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Heck-type cross-coupling between halo-*exo*-glycals and *endo*-glycals: a practical way to achieve C-glycosidic disaccharides

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ABSTRACT

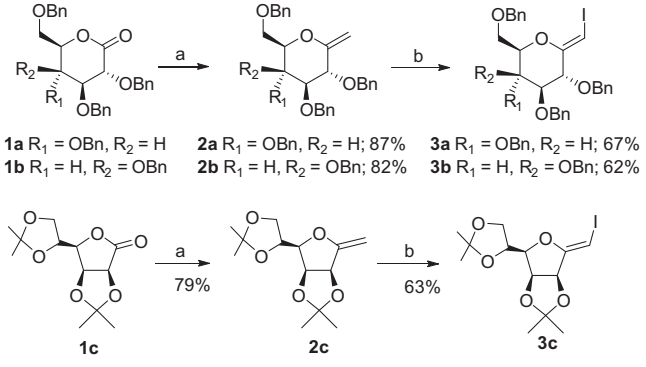
An effective Heck-type cross-coupling reaction between halo-*exo*-glycals and *endo*-glycals to achieve C-glycosidic disaccharides has been developed. Using $Pd(OAc)_2$ as the catalyst, dppp as ligand and K_2CO_3 as base, the reactions gave C-glycosidic products in good to excellent yields with exclusive stereochemistry.

Despite attracting growing interest in biological and medicinal research, carbohydrates still have several limitations blocking their application as drugs, particularly among which is the liability of the glycosidic bond.[1] In this context, C-glycosides, congeners comparatively stable against hydrolysis, acids and especially enzymatic degradation, seem to serve as possible surrogates.[2] Prevalent in abundant natural products, C-glycosides have been found to display diverse biological properties, suggesting their potential to act as enzyme inhibitors and antibacterial or antitumor reagents.[3] Consequently, they are currently attracting expansive synthetic interests. In recent years, a variety of synthetic methods such as the transition metal mediated coupling of glycals with aryl halides or arylboronic acids have been developed for the preparation of C-glycosides.[4] However, there have been only limited reports concerning the synthetic approaches to access C-glycosidic bonds between saccharide units.[5] Therefore, a practical approach for the assembly of C-glycosidic disaccharides would be highly desirable.

Exo-Glycals are interesting compounds from a biological standpoint and have been used as glycosidase inhibitors, suggesting their value in drug discovery and research.[6] On the other hand, *exo*-glycals have also been well recognized as important synthetic intermediates due to their capability for further elaboration resulting from the enol ether double bond. Previous work has demonstrated that halo-*exo*-glycals (for example, **3a** and **3b**) can be used for the preparation of aryl substituted *exo*-glycals through various ways like Suzuki reaction and Sonogashira reaction.[7] Inspired by these results, taking into consideration pertinent examples of transition metal mediated coupling of glycals with aryl halides , we deemed it worth a trial to apply halo-*exo*-glycals and *endo*-glycals as key building blocks to achieve C-glycosidic disaccharides via Heck reaction as reported herein.

The precursors for this study were prepared from methylenation of sugar derived lactones **1a-c** (by Petasis reagent), which upon stereoselective iodination with iodonium dicollidinium triflate (IDCT) afforded desired halo-*exo*-glycals **3a-c** (Scheme 1).[7]

We first explored the reaction of gluctopyranose derived alkenyl iodide (**3a**) with 3,4,6-tri-*O*-benzyl-D-glucal (**4a**) as model



Scheme 1. Synthesis of halo-*exo*-glycals **3a–c**. Reagents and conditions: (a) Petasis reagent, toluene, 75 °C; (b) IDCT, DCM, rt.

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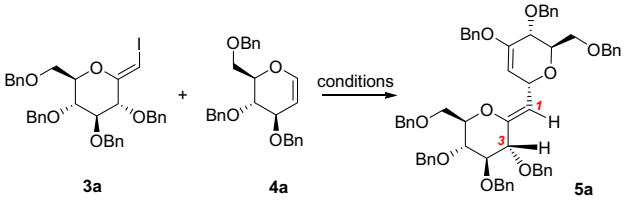
Table 1
Screening of conditions of the Heck type cross coupling of **3a** and **4a**[a]



