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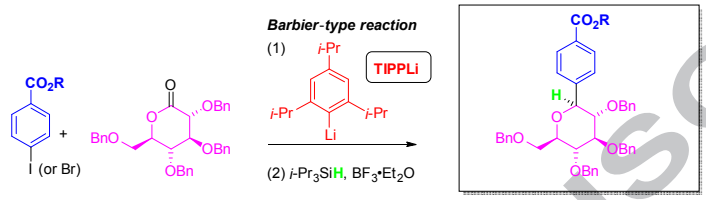

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Functionalized aryl-β-*C*-glycoside synthesis by Barbier-type reaction using 2,4,6-triisopropylphenyllithium

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ABSTRACT

We developed an efficient synthetic route for functionalized aryl-β-*C*-glycosides, which are difficult to prepare by conventional methods. An aryl halide having an ester, cyano, or carbonyl group was treated with 2,4,6-triisopropylphenyllithium in the presence of a δ-lactone (Barbier-type reaction conditions) to afford a coupling product. The following deoxygenation gave the desired aryl-β-*C*-glycoside in good yield.

Aryl-*C*-glycosides are an important group of naturally occurring products that exhibit various biological activities.[1-3] Moreover, some synthetic aryl-*C*-glycosides have been exploited in recent years as therapeutic agents for type 2 diabetes.[4]

For these reasons, aryl-*C*-glycosides have attracted much attention and consequently, many preparation methods have been developed.[5] The main synthetic approaches reported in the literature thus far are Lewis acid promoted electrophilic reactions of glycosyl donors,[6] Fries-type reactions of phenols (*O*–*C* migration),[7] nucleophilic additions of organometallic reagents to protected aldonolactones followed by reduction of the yielded lactols,[8] and transition metal-mediated *C*-glycosylations.[9]

Although these preparation methods are numerous, new and complementary methodologies with higher efficiency are still desired. As for the *C*-glycosides having electron-withdrawing substituents on the aromatic ring, direct preparation methods are limited; an electrophilic reaction of glycosyl donors with electron-deficient aromatic rings hardly proceeds because the nucleophilicity of these rings decreases considerably. A catalytic approach was thus adopted in an attempt to address this issue.[9a-d]

We turn next to a nucleophilic addition/reduction sequence using aldonolactones as glycosyl donors, which have been developed by Kishi and others.[8] This methodology has been popularly utilized for preparations of aryl *C*-glycosides because of its generality, high anomeric stereoselectivity, and scalability based on the simple procedure.[10] However, ester or cyano groups on the aromatic ring react with highly reactive lithiating and magnesiating reagents or generated arylmetals. To address this limitation, an indirect approach has been used by employing the corresponding protected alcohols or acetals instead of ester groups on the aromatic ring. This is followed by the required deprotection–oxidation steps.[11]

Currently, a wide variety of chemoselective metalating reagents for halogen–metal exchange reactions with electrophilic functional groups have been studied and developed.[12] We disclosed that a functionalized aryllithium generated by a halogen–lithium exchange reaction using mesityllithium (MesLi) successfully reacted with a protected δ-gluconolactone.[4d] Another example is a *C*-nucleoside synthesis using *i*-PrMgCl·LiCl as described by Pankiewicz, which is a Grignard reaction of 3-iodobenzonitrile with perbenzylated ribonolactone followed by removal of the anomeric hydroxy group to afford 3-cyanophenyl-*C*-riboside.[13] Although these limited examples were reported, there is no comprehensive study to date. Herein, we report a robust preparation method for functionalized aryl-β-*C*-glycosides using 2,4,6-triisopropylphenyllithium (TIPPLi), which is a bulky and efficient chemoselective lithiating agent.

