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COMMUNICATION

Green glycosylation promoted by reusable biomass carbonaceous solid acid: an easy access to β-stereoselective terpene galactosides†

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An efficient green protocol has been developed for the atom economic glycosylation of unprotected, unactivated glycosyl donors and glycosylation of glycosyl trichloroacetimidates with the aid of reusable eco-friendly biomass carbonaceous solid acid as catalyst.

Glycosylation provides an unique platform to synthesize an array of carbohydrate-derived novel therapeutic agents.[1] It has gained much attention and witnessed a vast development ever since the historical discovery of Koenigs-Knorr method and its amended versions.[2] Over the past few decades, there has been significant amount of advancement in glycosyl donors and acceptors.[3] It is essential to chose appropriate donor and employ suitable promoter to attain regio- and stereoselective glycoside synthesis. The most common promoters include strong and highly moisture sensitive Lewis acids, such as $BF_3{\cdot}Et_2O$,[4] TBSOTf,[5] Tf_2O,[6] ZnBr,[7] $LiClO_4$,[8] LiOTf,[9] AgOTf[10] and TMSOTf.[11] These promoters need dry reaction conditions, low temperatures and required in stoichiometric amounts. Moreover, they mostly furnish glycosides as α/β anomers. When using mineral and Lewis acid catalysts, the final glycoside isolation requires aqueous work-up and neutralization steps, which subsequently results in the disposal of massive amounts of hazardous waste. Most of the times, cost of the pollutants is significantly greater than the cost of the product. The principles of "Green Chemistry" emphasize the usage of environmentally benign catalysts/chemicals in order to have minimal deteriorating effects on the environment.[12] As an alternative to homogenous catalysis, nowadays environmentally sustainable nontoxic solid acid catalysts with strong acidic sites have become more prominent in organic transformations. Several solid acid catalysts have been reported in the literature, such as high silica zeolites,[13] ion exchange resins[14] and mesoporous materials.[15] Solid acid catalysts have several advantages[16] over liquid acids such as (a) no work-up procedures, (b) easy separation and (c) easy recovery and reusability.

To date several silica- and alumina-supported solid acid catalysts have been developed and employed in glycosylation.[17] For example Toshima and coworkers performed glycosylation by using a sulfated zirconia and montmorillonite K-10 as activators.[18] Corma *et al.* reported the Fischer glycosylation by using zeolites.[19] Unfortunately, many of the reported solid acids did not control the stereoselectivity at the anomeric centre, and hence provided glycosides as anomeric mixture. More importantly, most of solid acids are mechanically unstable in various solvents, therefore practically they are not recyclable.

In order to address the above-mentioned practical difficulties and in our continuous effort to explore new glycosylation protocols,[20] herein we wish to report glycosylation of various unprotected, unactivated monosaccharides and glycosyl trichloroacetimidates promoted by sulfonated biomass carbonaceous material, which is inexpensive, moisture stable and environmentally benign with high catalytic performance. The most striking feature of this catalyst is its remarkable reusable capacity and, when employed with activated sugars, it delivered desired *O*-glycosides with exclusive anomeric selectivity. The sulfonated carbonaceous solid acid material was synthesized according to the given literature procedure.[21] It consists of flexible polycyclic carbon sheets, which bear phenolic hydroxyl (–OH), carboxylic acid (–COOH) and sulfonic acid ($–SO_3H$) groups. Elemental analysis of the solid acid revealed its sulfur content, which was found to be 1.13%. Since all sulfur atoms in the carbon material were in the form of SO_3H groups, the density of SO_3H groups in solid acid was thus estimated to be 0.35 mmol g^{-1}. The solid acid was further characterized by X-ray diffraction (XRD).

To begin with, we tried to test the catalytic efficiency of the solid acid by performing glycosylation on unprotected and unactivated sugars. Glycosylation of unprotected alcohols[22] remains particularly challenging due to self-condensation, ring chain tautomerism and *in situ* anomerization.[23] From a greener prospective, glycosylation of unprotected sugars is atom economic since it avoids unwieldy protection-deprotection steps thus leading to high atom economy and improved *E*-factor.[24] Moreover direct synthesis of *O*-glycosides from *O*-unprotected donors accounts for (a) enhancing the reactivity, (b) controlling

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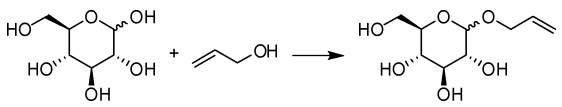
† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization data. See DOI: 10.1039/c0gc00883d

