ORGANIC LETTERS

2012
Vol. 14, No. 6
1480–1483

Stereoselective C-Glycosylation Reactions with Arylzinc Reagents

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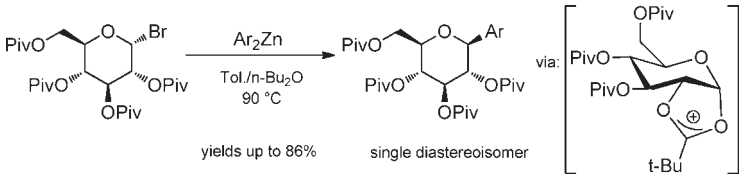
Received January 27, 2012

ABSTRACT



A general, transition-metal-free, highly stereoselective cross-coupling reaction between glycosyl bromides and various arylzinc reagents leading to β-arylated glycosides is reported. The stereoselectivity of the reaction is explained by invoking anchimeric assistance via a bicyclic intermediate. Stereochemical probes confirm the participation of the 2-pivaloyloxy group. Finally, this new method was applied to a short and efficient stereoselective synthesis of Dapagliflozin and Canagliflozin.

C-Glycosides are ubiquitous natural products of high medicinal significance[1] that therefore have received considerable synthetic attention.[2] In addition to naturally occurring *C*-glycosides, synthetic versions have often been used by medicinal chemists as stable analogs of natural substances containing C−O and C−N bonds. One class of medicinally important aryl glycosides, active against diabetes, and currently in late-phase development, are the SGLT-2 inhibitors,[3] exemplified by Dapagliflozin (**1**) and Canagliflozin (**2**), shown in Figure 1.

The traditional synthesis of aryl glycosides is based on the reaction of protected aldonolactones with aryllithium or aryl Grignard reagents, to yield lactols which need to be reduced in a second step.[4] Such reductions can be, in some cases, quite stereoselective.[5] However, low reaction temperatures are required in order to avoid opening of the intermediate lactol.[1]

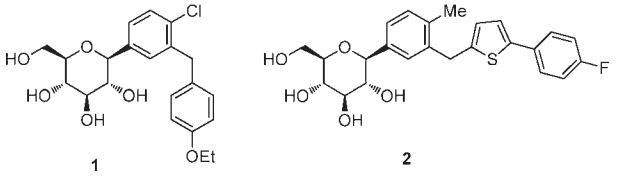


Figure 1. Structure of key SGLT-2 inhibitors.

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(1) (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rev.* **2005**, *22*, 742. Q. (b) Simons, W. C. *Synthesis* **2004**, 1533. (c) Stanbasky, J.; Hocek, M.; Kosovsky, P. *Chem. Rev.* **2009**, *109*, 6729.

(2) (a) Lee, D. Y. W.; He, M. *Curr. Top. Med. Chem.* **2005**, *5*, 1333. (b) Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913. (c) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55. Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1. (d) Kulkarni, S. S.; Gervay-Hague, J. *Org. Lett.* **2006**, *25*, 5765.

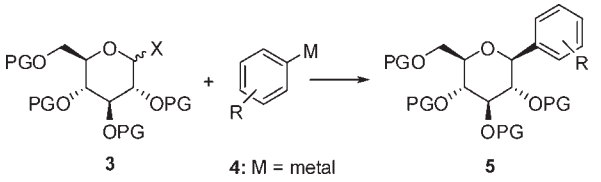
(3) (a) Review: Chao, E. C.; Henry, R. R. *Nat. Rev. Drug Discovery* **2010**, *9*, 551. (b) Rawat, P.; Kumar, M.; Rahuja, N.; Srivastava, D. S. L.; Kumar, A.; Maurya, R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 228. (c) Nomura, S.; Sakamaki, S.; Hongu, M.; Kawanishi, E.; Koga, Y.; Sakamoto, T.; Yamamoto, Y.; Ueta, K.; Kimata, H.; Nakayama, K.; Tsuda-Tsukimoto, M. *J. Med. Chem.* **2010**, *53*, 6355. (d) Meng, W.; et al. *J. Med. Chem.* **2008**, *51*, 1145.

(4) (a) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752. (b) Streicher, H.; Reiner, M.; Schmidt, R. R. *J. Carbohydr. Chem.* **1997**, *16*, 277. (c) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610.