3a **4a** **5a**

Entry	Catalyst (10 mol %)	Base	Ligand	Solvent	*T* (°C)	Time (h)	Yield (%)
1	$Pd(OAc)_2$	K_2CO_3	—	DMF	rt	24	23
2	$Pd(OAc)_2$	K_2CO_3	—	DCM	rt	24	—
3	$Pd(OAc)_2$	TEA	—	DMF	rt	24	Trace
4	$Pd(OAc)_2$	K_2CO_3	—	DMF	80	24	50
5	$PdCl_2(PPh_3)_2$[b]	K_2CO_3	—	DMF	80	18	44
6	$Pd(OAc)_2$	K_2CO_3	PPh_3	DMF	80	4	66
7	$Pd(OAc)_2$	K_2CO_3	dppp	DMF	80	3	90
8	$Pd(OAc)_2$	K_2CO_3	$P(Tol)_3$	DMF	80	4	71

[a] In all the entries, 1 equiv of **3a** and 3 equiv of **4a** were used in the presence of 1 equiv of TBACl.
[b] 20 mol % $PdCl_2(PPh_3)_2$ was used.

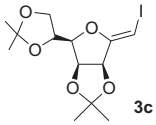
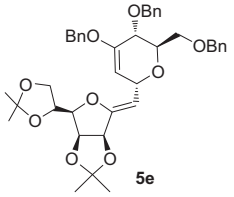
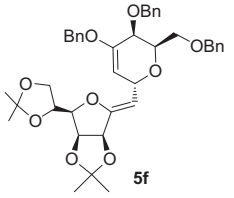
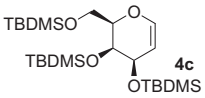
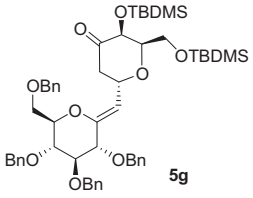
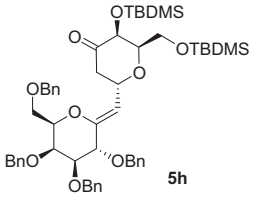
experiment (Table 1). Treatment of **3a** with **4a** at room temperature in DMF catalyzed by 10 mol% $Pd(OAc)_2$ with K_2CO_3 as base in the presence of tetra-butyl ammonium chloride (TBACl) as phase transfer catalyst for 24 h afforded the corresponding C-glycoside **5a** as a single diastereomer in 23% yield (entry 1). While the solvent was changed to dichloromethane (DCM), no desired product was detected within 24 h (entry 2). A similar result was obtained when triethylamine (TEA) was used as the base instead, giving only trace coupling product **5a** in DMF detected by TLC (entry 3). On the other hand, when the reaction temperature was raised to 80 °C, with K_2CO_3 and DMF as the optimal base and solvent, respectively, the yield of **5a** was increased to 50% (entry 4). Based on this condition, when 20 mol% $PdCl_2(PPh_3)_2$ was employed as a surrogate for $Pd(OAc)_2$, the coupling reaction could also proceed fairly well, though in a slightly lower yield (entry 5). Further investigation demonstrated that the ligand effect was crucial for this coupling (entries 6-8). Among the screened ligands, 1,3-bis(diphenylphosphino)propane (dppp) gave an outstanding performance, which induced a 90% yield of product within a 3 h reaction time (entry 7). Thus, the best coupling condition for the preparation of C-glycosidic disaccharides **5a** was elaborated as described in entry 7. Notably, the solvent does not require thorough desiccation, nor does the reaction need inert gas protection.

With the optimal coupling condition in hand, the scope of the reaction was investigated by varying both the halo-*exo*-glycals and the *endo*-glycals (Table 2).[8] In each case, the desired cross-coupling product was obtained in a good yield as a single anomer. The anomeric configuration of the coupling products was determined

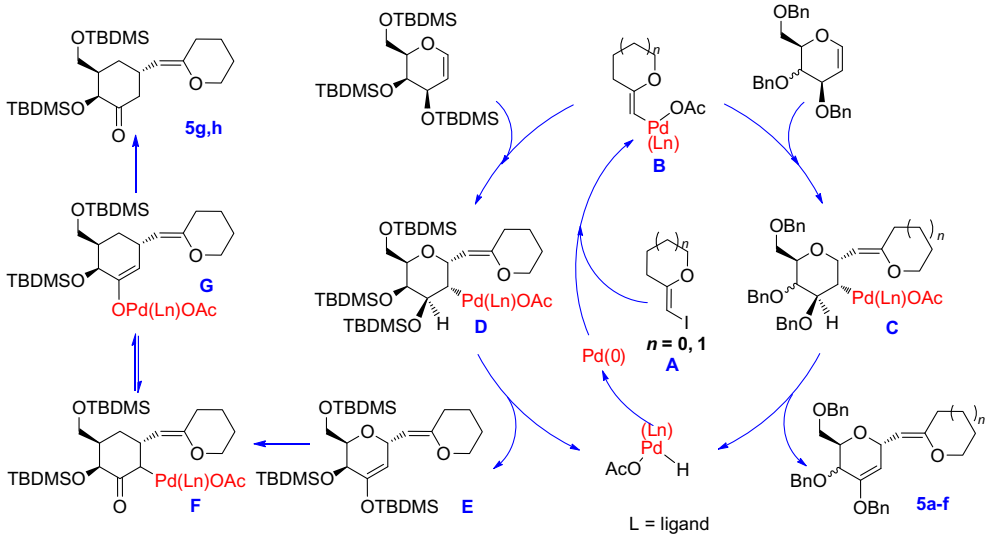
Table 2
Heck type cross-coupling of halo-*exo*-glycal and *endo*-glycal[a]

