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Substoichiometric $FeCl_3$ Activation of Propargyl Glycosides for the Synthesis of Disaccharides and Glycoconjugates

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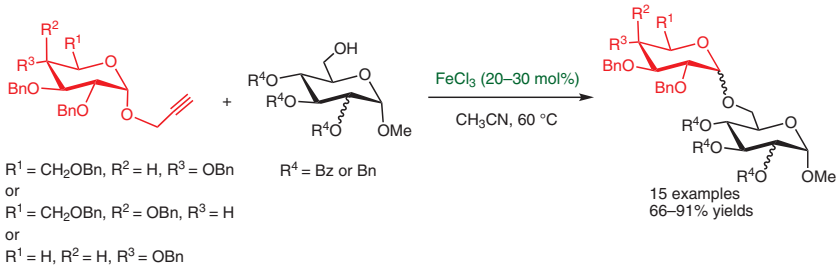

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Abstract Glycosides as glycosyl donors using $FeCl_3$ have been described. Under optimal reaction conditions, three kinds of propargyl glycosides were found to react with steroids and sugar-derived glycosyl acceptors to afford the corresponding disaccharides and glycoconjugates in good to excellent yields (66–91%). Meanwhile, the method can also realize one-pot synthesis of disaccharides, making it an effective, affordable, and green glycosylation procedure.

Key words propargyl glycosides, $FeCl_3$, disaccharides, glycoconjugates, glycosylation

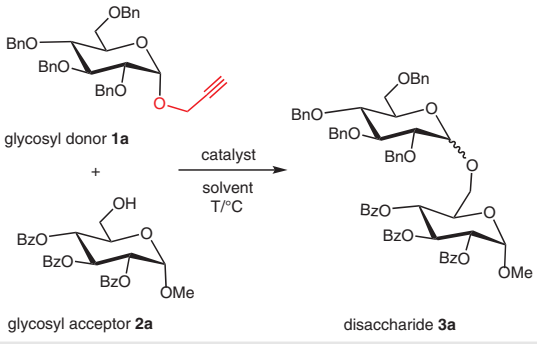
Oligosaccharides and glycoconjugates (glycolipids and glycoproteins) widely exist in a large number of biomolecules.[1–3] Many biological studies of these compounds at the molecular level have shed light on the biological significance in anticancer activity and molecular recognition for transmission of biological information.[4–7] However, it is difficult to obtain them from natural materials because of low concentrations and microheterogeneous forms.[8,9] Synthesis of such molecules is an important area of modern research to procure them in pure forms and in good quantities.[10]

Disaccharides are the simplest oligosaccharides and the synthesis of them from monosaccharides is the basis for the synthesis of complex oligosaccharides. From the point of chemical synthesis, one of the most useful procedures to achieve disaccharides is glycosylation reaction. The glycosyl donor generates an intermediate oxocarbenium ion using a suitable catalyst to further react with an acceptor to form a glycosidic linkage.[11–13] In the past decade, chemists have developed a variety of glycosyl donors and much interest has been devoted to the investigation of glycosylation protocols based on activation of the C–C triple bonds.[14–17] One of the most important used sets of them is propargyl glycosides, which have the advantages of simple structure, easy preparation and storage.[18] However, most of the methods for the activation of propargyl glycosides were limited to the use of toxic or noble catalysts such as $Hg(OTf)_2$, $AuCl_3$, $AuBr_3$, or $AuCl_3$ with $AgSbF_6$, which makes them difficult to be widely used in the synthesis of glycosides.[19–27] Beyond that, some reactions also depended on the use of 4 Å molecular sieves. Sureshkumar et al. reported the $AuBr_3$ promoted glycosylation reaction between propargyl 1,2-orthoesters and various aglycones in the presence of 4 Å powdered molecular sieves and delivered the product in satisfactory yield.[21,28] Therefore, a new and green catalytic system to activate propargyl glycosides is still needed. Compared with above catalysts, iron is inexpensive and harmless. Ferric salts have been widely used for a variety of organic reactions because of their superior and unique catalytic properties, and iron(III) chloride was found to be an effective Lewis acid for activating alkynes under extremely mild conditions.[29–39] Very recently, we reported the iron-catalyzed synthesis of α-2,6-dideoxy-*O*-glycosides.[40,41] In this article, we report that $FeCl_3$ as an efficient and affordable catalyst effectively activates propargyl glycosides to lead to disaccharides and glycoconjugates under mild conditions.

To test the feasibility of our idea, examination and optimization of the reaction parameter were explored using propargyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1a**) as the glycosyl donor and methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**2a**) as the acceptor by varying different common ferric salts and conditions (Scheme 1, Table 1).

