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Conference paper

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Stereoselective *C*-glycosylation of furanosyl halides with arylzinc reagents[1]

Abstract: Were are reporting a highly diastereoselective, transition-metal-free approach of *C*-aryl glycosides in the pyranoside and furanoside series by the direct coupling of glycosyl halides with diarylzinc reagents in a toluene/di-*n*-butyl ether solvent mixture.

Keywords: C–C bond formation; *C*-glycosylation; OMCOS-17; organometallic chemistry; solvent effects; zinc.

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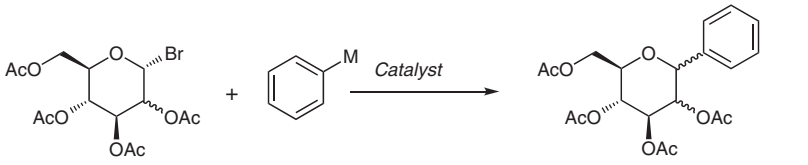
Introduction

C-Glycosides are attractive skeletons for the medicinal chemist because they are more resistant to enzymatic hydrolysis than *O*-glycosides, and therefore are considered potential drug candidates [1]. Especially important is the new class of SGLT-2 inhibitors, used for the treatment of type 2 diabetes, which includes, *i.a.*, Canagliflozin, Dapagliflozin, Ipragloflozin, Empagliflozin [2]. To complement the classical synthesis of *C*-glycosides from sugar lactones, the direct and highly diastereoselective arylation of furanosyl and pyranosyl halides is highly desirable and efforts in this direction have been recently reported [3]. For example, Gagné and Cossy have developed a direct *C*-glycosylation in presence of transition-metal catalysts.

The elegant solution reported by Gagné describes a Ni-catalyzed coupling of organozinc reagents with glycosyl bromides (Scheme 1). The coupling product phenyl tetreaacetylglucosyl **2** is obtained with good stereoselectivity (α/β ratio of 1:12). For the mannoside derivative, the α isomer is obtained as major product (α/β ratio of 20:1). The reaction was shown to proceed via a radical pathway, where "catalyst control" dictates the α/β ratio at the anomeric center. More recently, Cossy has demonstrated efficient *C*-glycosylation with $Co(aca)_3$/tmeda in presence of Grignard reagents. High diastereoselectivity for the α isomer is obtained in presence of the tetraacetylmannosyl bromide substrates. Nevertheless starting from tetraacetyl glycosyl bromide, an average selectivity of 3/1 is obtained in favor of the α isomer. The Cossy methodology is a good

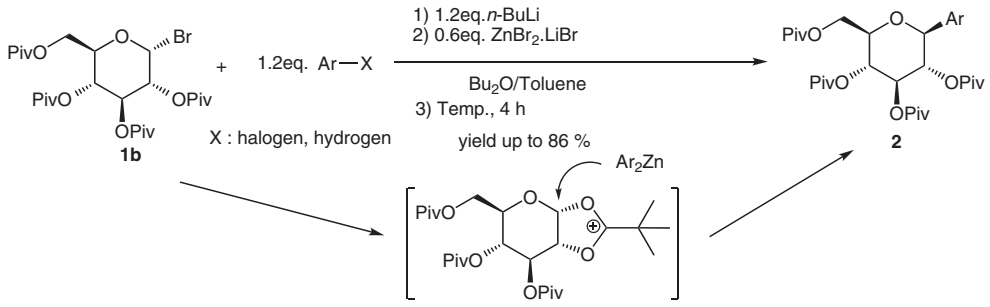


1 **2**

Gagné: M = ZnI; Cat. = $Ni(cod)_2$/tBu-Terpyr 10 mol%
Cossy: M = MgBr, Cat. = $Co(acac)_3$/tmeda 5 mol%

	Glucose sustrate	*Mannose substrate*
	α/β 1/12	*α/β 20/1*
	α/β 3/1	*α/β 9/1*

Scheme 1 Transition-metal catalyst *C*-glycosylation.



