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C-Glycosylation enabled by *N*-(glycosyloxy) acetamides†

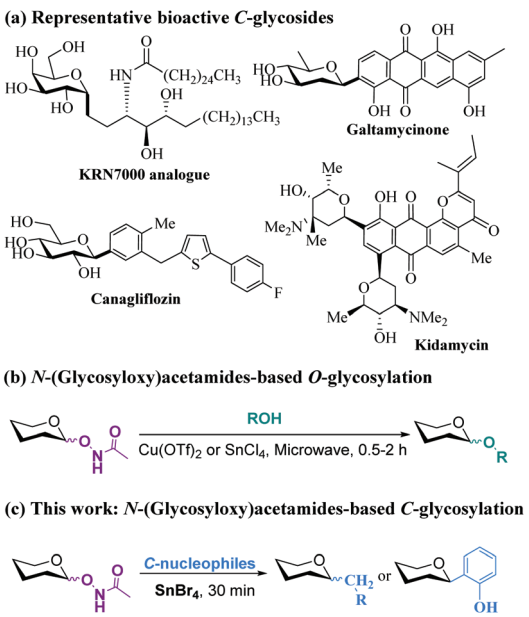
Miao Liu,[a] Bo-Han Li,[b] Tian Li,[a] Xia Wu,[a] Meng Liu,[a] De-Cai Xiong*[a] and Xin-Shan Ye *[a]

The *C*-glycosylation of *C*-nucleophiles including allyltrimethylsilane, silyl enol ethers and phenols with *N*-(glycosyloxy)acetamides as glycosyl donors has been realized. This protocol provides a convenient and practical route for the synthesis of alkyl *C*-glycosides and aryl 2-deoxy-β-*C*-glycosides under mild reaction conditions.

C-Glycosides are a class of important compounds with a carbohydrate unit linked to another carbohydrate unit or an aglycone through a carbon–carbon bond.[1] Compared with the corresponding *O*-glycosides and *N*-glycosides, *C*-glycosides show better enzyme stability and hydrolysis resistance.[2] On the other hand, *C*-glycosides are present in a diverse range of biologically active natural products and drugs such as a KRN7000 analogue,[3] Canagliflozin,[4] Kidamycin,[5] and Galtamycinone[6] (Scheme 1a). Therefore, the synthesis of *C*-glycosides has been one of the significant and critical topics in organic chemistry.[2d,7] Among the numerous methods for the construction of the C–C glycosidic bond, the coupling reaction of glycosyl donors with *C*-nucleophiles in the presence of an activator is a straightforward and highly efficient route. For instance, glycosyl halides,[8] glycals,[9] glycosyl acetates,[10] thioglycosides,[11] sulfoxides,[12] 1,2-anhydro sugars,[13] and glycosyl phosphates[14] have been widely employed for *C*-glycosylation. Although a lot of elegant strategies and methods in this field have been available over the last few decades,[15] the development of efficient and stereoselective protocols for the synthesis of *C*-glycosides remains challenging. New approaches for the synthesis of diverse *C*-glycosides are highly desirable.

Recently, we developed a new *O*-glycosylation method by the use of *N*-(glycosyloxy)acetamides as glycosyl donors and a Lewis acid [$Cu(OTf)_2$ or $SnCl_4$] as a promoter (Scheme 1b).[16] The easily accessible and stable donors as well as mild reaction conditions sparked our interest in exploring other applications of this method. As part of our continuing effects on the synthetic methodologies toward *C*-glycosyl compounds,[17] herein we report the *C*-glycosylation of *C*-nucleophiles with *N*-(glycosyloxy)acetamides (Scheme 1c).

We commenced our study by investigating the *C*-glycosylation of allyltrimethylsilane (**2a**) with perbenzyl *N*-(glucosyloxy)acetamide (**1a**). Initially, following the optimized *O*-glycosylation conditions, the reaction was conducted in CH_2Cl_2 with $Cu(OTf)_2$ as the activator. Unfortunately, the desired allyl *C*-glycoside **3a** was obtained in only 10% yield (Table 1, entry 1). Subsequently, various solvents, including



Scheme 1 Representative bioactive *C*-glycosides and *N*-(glycosyloxy) acetamide-based glycosylations.