Initially, we examined the glycosylation in the presence of 0.3 equivalents of $FeCl_3$ in dry acetonitrile as solvent which led to only 30% conversion after 15 h (Table 1, entry 1). We next checked the reactivity of $FeCl_3{\cdot}6H_2O$ under the same set of reaction conditions, but disappointingly its reactivity was no better than that with $FeCl_3$ (Table 1, entry

2). Further, iron(II) salts like $FeCl_2$ and $Fe_2(SO_4)_3$ were found to be unreactive under the same reaction conditions (Table 1, entries 3 and 4). Based on these results, we decided to optimize other reaction conditions. Encouragingly, with the increase of the amount of the glycosyl donor **1a**, reactions afforded the product in moderate to good yields in the presence of 0.3 equivalents of $FeCl_3$ in acetonitrile (Table 1, entries 5–8). The stoichiometric amount of catalyst was also studied, and we found that 0.3 equivalents were sufficient to promote the reaction (Table 1, entries 7, 9, and 10). It was found that the reaction can also be carried out in 1,2-dichloroethane and moderate yields of disaccharide **3a** were obtained (Table 1, entry 11). Dichloromethane and tetrahydrofuran, which are also widely used in glycosylation, were not suitable in this case (Table 1, entries 12 and 13). Further optimization revealed that the reaction did not



Scheme 1 Iron-catalyzed glycosylation of propargyl glycosides

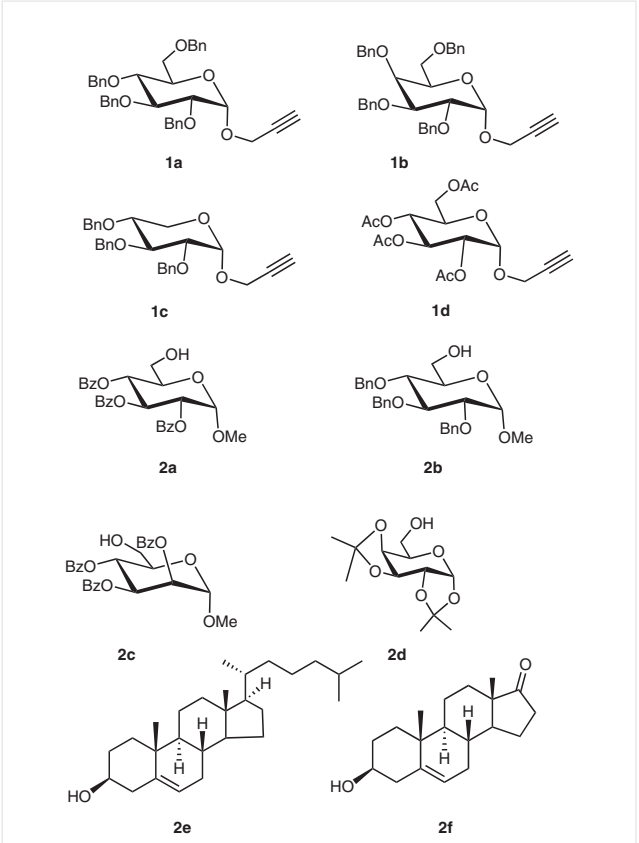


Figure 1 Glycosyl donors and acceptors

Table 1 Optimization of the Glycosylation Reaction Conditions

Entry	Cat. (0.3 equiv)	**1a**/**2a** (equiv)	Solvent	Temp (° C)	Time (h)	Yield for **3a** (%)[a]
1	$FeCl_3$	1:1.2	CH_3CN	60	15	30
2	$FeCl_3{\cdot}6H_2O$	1:1.2	CH_3CN	60	15	21
3	$FeCl_2$	1:1.2	CH_3CN	60	12	NR[b]
4	$Fe_2(SO_4)_3$	1:1.2	CH_3CN	60	15	NR
5	$FeCl_3$	1:2	CH_3CN	60	15	74
6	$FeCl_3$	1.2:1	CH_3CN	60	15	51
7	$FeCl_3$	2:1	CH_3CN	60	15	83
8	$FeCl_3$	4:1	CH_3CN	60	10	77
9	$FeCl_3$(0.1 equiv)	2:1	CH_3CN	60	10	20
10	$FeCl_3$(0.5 equiv)	2:1	CH_3CN	60	10	85
11	$FeCl_3$	2:1	DCE	60	15	58
12	$FeCl_3$	2:1	DCM	40	12	NR
13	$FeCl_3$	2:1	THF	60	12	trace
14	$FeCl_3$	2:1	CH_3CN	40	12	NR
15	$FeCl_3$	2:1	CH_3CN	80	10	76

[a] Isolated yield.
[b] NR = no reaction.

proceed at all below 40 °C and the byproducts production increased slowly at 80 °C although the rate of reaction improved considerably (Table 1, entries 14 and 15).