10.1021/ol300220p
Published on Web 03/02/2012

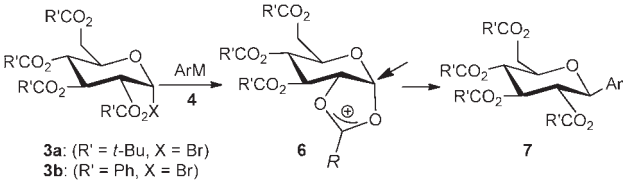
Due to the growing commercial and therapeutic importance of aryl glycosides, a synthetic approach that used the direct coupling of an organometallic species with a suitably activated carbohydrate moiety, thereby avoiding the oxidation/reduction sequence, would be highly desirable. In this approach, the leaving group (X) on the carbohydrate moiety **3**, the metal (M) of the aryl nucleophile **4**, the protecting group PG, and solvent as well as (any) catalyst would have to be selected with the utmost care in order to render the approach high-yielding, general, and stereospecific (Scheme 1).

Scheme 1. "Direct" *C*-Glycosylation



An elegant solution was reported by Gagné, who described a Ni-catalyzed coupling of organozinc reagents with glycosyl bromides.[6] The coupling product of type **5** (PG = Ac) is obtained with good stereoselectivity (β/α ratio of 12:1 for R = H). The reaction was shown to proceed via a radical pathway, where "catalyst control" dictates the β/α ratio at the anomeric center. The high Ni-loading (10 mol %) and the high toxicity of nickel salts hampers potential industrial applications of this coupling reaction. Alternatively, an ionic pathway can be envisioned.[7] This "substrate-control" approach would proceed via an anomeric oxonium ion **6**, and the adjacent 2-carboxylate would ensure a well-defined stereochemistry via anchimeric participation (**6**). Nucleophilic substitution with an organometallic reagent (Ar−M) would provide the β-arylated products via inversion at the anomeric center (Scheme 2).

Scheme 2. "Substrate-Controlled" *C*-Glycosylation



Indeed, organozinc reagents behave as nucleophiles in a number of substitution reactions (especially with allylic halides),[8] whereas examples of the addition of "harder" organometallic reagents (Al and Mg-based) to glycosyl halides are sparse, generally low yielding, and marred by variable stereoselectivity and/or marginal generality.[9]

In this communication we describe a new approach to β-aryl glycosides **5** (including drug candidates **1** and **2**) involving a transition-metal-free cross-coupling reaction with organozinc reagents which proceeds with complete β-selectivity and in good to excellent yields.

We chose the glycosyl bromide **3a** as a stable and crystalline substrate. The pivaloyl protecting group[10] would readily participate in the formation of intermediate **6**, but would be resistant to the direct attack of organometallic reagents. Thus, the glycosyl bromide **3a** in THF was treated with commercial PhZnCl in THF. Consistent with Gagné's results, no reaction occurred at ambient temperature in the absence of catalyst, and upon heating the only product detected was the 4-Cl-butanol adduct (**3c**: R′ = *t*-Bu; X = $O(CH_2)_4Cl$) from the opening of the THF ring and *O*-glycosylation.[11] In addition, chloride ion substitution at the anomeric carbon was also observed, producing a substantial amount of unreactive **3d** (R′ = *t*-Bu; X = Cl) as determined by GC/MS analysis. This reaction was observed with all ethereal solvents tested, such as diethyl ether, 2-methyl-THF, di-isopropyl ether, methyl *tert*-butyl ether, cyclopentyl methyl ether (CPME), and di-*n*-butyl ether (DBE), but the rate of decomposition of **3a** in these ethereal solvents is slower than that for THF.

Capitalizing on the observation that solvents such as CPME and DBE react with **3a** more slowly than THF in the presence of Zn(II) salts, we have found that a combination of toluene and either of these ethereal solvents affords useful yields of the desired product with complete stereocontrol (>99:1). In a model reaction (Scheme 3) the metalation reaction was carried out on iodotoluene (**4a**) using *n*-BuLi or lithium tri-*n*-butyl magnesate in 2:1 toluene/DBE followed by transmetalation with the $ZnBr_2$−LiBr complex in dibutyl ether. LiBr is essential as it allows

(5) Ellsworth, B. A.; Doyle, A. G.; Patel, M.; Caceres-Cortes, J.; Meng, W.; Deshpande, P. P.; Pullockaran, A.; Washburn, W. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3243.

(6) (a) H. Gong, H.; Andrews, R. S.; Zuccarello, J. L.; Lee, S. J.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 879. (b) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177. (c) Gong, H.; Sinisi, R.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 1908.

(7) Nukada, T.; Berces, A.; Zgierski, M. Z.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291.