[a]*State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China. E-mail: xinshan@bjmu.edu.cn, decai@bjmu.edu.cn*

[b]*Institute of Systems Biomedicine, School of Basic Medical Sciences, Peking University, Beijing 100191, China*

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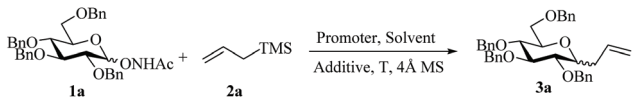
Table 1 Optimization of the reaction conditions[a]



Entry	Promoter (equiv.)	Solvent	T (°C)	Yield[b] (%)
1	$Cu(OTf)_2$ (4.0)	CH_2Cl_2	30	10
2	$Cu(OTf)_2$ (4.0)	CH_3CN	30	0
3	$Cu(OTf)_2$ (4.0)	Ether	30	10
4	$Cu(OTf)_2$ (4.0)	$CHCl_3$	30	35
5	$Cu(OTf)_2$ (4.0)	CH_3NO_2	30	40
6	$Cu(OTf)_2$ (4.0)	$CHCl_3$	50	45
7	$Cu(OTf)_2$ (4.0)	$CHCl_3/CH_3NO_2$ = 1/1	50	75
8	$Cu(OTf)_2$ (4.0)	$CHCl_3/CH_3NO_2$ = 2/1	50	37
9	$Cu(OTf)_2$ (4.0)	$CHCl_3/CH_3NO_2$ = 1/2	50	50
10	$BF_3{\cdot}Et_2O$ (2.0)	$CHCl_3/CH_3NO_2$ = 1/1	rt	78
11	BCl_3 (2.0)	$CHCl_3/CH_3NO_2$ = 1/1	Rt	Trace
12	BBr_3 (2.0)	$CHCl_3/CH_3NO_2$ = 1/1	rt	Trace
13	$HBF_4{\cdot}Et_2O$ (2.0)	$CHCl_3/CH_3NO_2$ = 1/1	rt	72
14	$(Butyl)_2BOTf$ (2.0)	$CHCl_3/CH_3NO_2$ = 1/1	rt	55
15	$ZrCl_4$ (2.0)	$CHCl_3/CH_3NO_2$ = 1/1	rt	Trace
16	$Sn(OTf)_2$ (2.0)	$CHCl_3/CH_3NO_2$ = 1/1	rt	61
17	$SnCl_4$ (2.0)	$CHCl_3/CH_3NO_2$ = 1/1	rt	82
18	$SnBr_4$ (2.0)	$CHCl_3/CH_3NO_2$ = 1/1	rt	93
19	$SnBr_4$ (1.5)	$CHCl_3/CH_3NO_2$ = 1/1	rt	95
20	$SnBr_4$ (1.2)	$CHCl_3/CH_3NO_2$ = 1/1	rt	91
21	$SnBr_4$ (1.0)	$CHCl_3/CH_3NO_2$ = 1/1	rt	87

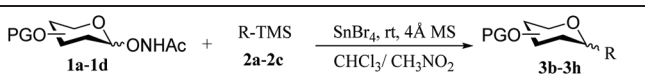
[a] Reaction conditions: **1a** (30.0 mg, 0.05 mmol), **2a** (15.9 μL, 0.1 mmol), 4 Å MS (100 mg) and solvent (1.0 mL). [b] Isolated yield.

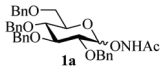
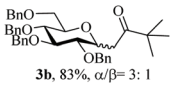
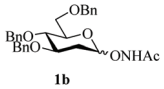
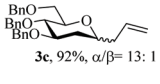
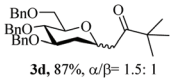
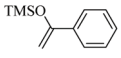
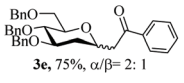
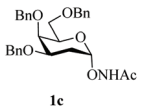
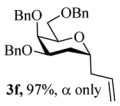
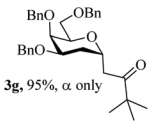
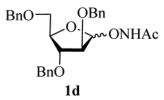
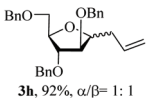
CH_3CN, ether, $CHCl_3$, and CH_3NO_2, were tested and the yield of **3a** seemed to improve on changing the solvent (Table 1, entries 3–5; Table S1†). In $CHCl_3$ and CH_3NO_2 at 30 °C, 35% yield and 40% yield, respectively, were achieved (Table 1, entries 4–5). On increasing the reaction temperature to 50 °C, the yield of the coupled product **3a** improved to 45% in $CHCl_3$ (Table 1, entry 6). When a mixed solvent of $CHCl_3$ and CH_3NO_2 was used, the yield of **3a** increased to 75% (Table 1, entry 7). A ratio of 1 : 1 was found to be the optimal solvent ratio of $CHCl_3$ to CH_3NO_2 in terms of the yield (Table 1, entries 7–9). The additives did not increase the yield of **3a** (Table S2†). Further screening of the Lewis acids revealed that $BF_3{\cdot}Et_2O$, $HBF_4{\cdot}Et_2O$, $SnCl_4$, and $SnBr_4$ can be employed as efficient activators (Table 1, entries 10–18). $SnBr_4$ gave the best yield (Table 1, entry 18, 93% yield). It was found that decreasing the amount of $SnBr_4$ to 1.0 equiv. or 1.2 equiv. leads to reduced yield of the target product (Table 1, entries 20–21). The optimal loading of $SnBr_4$ is 1.5 equiv. (Table 1, entry 19). It is worth noting that the reaction can be completed within 0.5 h. The α/β ratio of product **3a** is about 5/1. Therefore, the optimal conditions were identified to be as follows: $SnBr_4$ (1.5 equiv.) as the activator and $CHCl_3/CH_3NO_2$ (v/v = 1/1) as the solvent in the presence of 4 Å molecular sieves at room temperature for 0.5 h.