Firstly, halogen–metal exchange reactions were examined between *tert*-butyl 4-iodobenzoate (**1a**) and various metalating reagents (Table 1, entries 1–5). The reactions were quenched with CD_3OD to afford the corresponding deuterated product **3a** in good yields when using *n*-Bu_3MgLi,[14] *i*-PrMgCl·LiCl,[15] and MesLi[16] (entries 3–5), in contrast to *n*-BuLi and *t*-BuLi (entries 1 and 2). These resulting arylmetals also reacted with perbenzylated glucono δ-lactone **2** to give lactol **3b** (entries 1–5).

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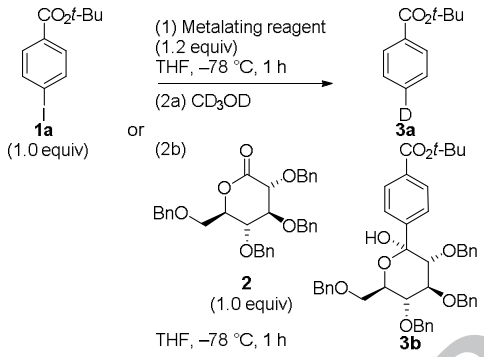
These coupling reactions afforded only *C*-β adduct (**3b**); however, it remains unclear at present that the *C*-β stereoselectivity was derived from the result of the stereoselective addition or from the result of the isomerization to the thermodynamically stable *C*-β isomer under the acidic quenching conditions. We next performed this coupling with Barbier-type reaction conditions leading to the improved yield of **3b** (entries 4 and 5). Based on our observation of a small amount of adduct between MesLi and lactone **2**, TIPPLi[16b] was examined as a hindered halogen–lithium exchange reagent that can be readily prepared from commercially available 2,4,6-triisopropylphenylbromide (**4**, TIPPBr) and *n*-BuLi at –78 °C. It was revealed that a Barbier-type reaction using TIPPLi afforded adduct **3b** in an excellent yield of 90% (entry 6). The other phenyllithiums such as 2,4,6-tri-*tert*-butylphenyllithium, 2,3,4,5,6-pentamethylphenyllithium, and 4-methoxy-2,6-dimethylphenyllithium were less effective than TIPPLi (data not shown).

Table 1
Halogen–metal exchange reactions and coupling reactions of resulting functionalized arylmetals

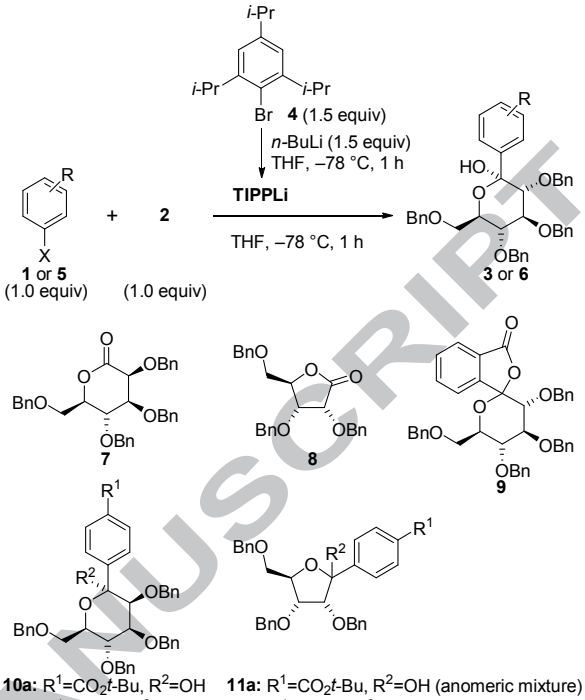


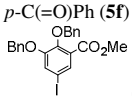
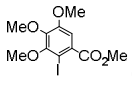
Entry	Reagent	**3a** (Yield, %)[a]	**3b** (Yield, %)[a,b]
1	*n*-BuLi	26	28 / N.T.[c]
2	*t*-BuLi	16	12 / N.T.
3	*n*-Bu_3MgLi	92	49[d] / N.T.
4	*i*-PrMgCl·LiCl[e]	92	55 / 71
5	MesLi	76	68 / 76
6	TIPPLi	70	62 / 90

[a] Isolated yield.
[b] Grignard-type addition / Barbier-type addition.
[c] Not tested.
[d] The reaction was performed at –78 °C, then allowed to warm to 0 °C.
[e] Performed at –60 °C.