(8) (a) Knochel, P.; Jones, P. *Organozinc Reagents*, Eds.; Oxford University Press: Oxford, U.K., 1999. (b) Kobayashi, K.; Naka, H.; Wheatley, A. E. H.; Kondo, Y. *Org. Lett.* **2008**, *10*, 3375. (c) Kobayashi, K.; Ueno, M.; Wheatley, A. E. H.; Kondo, Y. *Chem. Commun.* **2006**, 3549.

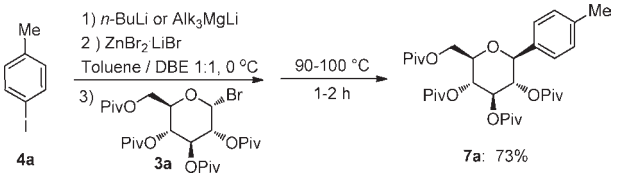
(9) (a) Via intramolecular migration of arylsiloxanes: Nakazaki, A.; Uzuki, J.; Tomooka, K. *Synlett* **2008**, 2064. Rousseau, C.; Martin, O. R. *Org. Lett.* **2003**, *5*, 3763. (b) Via cuprates: Hainke, S.; Singh, I.; Hemmings, J.; Seitz, O. *J. Org. Chem.* **2007**, *72*, 8811. (c) With soft nucleophiles: Pasetto, P.; Walczak, M. C. *Tetrahedron* **2009**, *65*, 8468. Yamauchi, T.; Shigeta, M.; Matsumoto, T.; Suzuki, K. *Heterocycles* **2005**, *66*, 153. Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961. (d) Via Grignard reagents: Ruttens, B.; Blom, P.; Van Hoof, S.; Hubrecht, I.; Van der Eycken, J.; Sas, B.; Van Hemel, J.; Vandenkerckhove, J. *J. Org. Chem.* **2007**, *72*, 5514. Kulkarni, S. S.; Gervay-Hague, J. *Org. Lett.* **2006**, *8*, 25. Panigot, M. J.; Humphries, K. A.; Curley, R. W., Jr. *J. Carbohydr. Chem.* **1994**, *13*, 303. Hurd, C. D.; Holysz, R. P. *J. Am. Chem. Soc.* **1950**, *72*, 1732. Hurd, C. D.; Bonner, W. A. *J. Am. Chem. Soc.* **1945**, *67*, 1972. (e) Via organozinc reagents: Zhdanov, Y. A.; Dorofeenko, G. N.; Bogdanova, G. V. *Dokl. Akad. Nauk SSSR* **1958**, *119*, 495. (f) Via organotrifluoroborates: Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 42. (g) *O*- to *C*-glycoside rearrangement: Ben, A.; Yamauchi, T.; Matsumoto, T.; Suzuki, K. *Synlett* **2004**, 225.

(10) (a) Dabideen, D. R.; Gervay-Hague, J. *Org. Lett.* **2004**, *6*, 973. (b) Helferich, B.; Zirner, J. *Chem. Ber.* **1963**, *96*, 374.

(11) Nonacyl protecting groups such as benzyl do not yield more than traces of coupling products, because such glycosyl halides are too unstable to our conditions.

dissolution of $ZnBr_2$ in DBE. The solvent composition was also crucial to the success of the Li/Zn-transmetalation and the coupling reaction, with the toluene/DBE ratio set at 1:1 (v/v), as a compromise between solubility and reactivity. The bromosugar **3a** was added to the resulting suspension of the arylzinc species, and the mixture was heated to 90−100 °C for 1−2 h (Scheme 3). To our delight, the desired C-glycoside **7a** was isolated as a single anomer (β) in 78% yield. We have studied the scope of this new coupling reaction using the optimized conditions (Table 1). In all examples involving **3a** (entries 1−12), the β-isomer was exclusively obtained, as determined by ^{1}H NMR.

Scheme 3. Model Reaction



Aryl iodides were best metalated with either *n*-BuLi or lithium tri-*n*-butyl magnesate at various temperatures (−78 °C to rt) whereas aryl bromides require the latter reagent or *s*-BuLi at higher temperatures (−10 to 0 °C).[12] Some aromatic derivatives can be lithiated directly (Table 1, entries 8 and 11).