We next examined the scope and generality of the present reagent system with a wide range of glycosyl donors **1a–d** and acceptors **2a–f** (Figure 1). Initially, we explored the utility of propargyl glycosides for disaccharide synthesis. As shown in Figure 2, the $FeCl_3$-promoted glycosylation reaction between glucosyl donor **1a** and various sugar-based aglycones comprising benzoyl-protected sugars **2a**,**c** and benzyl-protected sugar **2b** gave the respective disaccharides **3a–c**. Unfortunately, this method does not apply to acid-sensitive acceptors such as **2d**. It is pertinent to mention that the current glycosylation strategy was extended to galactosyl and xylosyl propargyl glycosides **1b**,**c** to obtain disaccharides **3d–f** and **3g–i**, respectively (Figure 2). However, this method does not apply to acyl-protected donor **1d** because of the disarmed effect which will decrease the reactivity of glycosyl donors significantly. Glycosylation between these propargyl glycosides and sugars was performed, respectively, under optimized conditions to obtain the corresponding disaccharides in good to excellent yields. The utility of propargyl glycosides was gauged in the perspective of glycoconjugate formation using aglycones comprising cholesterol (**2e**) and dehydroepiandrosterone (**2f**). Glucosyl propargyl glycoside **1a** behaved as glycosyl donor in all the reactions giving the corresponding compounds **3j**,**k** (Figure 2). We also extended the scope of this method to galactosyl **1b** and xylosyl **1c** propargyl glycosides resulting in the formation of glycosides **3l**,**m** and **3n**,**o** in moderate yields. The glycosylation reaction between glycosyl donor and steroids resulted in lower yields presumably due to the poor solubility of steroids in acetonitrile. The structures of the products **3a–o** were determined by ^{1}H NMR and ^{13}C

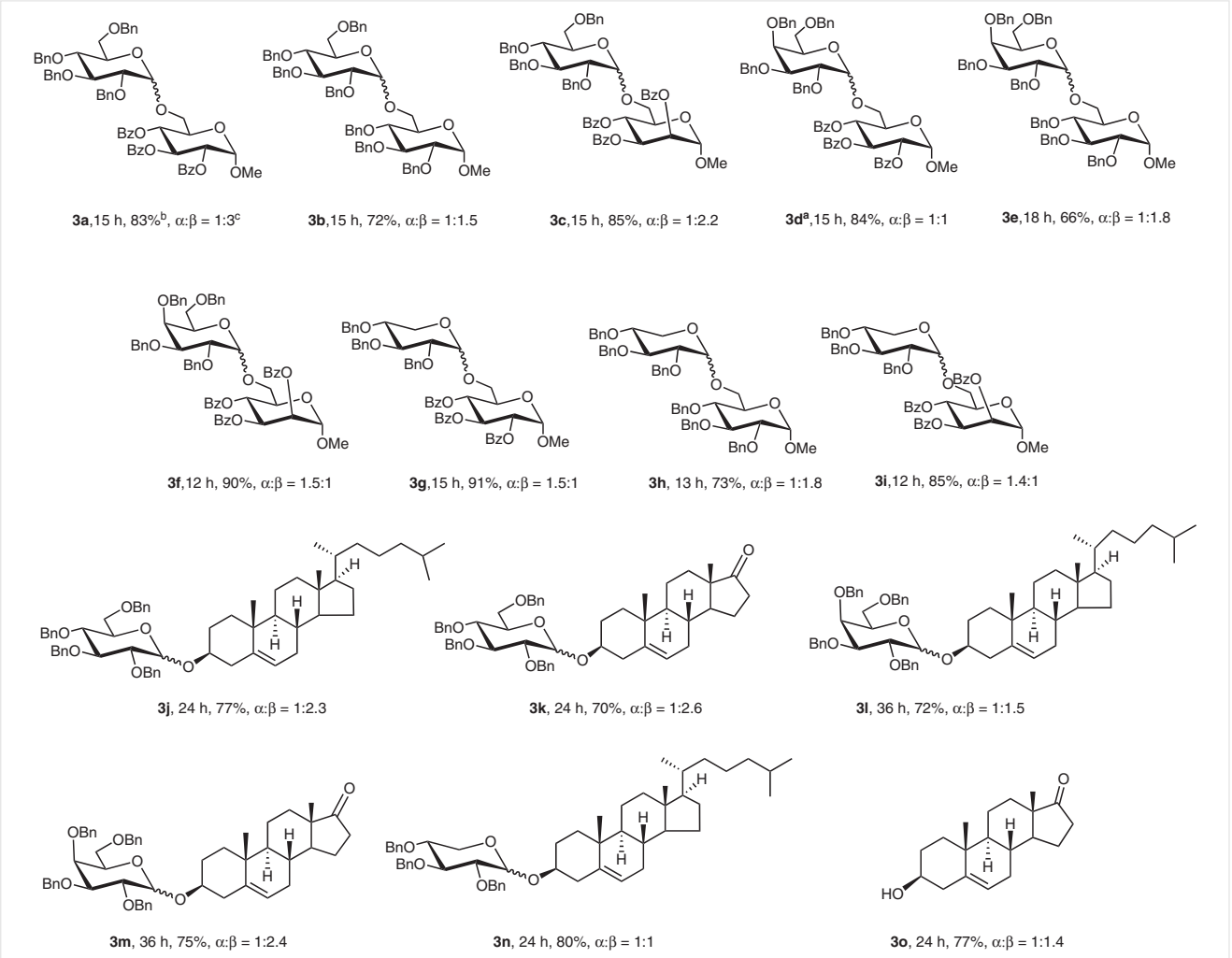
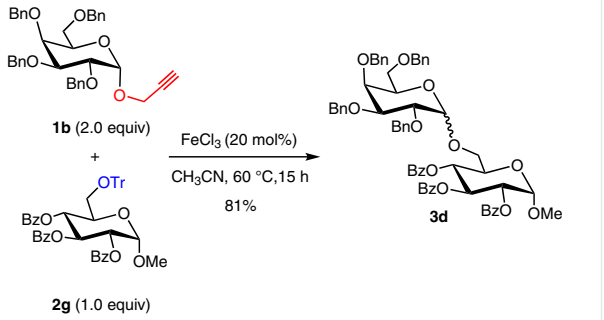