Table 1 Catalytic efficiency of solid acid compared against various Lewis acids[a]



Entry	Catalyst	Catalyst loading (mol%)	Temp./°C	Time/h	Yield (%)[b]	α/β ratio[c]
1	Solid acid	1	25	24	26	73 : 27
2	Solid acid	1	80	14	82	73 : 27
3	Solid acid	5	80	8	84	73 : 27
4	$ZnCl_2$	5	80	24	42	65 : 35
5	$BF_3{\cdot}OEt_2$	5	80	24	71	63 : 37
6	$FeCl_3$	5	80	24	24	69 : 31
7	AgOTf	5	80	24	—	—
8	$Sc(OTf)_2$	5	80	24	49	73 : 27
9	$InCl_3$	5	80	24	—	—
10	$AuCl_3$	5	80	24	41	70 : 30
11	$Yb(OTf)_3$	5	80	24	45	68 : 32

[a] The reaction was conducted with 1 eq. of D-glucose and 10 eq. of allylic alcohol. [b] Isolated yields. [c] Determined by ^{1}H NMR.

the α/β selectivity and (c) making the process modifications with more ease by reducing the number of synthetic steps.

A systematic study of glycosylation was undertaken by performing neat glycosylation between D-glucose and allyl alcohol to test the catalytic activity and performance. Glycosylation was sluggish when the reaction was carried out at room temperature with 1 mol% of the catalytic loading and resulted in desired allyl glycoside (α/β = 73 : 27) in 26% yield.

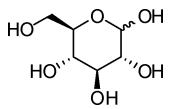
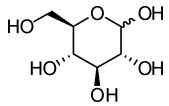
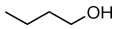
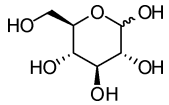
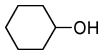
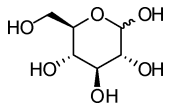
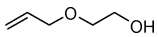
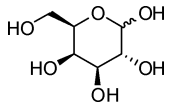
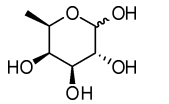
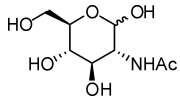
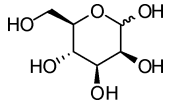
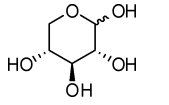
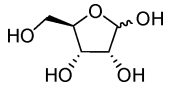
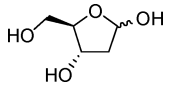
However, when the temperature has been raised to 80 °C, we were intrigued by the formation of the glycoside in 82% yield (Table 1, entry 2). We have tried different temperatures such as 40 °C and 60 °C. Best yields were obtained when the temperature was maintained at 80 °C. A detailed probe into the optimization showed that the reaction time required for complete conversion of monosaccharide to corresponding glycoside is inversely proportional to the amount of solid acid loaded and temperature (Table 1, entries 1–3). However, it was found that increasing the catalytic loading to 10 mol% could not make an impact on reaction time and yield. A series of experiments were conducted to compare the efficiency of solid acid catalyst against commonly used Lewis acid catalysts. Under the same conditions (5 mol% Lewis acid catalyst and at 80 °C), the model glycosylation of glucose with allyl alcohol was carried out. The results are summarized in Table 1. It was observed that all the Lewis acids could not successfully converted the monosaccharide into glycoside even after prolonged reaction times except $BF_3{\cdot}OEt_2$ which gave allyl glycoside (α/β = 63 : 37) in acceptable yield (71%). To our surprise AgOTf and $InCl_3$ proved to be inefficient candidates to carry out the glycosylation transformation (Table 1, entries 7 and 9). However, Lanthanide triflates such as $Sc(OTf)_2$ and $Yb(OTf)_3$ are able to furnish the allyl glycoside in moderate yields. This study clearly shows the preeminent catalytic efficiency of biomass solid acid over Lewis acids in terms of yields, reaction time and stereoselectivity when exerted with unprotected and unactivated sugars.