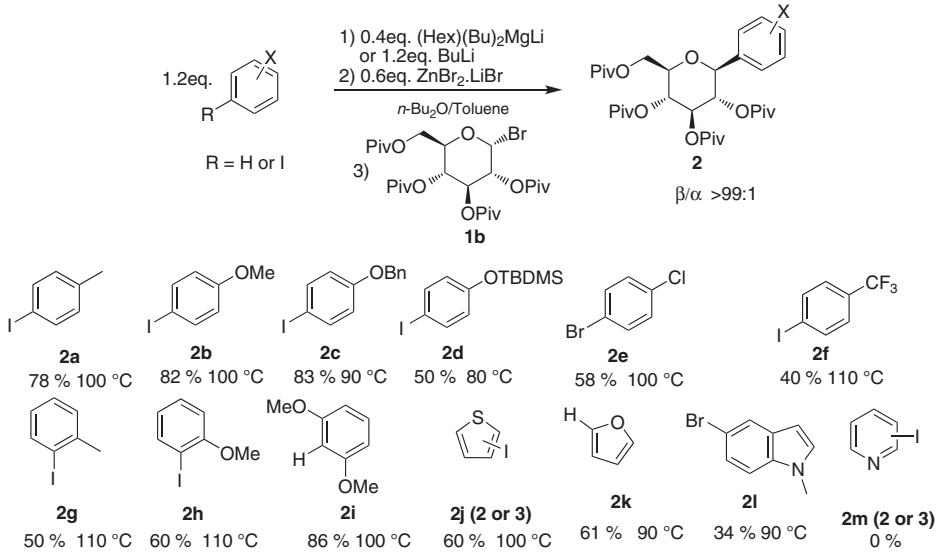
Scheme 2 Diastereoselective arylation of glucosyl bromides.

complementar to the Gagné work in the case of the glucose derivative. While these methods give excellent selectivities, a transition metal free method was pursued in our laboratories for large scale production purposes.

We herein report the development of a transition-metal-free *C*-glycosylation. Our method employs diarylzinc reagents and glycosyl bromides in a toluene/di-*n*-butyl ether solvent mixture, which provide *C*-glycosides with excellent stereoselectivity [4]. The selectivity is explained by anchimeric assistance of the neighboring pivaloyl group (Scheme 2).

Coupling reactions of arylzinc reagents with pyranosyl bromides

We have developed a simple protocol for the coupling of glycosyl bromides with aryzinc species. Upon lithiation of the arene or aryl halide in toluene and transmetalation with $ZnBr_2$.LiBr, the pivaloyl-protected bromo sugar **1** is added to the reaction mixture. Metalation can also be achieved with a magnesate species or n-butyllithium, which then smoothly transmetalates to the arylzinc species. The judicious choice of solvents is critical, as many ethereal co-solvents (especially THF) proved incompatible with these coupling conditions. Upon heating, the desired β-*C*-glycoside product is produced as a single diastereoisomer in good yield (Scheme 3). With *para*-substituted aryl derivatives bearing electron-donating substituents (**2a–2d**), fair to good yields are



Scheme 3 Scope of the arylation of glucosyl bromide (with isolated yield and coupling temp.).

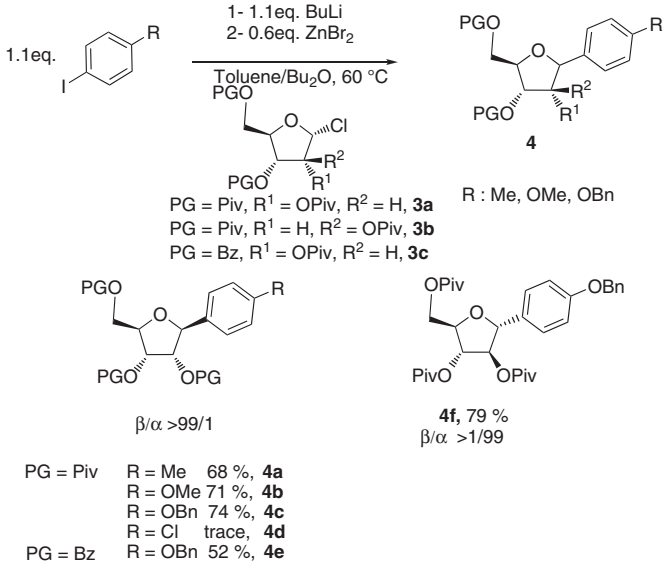
obtained. Yields are affected negatively by electron-withdrawing groups (**2e**, **2f**) even at elevated temperatures (>100 °C). *Ortho*-substitution is well tolerated and the formation of coupled products (**2g–2i**) proceeds in fair to good yields. Heteroaryl species such as thienyl- (**2j**) and furylzinc (**2k**) are also successfully coupled. Interestingly, pyridylzinc species do not couple under our conditions.