The scope of this TIPPLi promoted Barbier-type reaction was investigated (Table 2). The results indicated that the reactions between perbenzylated lactone **2** and aryl iodides having an ester, cyano, or carbonyl group proceeded smoothly to afford lactols (entries 1, 3, 5, and 7–9). It should also be noted that the reaction proceeded successfully not only with bulky *tert*-butyl 4-iodobenzoate (**1a**) but also with methyl 4-iodobenzoate (**5a**) to give lactols (**3b** and **6a**) in excellent yield without any self-condensation (entries 1 and 3). Methyl 2-iodobenzoate (**5e**) underwent the reaction smoothly to produce spiroketal **9** in 69% yield as an anomeric mixture (*C*-α:β = 7:1, entry 7), whereas methyl 2-iodo-3,4,5-trimethoxybenzoate (**5h**) did not undergo this reaction (entry 10). The coupling reactions between different aldonolactones (perbenzylated mannolacton **7** or ribonolactone **8**) and *tert*-butyl 4-iodobenzoate (**1a**) were also studied and provided the corresponding lactols in 90% yield (**10a**, *C*-β only, entry 11) or in 63% yield (**11a**, an anomeric mixture, *C*-α:β = 1:2.7, entry 12). In addition, aryl bromides were examined to give a good to moderate yield of the products (entries 2, 4, and 6). In

Table 2
Barbier-type reactions with perbenzylated lactone **2**



Entry	R	X	Product	Yield (%)[a]
1	*p*-CO_2t-Bu (**1a**)	I	**3b**	93
2	*p*-CO_2t-Bu (**1b**)	Br	**3b**	60
3	*p*-CO_2Me (**5a**)	I	**6a**	81
4	*p*-CO_2Me (**5b**)	Br	**6a**	19
5	*p*-CN (**5c**)	I	**6b**	80[b]
6	*p*-CN (**5d**)	Br	**6b**	75[b]
7	*o*-CO_2Me (**5e**)	I	**9**	69[c]
8	*p*-C(=O)Ph (**5f**)	I	**6c**	52
9	 (**5g**)		**6d**	79
10	 (**5h**)		**6e**	0
11	*p*-CO_2t-Bu (**1a**)	I	**10a**	90[d]
12	*p*-CO_2t-Bu (**1a**)	I	**11a**	63[e]

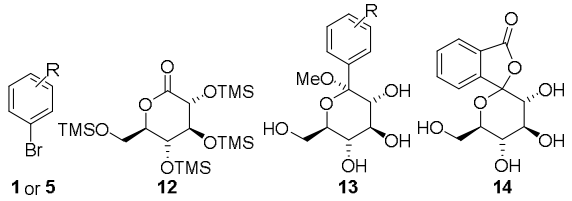
[a] Isolated yield.
[b] 1.2 equiv of TIPPLi was used.
[c] An anomeric mixture of spiroketal **9** (*C*-α:β = 7:1).
[d] Tetra-*O*-benzyl-$_D$-manno-1,5-lactone (**7**) was used instead of **2**. The product was *C*-β only.
[e] Tri-*O*-benzyl-$_D$-ribo-1,4-lactone (**8**) was used and an anomeric mixture (*C*-α:β = 1:2.7) was obtained.

these cases, tetra-*O*-benzyl-$_D$-manno-1,5-lactone (**7**) was also isolated in ca. 10% yield. It is presumed that a deprotonation reaction at the α-position of lactone **2** occurred.