Pleased by this result, we began to probe the breadth of this catalytic application on various unprotected and unactivated monosaccharides. The scope of the neat glycosylation on various sugar moieties such as D-galactose, D-mannose, D-fucose, D-xylose, D-ribose, 2-deoxy-D-ribose, *N*-acetyl glucosamine was investigated. We chose allyl alcohol as aglycone because of the fact that allyl glycosides find substantial applications in the synthesis of oligosaccharides, for example (a) reducing sugars were attained *via* the deprotection of anomeric *O*-allyl moiety at any length of the saccharide chain by using various reagents,[25] (b) reducing sugars could be coupled with proteins to obtain corresponding glycoconjugates,[26] (c) with the assistance of a spacer-arm, anomeric *O*-allyl group could be availed to synthesize glycoconjugates,[27] and (d) asymmetric functionalization of *O*-allyl moiety paves a new way to synthesize enantiomerically pure compounds, thereby contributing to the asymmetric organic synthesis.[28] Under the standard experimental conditions, all the monosaccharides furnished corresponding allyl glycosides in good to excellent yields (72–96%, Table 2, entries 5–11). As predicted, mannose gave allyl glycoside as pure α-diastereomer (Table 2, entry 8) and it is worthy of note that fucose and 2-deoxy-D-ribose afforded the corresponding allyl glycosides with good selectivities (Table 2, entries 6 and 11 respectively). Meanwhile, galactose, xylose and ribose afforded respective allyl glycosides in good to excellent yields with moderate to good selectivities (Table 2, entries 5, 9 and 10 respectively). It is important to note that all the glycosylation reactions are distinguished with the exclusive formation of thermodynamically more stable pyranosides than the corresponding kinetically favored furanosides. Having synthesized various synthetically useful allyl glycosides, we extended the scope of the catalytic activity by synthesizing long chain glycosides. From a synthetic point of view, there has been enormous interest in alkylpolyglycosides (APG),[29] which are a part of carbohydrate-derived surfactants. APGs are known to play significant role in food and cosmetic industries, as they are preferred candidates to serve as non-ionic surfactants for cosmetics and as food emulsifiers.[30] These factors encouraged us to synthesize n-butyl glycopyranoside and n-octyl glycopyranoside through direct glycosylation. Both the APGs were isolated in good yields with acceptable anomeric selectivities (Table 2, entries 1 and 2).

Then we embarked on checking the recyclability of the solid acid catalyst, which is the most crucial factor that reckons its practical utility while employing in glycosylation reactions. After recovering the carbonaceous solid acid *via* a simple filtration and removing the volatile solvents under vacuum, the catalyst was reused without further activation in catalyzing the reaction between unprotected mannose and allyl alcohol. To our delight, glycosylation proceeded smoothly even after 7 runs without any extension of reaction time or marked loss in yield (Fig. 1). In each experiment, allyl mannoside has maintained α-anomeric selectivity.

Finally, we scrutinized the catalytic efficacy of the solid acid by glycosylating glycosyl trichloroacetimide with various terpenoid alcohols to synthesize biologically active carbohydrate-containing terpenoids and steroids. Nowadays, diversity oriented synthesis (DOS) for synthesizing oxygen-rich small molecules with definite stereochemistry has gained much attention.[31] Terpenes possess a significant amount of biological

Table 2 Neat glycosylation of unprotected and unactivated glycosyl donor with acceptors[a]

Entry	Glycosyl donor	Acceptor	Time/h	Yield (%)[b]	α/β ratio[c]
1			8	62	44 : 56
2			8	68	56 : 44
3			8	55	71 : 29
4			8	70	68 : 32
5			8	72	60 : 40
6			8	82	90 : 10
7			8	75	50 : 50
8			8	94	100 : 0
9			8	90	70 : 30
10			8	96	75 : 25
11			8	80	85 : 15

[a] The reaction was conducted with 1 eq. of glycosyl donor and 10 eq. of glycosyl acceptor. [b] Isolated yields. [c] Determined by ^{1}H NMR.

activity[32] and reports on synthesis of exclusive β-selective terpene and steroidal galactose analogues are rare. Synthesis of terpene glycosides generally relies on enzymatic methods.[33]

Due to their potential candidature as antimicrobial, antifungal, antiparasitic, antitoxigenic and anticancer agents, we envisaged to synthesize β-terpene and steroidal galactosides with the aid of solid acid catalyst. Glycosylation between glycosyl trichloroacetimidate and citronellol in the presence of 5 mol% solid acid catalyst at 80 °C in toluene for 4 h afforded desired citronellol galactoside in excellent yield (82%) with exclusive β-anomeric selectivity (Table 3, entry 5). Encouraged by this result, we tried to construct glycosyl bond between various terpenes and galactose. *endo*-Fenchol, borneol and menthol gave the corresponding galactosyl derivates in excellent yields with absolute stereo selectivity (Table 3, entries 1, 2 and 3). Pregnenolone, a steroid harmone involved in the steroidogenesis of progesterone, also successfully transformed in to steroidal β-galactoside (Table 3, entry 4). To broaden the substrate scope and to show the catalytic utility we have synthesized protected serine galactoside and bulky moieties containing galactosides such as adamentane and ferrocene (Table 3, entries 6–8). To corroborate the solid acid's practical reusability as a glycosylation promoter, recycled catalyst was employed in the above set of experiments.