Figure 2 Glycosylation results of propargyl glycosides **1a–c** with acceptors **2a–f**. [a]The amount of $FeCl_3$ for the donors of **1b** and **1c** was 20 mol%. [b] Isolated yields. [c] α/β Ratio was determined by ^{1}H NMR analysis or mass ratio.

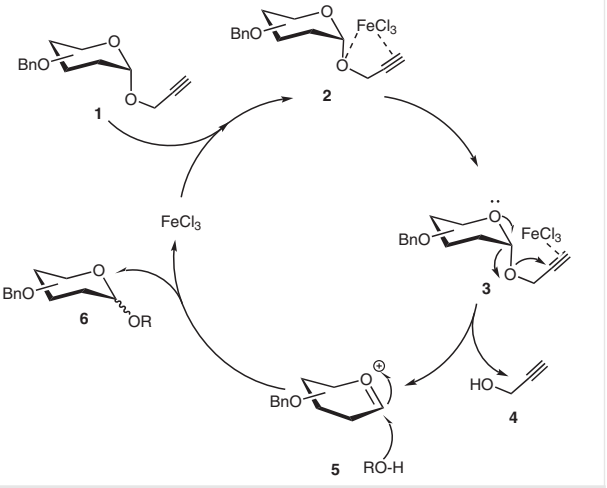
NMR spectroscopy and mass spectrometry, also by comparison with the reported data.[42–44] The ratio between α-isomer and β-isomer was determined by ^{1}H NMR analysis or their isolated yields.

One-pot reaction is economical and environmentally friendly and becoming a promising method in organic synthesis.[45–53] It is interesting that we can also realize the one-pot synthesis of disaccharides when propargyl glycosides reacted with glycosyl intermediates which contain a protecting group (triphenylmethyl, Tr) in the sugars using the optimized reaction conditions. 2,3,4,6- tetra-*O*-benzyl-α-D-galactopyranoside **1b** reacted with methyl 2,3,4-tri-*O*-benzoyl-6-triphenylmethyl-α-D-glucopyranoside (**2g**) in the presence of $FeCl_3$ to get the disaccharide **3d** in 81% yield after 15 h (Scheme 2).



Scheme 2 One-pot synthesis of disaccharides

The proposed reaction mechanism may be explained as follows (Scheme 3).[25,54] A π complexation of $FeCl_3$ with alkyne (compound **2**) should generate oxonium cation **5**. This intermediate is simultaneously trapped with aglycone to furnish the *O*-glycoside **6**.