In order to avoid this side reaction, coupling reactions involving bulkier trimethylsilyl (TMS) protected glucono δ-lactone **12**[4a] were investigated (Table 3). The coupling reaction mixture was quenched with methanol/methanesulfonic acid to serve methyl glycoside **13** in good yields (entry 1–6) with removal of the TMS protecting groups. Notably, the coupling reaction of methyl 4-bromobenzoate (**5b**) and the persilylated lactone **12** proceeded smoothly (entry 3), contrary to the aforementioned reaction with perbenzylated lactone **2** (entry 4, Table 2). Moreover, the reaction with methyl 2-bromobenzoate (**5j**) afforded spiroketal **14** in 91% yield as an anomeric mixture (*C*-α:β = 9:1, entry 4). This *C*-

α stereoselectivity was observed similarly in the case of the coupling reaction of methyl 2-iodobenzoate (**5e**) and perbenzylated lactone **2** (*C*-α:β = 7:1, entry 7, Table 2), whereas the *C*-β products were obtained when using *para*- or *meta*- substituted aryl halides.

Table 3
Barbier-type reactions with persilylated δ-lactone **12**[a]



1 or **5** **12** **13** **14**

Entry	R	Product	Yield (%)[b]
1	*p*-CO_2*t*-Bu (**1b**)	**13a**	72
2	*p*-CO_2*i*-Pr (**5i**)	**13b**	76
3	*p*-CO_2Me (**5b**)	**13c**	81
4	*o*-CO_2Me (**5j**)	**14**	91[c]
5	*p*-Cl, *m*-CO_2*i*-Pr (**5k**)	**13d**	76
6	*p*-Me, *m*-CO_2*i*-Pr (**5l**)	**13e**	74[d]

[a] The coupling reaction mixture was quenched with MeOH/$MeSO_3H$ at rt for 64 h.
[b] Isolated yield.
[c] Treated with 2M HCl–MeOH for 30 min to afford an anomeric mixture of spiroketal **14** (*C*-α:β = 9:1).
[d] 2.0 equiv of TIPPLi was used.

From the observations in the cases of **5e** (entry 7, Table 2) and **5j** (entry 4, Table 3), it appears that an α-attack of aryllithium compounds to the δ-lactone preferentially occurs under kinetic control conditions. On the basis of the Felkin torsional strain theory[17a-c] and the computational studies of the nucleophilic additions to cyclohexanone and related systems,[17d-h] it can be presumed that there is less torsional strain in the transition structure of the axial attack than that of the equatorial attack (Figure 1). In addition, there may be the influence of the electrostatic repulsion between the negative nucleophile and lone pair of the ring oxygen, favoring nucleophilic attack at the α face. In other cases, however, it is difficult to definitively explain the stereoselectivity at the coupling stage.[17i,j]

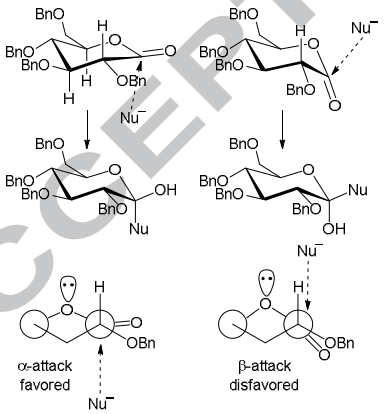
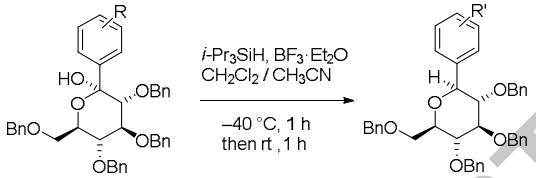


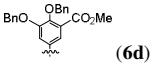
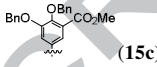
Figure 1. Stereoselectivity in nucleophilic addition to δ-lactone.