With the optimized conditions in hand, we first examined the substrate scope of alkyl *C*-nucleophiles such as allyltrimethylsilane and silyl enol ethers (Table 2). When donor **1a** and (2,2-dimethyl-1-methylenepropoxy)trimethylsilane (**2b**) were treated under the standard conditions, the desired product **3b** was obtained in 83% yield with a moderate α-stereoselectivity (entry 1). The glycosylation of allyltrimethylsilane (**2a**) with 2-deoxy-glucopyranosyl donor **1b** furnished the corresponding *C*-glycoside **3c** in excellent yield and with good stereoselectivity (entry 2). Silyl enol ethers **2b** and **2c** also underwent this reaction to give the products **3d** and **3e** in good yields (entries 3 and 4). Both 2-deoxy-galactopyranosyl donor **1c** and arabinofuranosyl donor **1d** were amenable for this *C*-glycosylation to deliver the alkyl *C*-glycosides in excellent yields (entries 5–7). The exclusive α-stereoselectivity was observed with compound **1c** as the glycosyl donor for the formation of *C*-glycosides (entries 5–6),[18] whereas no stereoselectivity was observed in the case of arabinofuranosyl donor **1d** (entry 7). Unfortunately, the protocol could not be applied to the disarmed donors. All reactions were finished within 30 min at room temperature. The anomeric configuration of all alkyl *C*-glycosides was unambiguously identified by their ^1H and ^{13}C NMR analyses as described in the literature.[19]

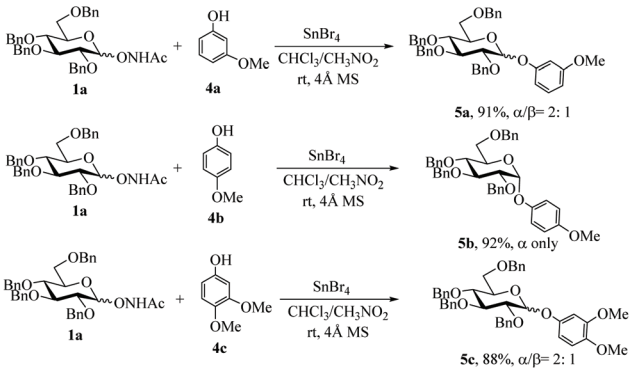
Next, the glycosylation of phenols with donor **1a** was performed to examine whether *C*-glycosides would be produced

Table 2 *C*-Glycosylation of allyltrimethylsilane or silyl enol ethers (**2a–2c**) with *N*-(glycosyloxy)acetamides (**1a–1d**)[a]



Entry	Donor	*C*-Nucleophile	Product (yield, α/β ratio)[b,c]
1			 **3b**, 83%, α/β= 3: 1
2			 **3c**, 92%, α/β= 13: 1
3	**1b**	**2b**	 **3d**, 87%, α/β= 1.5: 1
4	**1b**		 **3e**, 75%, α/β= 2: 1
5		**2a**	 **3f**, 97%, α only
6	**1c**	**2b**	 **3g**, 95%, α only
7		**2a**	 **3h**, 92%, α/β= 1: 1

[a] Conditions: Donor (0.05 mmol), *C*-nucleophile (0.10 mmol), $SnBr_4$ (0.075 mmol), 4 Å MS (100 mg), $CHCl_3$ (0.5 mL) and CH_3NO_2 (0.5 mL), 0 °C to rt. [b] Isolated yield. [c] Ratio determined using ^1H NMR spectra.



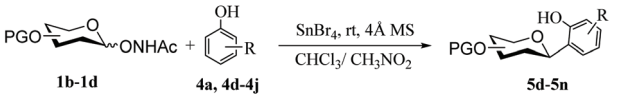
Scheme 2 The coupling reactions of **1a** and phenols **4a–4c**. Reaction conditions: **1a** (0.05 mmol), phenol (0.10 mmol), $SnBr_4$ (0.075 mmol), 4 Å MS (100 mg), $CHCl_3$ (0.5 mL) and CH_3NO_2 (0.5 mL), 0 °C to rt.

