBr_3$, the yield of the desired product **G1** with exclusive β-configuration was 69% after two hours (Table 1, entry 1), whereas InI_3gave nearly full conversion to **G1** within two hours (entry 2), probably because of its sufficient acidity. Reducing the loading of InI_3 to 5 mol% did not greatly diminish the conversion (entry 3). Subsequently, a further screen showed that other readily available indium reagents did not perform better than InI_3 (entries 4–6). InI_3 is an air-stable, water-tolerant Lewis acid catalyst. Although it catalyzes reactions more effectively under anhydrous conditions, the reagent can be exposed to air. Additionally, it is also worth mentioning that fully benzoylated glycosyl fluoride donors were found to be inactive in the glucosylation.

Having identified the optimal conditions (Table 1, entry 2), we then turned our attention to an investigation of the substrate scope. The glycosylation reaction with InI_3 was found to be amenable to the use of a variety of alcohols (Scheme 1). The chemoselectivity profile of these reactions was nicely illustrated by the fact that functional substituents such as halo, azido, nitro, alkenyl, alkynyl, ether, thio ether, ester, carbamate, and ketal moieties were tolerated in the transformation. In our protocol, some significant bioactive molecules were suitable substrates for the glucosidation readily to give the corresponding products **G1**–**7**. Allyl alcohol and 2-(trimethylsilyl)ethanol were also efficiently glucosylated to afford **G8** and **G9**, respectively. The 2-(trimethylsily1)ethyl and allyl moieties, which are commonly used as blocking groups at anomeric centers in glycochemistry, remained intact in the reactions, and it should be possible to convert these into activated forms for use in further glycoside synthesis. More interestingly, pent-4-enyl glucoside **G10**, which is a well-studied glycosyl donor, was

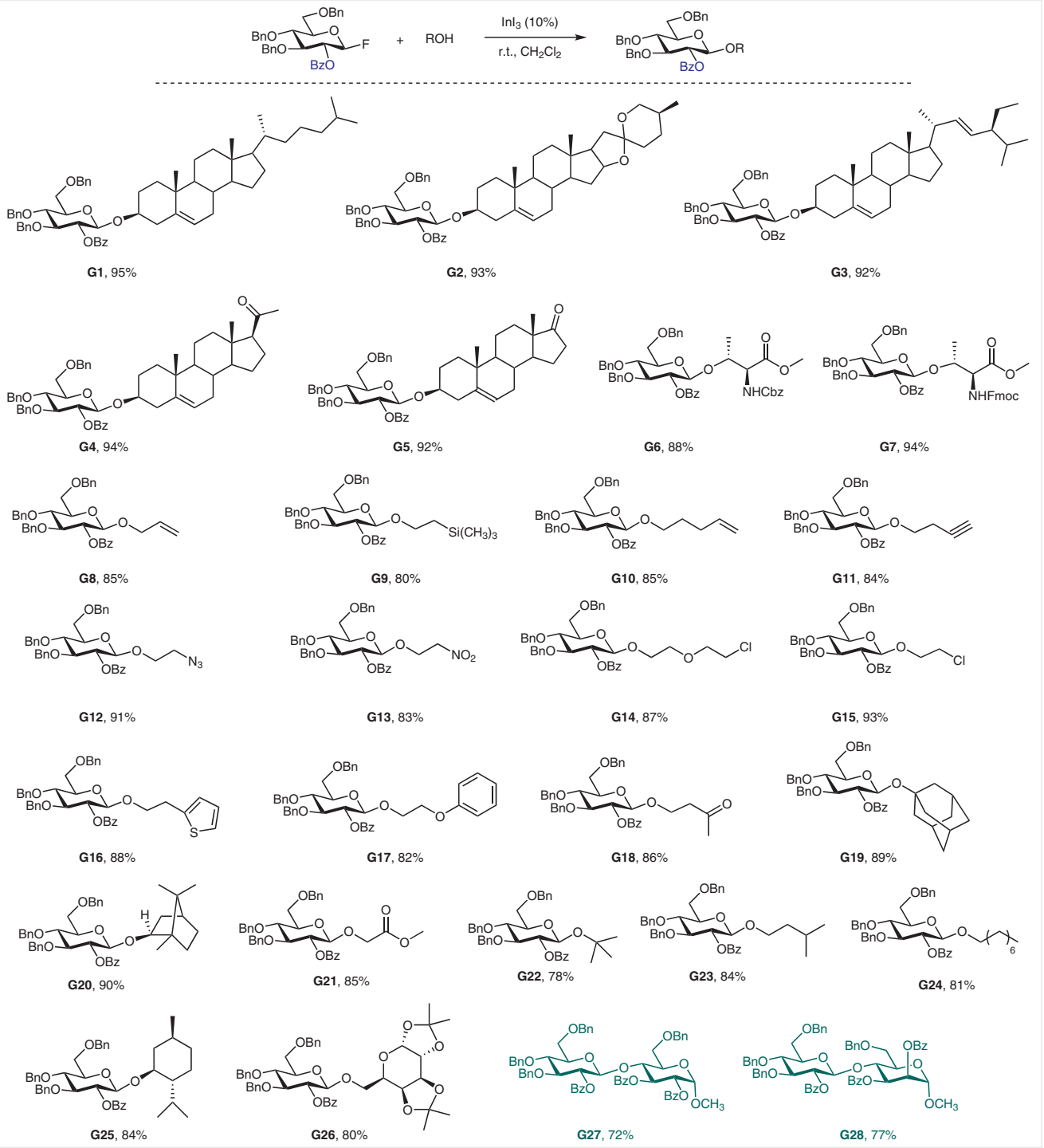
Table 1 Optimizing the Reaction Conditions for Glucosylation of Cholesterol with Glucosyl Fluoride **G**[a]