Next, we carried out reduction of lactols.[8,18] As shown in Table 4, reduction of lactol **3b** in the presence of *i*-Pr_3SiH[8c] and $BF_3{\cdot}Et_2O$ was achieved to afford aryl-β-*C*-glycosides **15a** (β only, entry 1), whereas low selectivity was observed when treating with Et_3SiH (α:β = 1:2.5, data not shown). The other lactols **6b**, **6d**, **10a**, and **11a** afforded the corresponding aryl-β-*C*-glycosides in moderate to good isolated yields under the same conditions (entries 2–5). The reduction of spiroketal **9** did not afford the

Table 4
Reduction of lactols



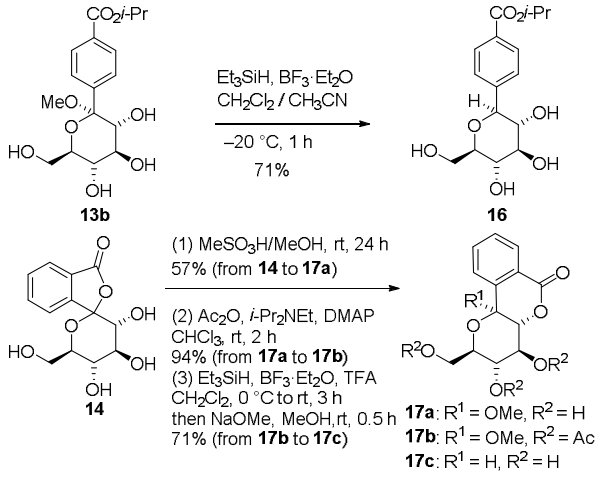
3b, 6b, 6d and 10a, 11a **15 and 10b, 11b**

Entry	R	R' (Product)	Yield (%)[a]
1	*p*-CO_2*t*-Bu (**3b**)	*p*-CO_2H (**15a**)	81
2	*p*-CN (**6b**)	*p*-CN (**15b**)	63
3	 (**6d**)	 (**15c**)	83
4	*p*-CO_2*t*-Bu (**10a**)	**10b**	90
5	*p*-CO_2*t*-Bu (**11a**)	**11b**	67

[a] Isolated yield.

desired deoxgenated product as it yielded only an isomerized one (see Supplementary Data).

Subsequently, methyl glucoside **13b** was deoxygenated with Et_3SiH and $BF_3{\cdot}Et_2O$ in a stereoselective manner (Scheme 1).[19] Reduction of spiroketal **14** was a little troublesome (Scheme 1). Treatment of **14** with Et_3SiH and $BF_3{\cdot}Et_2O$ did not produce the desired deoxygenated product but yielded an isomerized product (*C*-β) at the anomeric position instead. This was also the case for the perbenzylated spiroketal **9**. Therefore, **14** was isomerized to the isochromanone derivative **17a** by treating with methanol/methanesulfonic acid. After acetylation of **17a**, the resulting **17b** was reduced with Et_3SiH under the acidic conditions, followed by hydrolysis of the acetyl groups to afford a bergenin-type β-*C*-glucoside **17c** in good yield. It is noted that protection of the hydroxy groups of **17a** was necessary to avoid the formation of 1,5-anhydrate, and the usage of the acid combination ($BF_3{\cdot}Et_2O$/TFA) during silane reduction enhanced the reaction rate markedly.[20]



Scheme 1. Reduction of **13b** and **14.**

In conclusion, we have developed a practical and efficient preparation method of functionalized aryl-β-*C*-glycosides. A chemoselective halogen–lithium exchange reaction of functionalized aryl halides was accomplished through the use of the TIPPLi, which has bulky isopropyl groups that rarely react with

substrate sugar lactones. In addition, our study has given a new bergenin-type β-*C*-glucoside synthesis.

Supplementary data

Supplementary data (experimental procedures and spectral data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/XXXX.

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