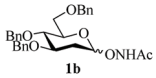
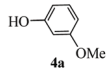
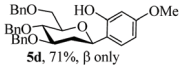
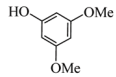
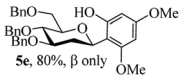
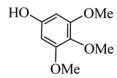
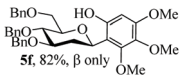
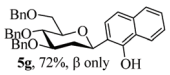
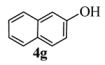
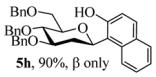
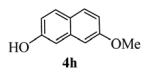
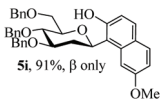
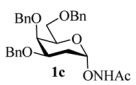
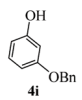
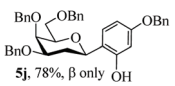
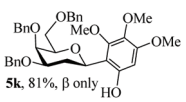
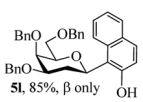
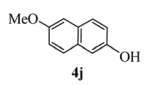
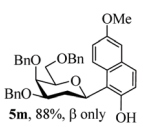
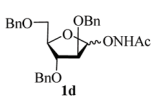
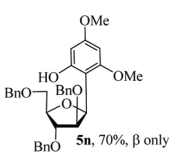
via an O–C rearrangement[20] (Scheme 2). The coupling reactions of donor **1a** with 3-methoxyphenol (**4a**) and 4-methoxyphenol (**4b**) were tried, and only the corresponding *O*-glycosides (**5a** and **5b**) were isolated as the major products under the standard conditions. The glycosylation of more electron-rich 3,4-dimethoxyphenol (**4c**) gave the same results. Interestingly, phenolic glycoside **5b** was isolated as a single α-isomer. The addition of a co-promoter such as $Sc(OTf)_3$,[21] TMSOTf,[22] and $BF_3{\cdot}Et_2O$[23] was unable to facilitate the O–C rearrangement, either at the beginning of the reaction or after the generation of *O*-glycosides. We speculate that the fully oxygenated pyranosyl donors might be unsuitable for the construction of aryl *C*-glycosides.

Subsequently, we turn our attention to 2-deoxy-*N*-(glycosyloxy)acetamide donors (Table 3). Gratifyingly, the reaction of 2-deoxy-*N*-(glucosyloxy)acetamide **1b** and **4a** provided the corresponding *C*-glycoside **5d** in 71% yield and with full β-stereoselectivity (entry 1). Phenols including 3,5-dimethoxyphenol (**4d**), 3,4,5-trimethoxyphenol (**4e**), 1-naphthol (**4f**), 2-naphthol (**4g**), and 7-methoxy-2-naphthol (**4h**) were well tolerated, affording the desired *C*-glycosides **5e–5i** in good to excellent yields (entries 2–6). When 2-deoxy-*N*-(galactosyloxy) acetamide **1c** was used as the glycosyl donor, the reaction also proceeded well, providing the corresponding aryl *C*-glycosides **5j–5m** in high yields and with excellent β-selectivity (entries 7–10). Surprisingly, the reaction of fully oxygenated arabinofuranosyl donor **1d** with phenol **4d** smoothly afforded **5n** in 70% yield in the form of a single β-configuration (entry 11). Complete β-selectivity was observed regardless of the nature of the phenols and the donors employed, which might be attributed to the formation of thermodynamically more stable β-*C*-glycosides at room temperature *via* the O–C rearrangement.[24]

In summary, we have developed a facile and mild *C*-glycosylation of *C*-nucleophiles with *N*-(glycosyloxy)acetamides as donors. This reaction proceeds by the use of $SnBr_4$ as the activator in the mixed solvent of $CHCl_3$–CH_3NO_2 at room temperature for 0.5 h. A variety of alkyl *C*-glycosides and aryl *C*-glycosides were obtained in good to excellent yields. In particular, the reaction of phenols with 2-deoxy-*N*-(glycosyloxy) acetamides gave an exclusive β-stereoselectivity *via* an O–C rearrangement. The disclosed method provides an alternative approach for the synthesis of *C*-glycosides with biological significance.

Table 3 β-Stereoselective *C*-glycosylation of phenols with *N*-(glycosyloxy)acetamides[a]



Entry	Donor	Phenol	Product (yield, α/β ratio)[b]
1			
2	**1b**		
3	**1b**		
4	**1b**		
5	**1b**		
6	**1b**		
7			
8	**1c**	**4e**	
9	**1c**	**4g**	
10	**1c**		
11		**4d**	

[a] Conditions: Donor (0.05 mmol), phenol (0.10 mmol), $SnBr_4$ (0.075 mmol), 4 Å MS (100 mg), $CHCl_3$ (0.5 mL) and CH_3NO_2 (0.5 mL), 0 °C to rt. [b] Isolated yield.

Conflicts of interest

There are no conflicts to declare.

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