Coupling reactions of arylzinc reagents with furanosyl chlorides

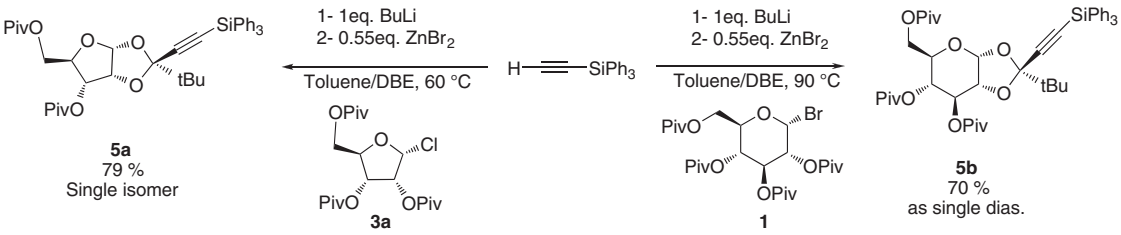
In order to extend the methodology to other important carbohydrate derivatives, we have applied our methodology to the formation of *C*-furanosides. Direct *C*-arylation methodologies of *C*-furanosides are better established than those leading to *C*-pyranosides. Various organometallic species such as Grignard reagents [5], arylzinc species [6], aryl aluminates [7], silyl enol ethers [8] have all proven to be somewhat effective, and intramolecular rearrangement of *O*- to *C*-glycosides [9] has also been reported. In the case of the arylzinc species, while diastereoselectivity is consistently good (usually >20:1), the yields are often poor [**3a, 6**], primarily due to the competitive hydrolysis of the furanoside halides [**3a**]. Very recently, Cossy's cobalt catalyzed system was demonstrated to be highly effective toward *C*-glycosylation of furanoside halides providing products in good yields and distereoselectivities >1/9 [10].

Armed with our experience in the pyranoside series, we have extended the methodology to aryl furanosides. All attempts at preparing furanoside bromide derivatives failed due to the modest stability of the halogenated products. To our delight, the chloro derivatives **3** proved excellent partners in the coupling reaction. Our *C*-glycosylation methodology in the toluene/di-*n*-butyl ether solvent mixture proved quite general. Furanosyl chlorides exhibit higher reactivity than the pyranoside halides, and the reaction proceeded best at lower temperature, typically at 60 °C, yielding the desired *C*-furanosides in fair to good yields (Scheme 4).

In all cases, the desired *C*-furanoside was detected as a single diastereoisomer, with the aryl group delivered *anti* to the neighboring ester group. The chloro derivative **3a** afforded the β isomer in good yields, the best yields observed with electron-rich aryl groups (**4a–c**). The chloroaryl derivative **4d** was detected only in traces by LC-MS. In this case, the degradation of furanosyl chloride **3a** is apparently faster than the coupling reaction. Replacement of pivalate protecting groups with benzoates (**3c**) negatively affects the yield (**4e**, 52 %). The arabinosyl chloride **3b** affords a good yield (**4f**) of the α-*C*-glycoside.



Scheme 4 Coupling with furanosyl chlorides.



Scheme 5 Coupling with alkynylzinc derivatives.

Coupling reactions of alkynylzinc reagents

Finally, to expand the range of useful nucleophiles, alkynylzinc reagents were subjected to the reaction conditions (Scheme 5) [11]. To our surprise, the bicyclic species **5a** was isolated in 79 % yield as a single diastereoisomer, both with the furanosyl chloride **3a** and with the glucosyl bromide **1.**

This result suggests that the size of the nucleophile is a determining parameter for site selectivity. The formation of these compounds indirectly supports the proposed anchimeric assistance mechanism which governs the high *anti*-selectivity of the *C*-glycosylation in presence of diaryl zinc reagents (Scheme 1).

Conclusion

In conclusion, we have developed an efficient and stereoselective coupling of arylzinc derivatives with both pyranosyl and furanosyl halides [12]. The steric and electronic effects relative to the aryl component were studied, and indirect evidence for an ionic mechanism involving anchimeric participation was provided. It is important to note that the success of this methodology is due to the use of a solvent mixture that includes an apolar solvent with small amount of an ether co-solvent. The ethereal solvent of choice is di-*n*-butyl ether. We are currently exploring the extension of this methodology to other organozinc derivatives and carbohydrate substrates of biological interest, and these results will be reported in due course.

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[12] General procedure: In a Schlenk tube with magnetic stirring, the halogenated derivative (1.1eq.) is dissolved in dry toluene (8 mL/g) under N_2. After cooling to 0 °C, $(Bu)_3MgLi$ (0.38eq.) is added dropwise. After complete conversion (one night), $ZnBr_2$-LiBr (0.61eq, 25 % in DBE) is added dropwise at 0° C. The halogenated pyranoside (1eq.) is added in one portion and the reaction mixture is heated to 90 °C, or the chlorinated furanoside (1eq.) is added dropwise to the reaction mixture at 60 °C. After complete conversion, the reaction mixture is quenched with NH_4Cl (33 w/w%, 4 mL/g) at 50 °C, the two layers are separated and the solvent is evaporated under reduced pressure at 30 °C.