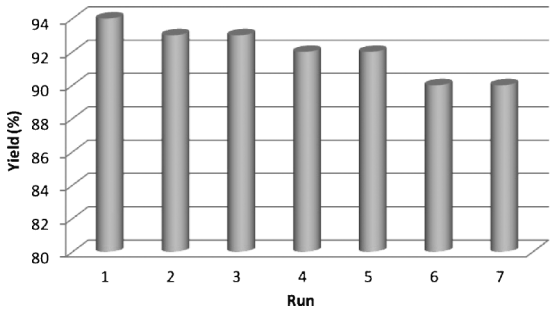
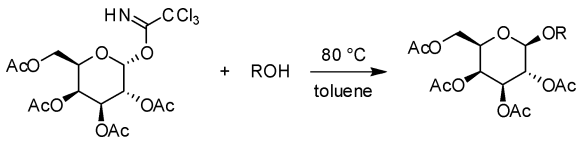


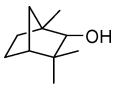
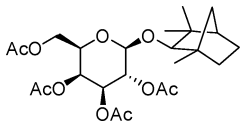
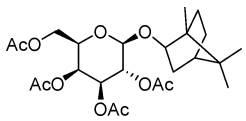
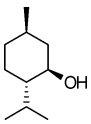
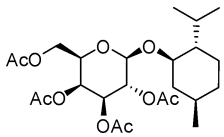
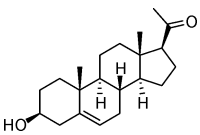
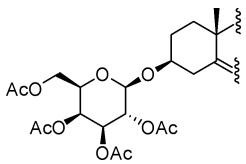
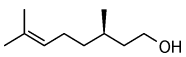
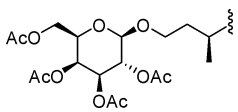
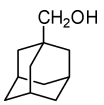
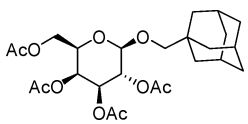
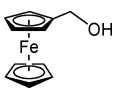
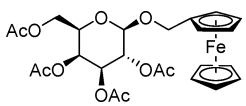
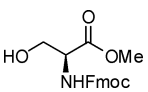
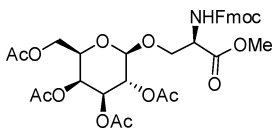
Fig. 1 Catalytic performance of recovered solid acid.

In conclusion, we have demonstrated the remarkable catalytic efficiency of environmentally sustainable biomass carbonaceous solid acid as glycosylating promoter. Various unprotected and unactivated glycosyl donors, which are usually prone to self-condensation and *in situ* anomerization while performing the glycosylation, were successfully glycosylated to afford corresponding glycosides. This catalyst could also be employed for the glycosylation of glycosyl trichloroacetimides. Some of the salient features of the catalyst are: (a) derived from naturally existing D-glucose hence quite economical to synthesize, (b) air and moisture stable therefore easy to handle, (c) reaction procedure is operationally simple which precludes the stringent and inert conditions; use of molecular sieves can be avoided, (d) easy recovery of the catalyst upon completion of the reaction through simple filtration there by avoiding hectic aqueous work ups and neutralization steps, (e) high reusable capacity; catalyst is reusable up to 7 times while persisting the high catalytic activity, (f) affords galactosides with exclusive β anomeric selectivity when used with glycosyl trichloroacetimides. With these advantages in hand, we strongly believe solid acid promoter could become an alternative to other glycosylating promoters. Its synthetic assets coupled with green principles could benefit the glyco-chemists in their regular laboratory usage. The employment of heterogeneous solid acid catalyst in other glycochemical transformation is currently underway in our laboratory.

We gratefully acknowledge Nanyang Technological University (RG50/08) and the Ministry of Education, Singapore (MOE 2009-T2-1-030) for the funding support of this research.

Table 3 Glycosylation of glycosyl trichloroacetimidates with various alcohols[a]



Entry	Aglycone	Product	Time/h	Yield (%)[b]
1			4	88
2			4	82
3[c]			2	94
4[c]			8	76
5[c]			4	82
6[c]			6	92
7[c]			6	94
8[c,d]			8	85

[a] The reaction was conducted with 1 eq. of glycosyl donor and 1.5 eq. of acceptor in toluene at 80 °C. [b] Isolated yields. [c] Recovered catalyst was used. [d] Dichloromethane was used as solvent.

Notes and references

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