Scheme 3 The possible mechanism for the glycosylation

In summary, we have described for the first time that $FeCl_3$ is an effective, green, and inexpensive promoter catalyst for the activation of propargyl glycosides.[55,56] The reactions proceed cleanly to obtain disaccharides and glycoconjugates in moderate to excellent yields at mild conditions without the need for molecular sieves. Meanwhile, the reaction system can also realize one-pot synthesis of disaccharides, indicating it as an economic and useful glycosylation procedure. Further studies toward this direction are under way in our laboratory and will be reported in due course.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591525.

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(55) **Typical Experimental Procedure**
Typically, to a mixture of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1a**, 0.1 mmol, 58 mg) and methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**2a**, 0.05 mmol, 25 mg) in a round-bottom flask (5 mL) under nitrogen atmosphere. The $FeCl_3$ (10 mg, 0.06 mmol) catalyst and anhydrous CH_3CN solvent (6 mL) was added to another round-bottom flask. Take the solution of $FeCl_3$(1.5 mL) to the former round-bottom flask, and the reaction was stirred at 60 °C for 15 h. After completion of the reaction (monitored by TLC), the organic phase was condensed under vacuum to get crude product, which was purified by silica gel column chromatography (PE/EtOAc = 6:1) to get **3a** in 83% yield. All new compounds were characterized by ^{1}H NMR,^{13}C NMR, and MS. Spectral and analytical data were in good agreement with the desired structures.
(56) **Selected Spectral Data – Compound 3a**
Colorless oil, α-anomer:^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 8.3, 1.2 Hz, 2 H), 7.97 (dd, *J* = 8.3, 1.2 Hz, 2 H), 7.91–7.85 (m, 2 H), 7.55–7.49 (m, 2 H), 7.46–7.28 (m, 24 H), 7.22 (m, 1 H), 7.15 (dd, *J* = 7.6, 1.7 Hz, 2 H), 6.16 (t, *J* = 9.4 Hz, 1 H), 5.55 (t, *J* = 9.9 Hz, 1 H), 5.24 (q, *J* = 3.5 Hz, 2 H), 4.93 (d, *J* = 11.0 Hz, 1 H), 4.84 (d, *J* = 11.0 Hz, 1 H), 4.80 (d, *J* = 11.0 Hz, 1 H), 4.78 (d, *J* = 12.5 Hz, 1 H), 4.76 (d, *J* = 3.5 Hz, 1 H), 4.65 (d, *J* = 12.2 Hz, 1 H), 4.56 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 11.0 Hz, 1 H), 4.40 (d, *J* = 12.1 Hz, 1 H), 4.36–4.31 (m, 1 H), 3.98 (t, *J* = 9.3 Hz, 1 H), 3.90–3.84 (m, 2 H), 3.67–3.62 (m, 2 H), 3.60 (dd, *J* = 11.0, 2.1 Hz, 1 H), 3.56 (dd, *J* = 9.7, 3.5 Hz, 1 H), 3.52 (dd, *J* = 10.7, 1.9 Hz, 1 H), 3.46 (s, 3 H).
β-Anomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00–7.85 (m, 6 H), 7.52–7.12 (m, 29 H), 6.17 (t, *J* =9.8 Hz, 1 H), 5.47 (t, *J* =9.9 Hz, 1 H), 5.25 (dd, *J* =10.2, 3.6 Hz, 1 H), 5.20 (d, *J* =3.6 Hz, 1 H), 5.05 (d, *J* =10.8 Hz, 1 H), 4.91 (d, *J* =10.9 Hz, 1 H), 4.80 (d, *J* =10.8 Hz, 1 H), 4.76 (d, *J* = 10.9 Hz, 1 H), 4.68 (d, *J* =10.9 Hz, 1 H), 4.53 (d, *J* =11.5 Hz, 1 H), 4.50 (d, *J* =11.6 Hz, 1 H), 4.47 (d, *J* =7.8 Hz, 1 H), 4.43 (d, *J* =12.2 Hz, 1 H), 4.41–4.34 (m, 1 H), 4.12 (dd, *J* =10.8, 2.0 Hz, 1 H), 3.81 (dd, *J* = 10.9, 7.6 Hz, 1 H), 3.66–3.63 (m, 2 H), 3.61 (d, *J* = 6.0 Hz, 1 H), 3.58 (d, *J* = 9.1 Hz, 1 H), 3.46–3.43 (m, 2 H), 3.37 (s, 3 H). ESI-MS: *m/z* calcd for $C_{62}H_{60}O_{14}$ Na [M + Na$^+$]: 1051.39; found: 1051.25.