Entry	Catalyst (mol%)	Time (h)	Yield[b] (%)
1	$InBr_3$(10)	2	69
2	InI_3(10)	2	98
3	InI_3(5)	2	90
4	$InCl_3$(10)	24	11
5	$In(OTf)_3$(10)	24	49
6	$In(NTf)_3$(10)	24	37

[a] Reaction conditions: **G** (0.1 mmol), cholesterol (0.12 mmol), catalyst (0.01 mmol), CH_2Cl_2 (2 mL), r.t., stirring.
[b] Isolated yield.

obtained smoothly from **G**. Chemical synthesis and modification of neoglycoconjugates has provided artificial immunogens, such as carbohydrate-specific vaccines. The synthesis of glycosides carrying spacer arms as linkers attached covalently to biopolymers or carriers is of great significance for studies on the role of glycans in numerous physiological and pathological processes. Olefinic moieties exhibit versatile reactivity for ready conversion into spacer functional-



Scheme 1 Reactions of glycosyl fluoride **G** with various alcohols. *Reagents and conditions*: **G** (0.1 mmol), alcohol (0.12 mmol), InI_3 (5 mg), CH_2Cl_2 (2 mL), stirring, r.t., under Ar, 2 h. Isolated yields based on the aldoses are reported.

ities, as has been illustrated by the Magnasson group.[9] Apart from **G10**, our method permitted the effective preparation of spacer-arm glucosides **G11–15** from commercially available aglycones. These long-chain glycosides bearing ethynyl (**G11**), azido (**G12**), nitro (**G13**), or chloro groups (**G14** and **G15**) are compatible with many of the synthetic reactions used in carbohydrate chemistry, particularly with click chemistry,[10] which permits the elaboration of structurally intricate bioconjugates. Notably, Cu(I)-catalyzed azide–alkyne cycloaddition reactions have found widespread applications in glycodrug discovery and glycopolymer synthesis.[11] Numerous other substrates, ranging from short-chain alcohols to those bearing long alkyl chains or bulky substituents reacted with **G** to give glycosides **G16–25** in good yields (82–90%). This method was also extended to typical primary and secondary alcohols containing carbohydrate motifs to give disaccharides **G26–28** efficiently. Fully assigned NMR spectroscopic data confirmed the uniform β-configuration of the glucosides shown in Scheme 1. Their anomeric protons resonate at around 5.0 ppm with coupling constant $J_{1,2}$ values of over 7.0 Hz. The effect of neighboring-group participation by the 2-*O*-benzoyl functionality to produce β-configured products provides an appealing strategy for accessing a broad range of 1,2-*trans*-glucopyranosides. The deprotection of the hydroxy group at C2, in combination with subsequent formation of a glycosidic bond, has been highlighted in numerous elegant syntheses of complex carbohydrates.[12] Our protocol serves to install a benzoate group at the C2-position of the glucosyl receptors, and is therefore applicable to the preparation of C2-branched glucose residues.

In conclusion, InI_3 has been shown to be an effective catalytic activator for a glucosyl fluoride with 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protection. A wide range of alcohols were glucosylated to provide the expected glucosides with exclusive β-stereoselectivity.[13] In most cases, high yields were obtained, and broad functional-group tolerance was observed. Furthermore, the findings described here constitute a significant advance in glycosyl fluoride activation and the reaction can install a latent hydroxy substituent at the C2-position of a donor, thereby permitting the preparation of C2-branched carbohydrate fragments. More studies on indium-catalyzed glycosylation are currently underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589121.

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(13) **(2-Trimethylsilyl)ethyl 2-*O*-Benzoyl-3,4,6-tri-*O*-Benzyl-β-D-glucopyranoside; Typical Procedure**
2-(Trimethylsilyl)ethanol (0.12 mmol) was added to a solution of glucopyranosyl fluoride **G** (56 mg, 0.1 mmol) in anhyd CH_2Cl_2 (2 mL) containing InI_3 (5 mg, 0.01mmol), and the mixture was stirred for 2 h at r.t. When the reaction was complete (TLC), the mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatograph [silica gel, PE–EtOAc (4:1)] to give a colorless oil; yield: 52 mg (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.2 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.38–7.26 (m, 8 H), 7.21–7.18 (m, 2 H), 7.12 (s, 5 H), 5.30–5.23 (m, 1 H), 4.82 (d, *J* = 10.8 Hz, 1 H), 4.73 (d, *J* = 11.2 Hz, 1 H), 4.66 (d, *J* = 2.4 Hz, 1 H), 4.63 (d, *J* = 3.6 Hz, 1 H), 4.59 (d, *J* = 2.8 Hz, 1 H), 4.58–4.51 (m, 2 H), 3.99 (dd, *J* = 10.0, 5.6 Hz, 1 H), 3.85–3.70 (m, 4 H), 3.59–3.48 (m, 2 H), 0.85 (td, *J* = 14.0, 12.0, 6.4 Hz, 2 H), –0.09 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 138.1, 137.9, 137.8, 132.9, 130.2, 129.8, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 127.8, 127.7, 127.6, 100.6, 82.9, 78.1, 75.2, 75.0, 73.9, 73.5, 68.9, 67.1, 18.0, –1.5. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{39}H_{47}O_7Si$: 655.3091; found: 655.3092.