Entry	Halo-*exo*-glycal	Glycal	Product	Yield (%)
1	**3a**	**4a**	**5a**	90
2	**3a**	**4b**	**5b**	92
3	**3b**	**4a**	**5c**	92
4	**3b**	**4b**	**5d**	87

Table 2 (*continued*)

Entry	Halo-*exo*-glycal	Glycal	Product	Yield (%)
5	 **3c**	**4a**	 **5e**	79
6	**3c**	**4b**	 **5f**	72
7	**3a**	 **4c**	 **5g**	63
8	**3b**	**4c**	 **5h**	53

[a] General conditions: 1 equiv of halo-*exo*-glycal, 3 equiv of *endo*-glycal, 1 equiv of TBACl, 2.5 equiv of K_2CO_3, 0.1 equiv of $Pd(OAc)_2$, 0.1 equiv of dppp, 80 °C in DMF.



Scheme 2. Proposed mechanism of the coupling reaction.

as α by analyzing the ^1H and ^{13}C NMR spectra, which was in agreement with mechanistic considerations and literature descriptions of similar compounds.[9] NOEs between the 1-H (vinylic protons) and 3-H protons (as indicated in the structure of **5a**) suggested a Z configuration of the *exo*-cyclic double bond.[7]

The glucto- and galactopyranose derived alkenyl iodides **3a** and **3b** reacted with *endo*-glycals **4a** or **4b** efficiently and afforded the products **5a-d** in excellent yields (87%–92%, entries 1–4). A slight decrease in yield was observed when mannofuranosyl type halo-*exo*-glycal **3c** was employed as the halide partner (entries 5 and 6). Interestingly, when *tert*-butyl(dimethyl)silyls (TBDMS) protected *endo*-galactal **4c** was employed to be coupled with halo-*exo*-glycals **3a** or **3b**, further isomerized ketone product was provided instead, with comparatively a lower yield (entries 7 and 8).

Although the details are still in obscurity, the possible reaction mechanism was proposed as described in Scheme 2. The mechanism

involves the oxidative addition of the halide (A to B), insertion of the olefin (B to C and B to D), and delivery of the product by a β-hydride elimination process (C to **5a**–**f** and D to E). A base then regenerated the palladium (0) catalyst. When the benzyl protected glycals (**4a** and **4b**) served as the olefin parts, the reactions stopped after β-hydride elimination to afford compounds **5a**–**f**. While for the TBDMS protected product E, a further oxidative addition occurred (E to F) due to the liability of the silyl group on enol ether under this reaction condition[4g], which ultimately resulted in the ketone products **5g** and **5h** through intermediate G.

In summary, an efficient Heck-type cross coupling between halo-*exo*-glycals and *endo*-glycals was developed. A set of C-glycosidic disaccharides were obtained in good to excellent yields with complete stereo control both on the sugar anomeric center and the *exo*-cyclic double bond. Further investigations to reveal the power of this methodology as a synthetic tool for the construction of natural products and bioactive compounds are on the way and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.118.

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8. Typical experimental procedure for Heck type cross-couplings between halo-*exo*-glycals and *endo*-glycals: to a round bottom bottle was added successively 1 equiv of halo-*exo*-glycal, 3 equiv of *endo*-glycal, 1 equiv of TBACl, 2.5 equiv of K_2CO_3, 0.1 equiv of $Pd(OAc)_2$, 0.1 equiv of dppp and DMF (no inert gas protection was needed). The reaction was carried out at 80 °C for 3 h. The reaction mixture was then diluted with water, extracted with ether, dried over anhydrous Na_2SO_4, and then concentrated. The crude material was purified by flash column chromatography on silica gel eluted with petroleum ether/EtOAc to afford **5a**–**h**.
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