Interestingly, the stoichiometry of the zinc halide salt had a significant effect on the yield and robustness of the reaction, and the use of 0.55 equiv of the $ZnBr_2$−LiBr complex was found to be optimal.[13]

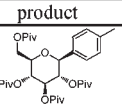
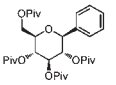
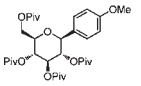
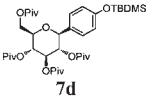
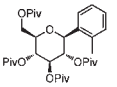
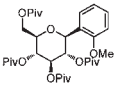
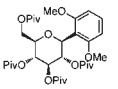
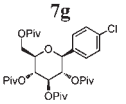
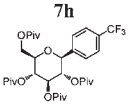
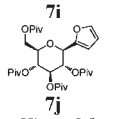
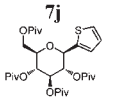
The reaction was found to be somewhat sensitive to steric hindrance, and it proceeded best with *para* substituted aromatics (entries 1−5), whereas the presence of *ortho* substituents (entries 5, 6) decreased the yields as the reaction temperature had to be increased to 110 °C. Electron-rich aromatics (entries 3, 5, 8) reacted more rapidly and in higher yields, but the reaction can be carried out in useful yields even with electron-poor aryl moieties (entries 9, 10). Heterocycles such as furan (entry 11) and thiophene (entries 12) can be also introduced as expected, but iodopyridines (entries 13, 14) failed to afford any coupled product.

Stereochemical studies were performed to distinguish between possible reaction pathways (i.e., anchimeric assistance via the intermediacy of **6** vs a direct S_N2-type displacement). Thus, the glucose derivative **3a** reacts with *p*-anisylzinc halide generated, as usual, from 4-iodoanisole (**4b**) to give exclusively the β-anomer in good yield, whereas the mannose analog **8** afforded only the α-anomer **9**, showing the importance of the anchimeric participation

(12) Table 1 reports the most convenient metalation conditions for each aryl derivative.

(13) Notably, use of more reactive nucleophiles, such as aryllithium, aryl Grignard, or aryl magnesates, led to extensive addition onto the ester protecting group even if the pivaloyl ester (as in **3a** R = *t*-Bu) was used.

Table 1. β-Aryl Glycosides (**7a**−**m**) Obtained by the Reaction of Zinc Organometallics with Glycosyl Bromide **3a**

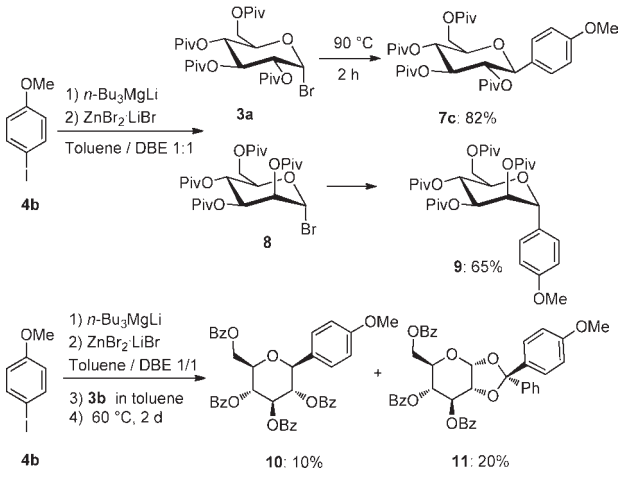
entry	ArX (ArH)	product	yield	β/α
1	4-MeC$_6$CH$_4$I[a]	 **7a**	78%	>99:1
2	C$_6$H$_5$I[b]	 **7b**	70%	>99:1
3	4-MeOC$_6$CH$_4$I[a]	 **7c**	82%	>99:1
4	4-MeOC$_6$CH$_4$I[a],[c]		73%	>99:1
5	4-(TBDMSO)C$_6$H$_4$I[a]	 **7d**	50%	>99:1
6	2-MeC$_6$H$_4$I[b],[d]	 **7e**	58%	>99:1
7	2-MeOC$_6$H$_4$I[b],[d]	 **7f**	60%	>99:1
8	1,3-(MeO)$_2$C$_6$H$_4$[c],[d]	 **7g**	86%	>99:1
9	4-ClC$_6$H$_4$Br[a]	 **7h**	58%	>99:1
10	4-CF$_3$C$_6$H$_4$I[b],[d],[f]	 **7i**	50%	>99:1
11	furan[b]	 **7j**	61%	>99:1
12	2-iodothiophene[b]	 **7k**	60%	>99:1
13	2-iodopyridine	**7l**	0%	-
14	3-iodopyridine	**7m**	0%	-

[a] Base: Lithium tributyl magnesate. [b] Base: *n*-BuLi, deprotonation at C-2. [c] Base: *s*-BuLi; deprotonation at C-2. [d] Coupling temperature 110 °C. [e] Coupling temperature: 60 °C for 2 days. [f] Arylzinc formed at −78 °C.

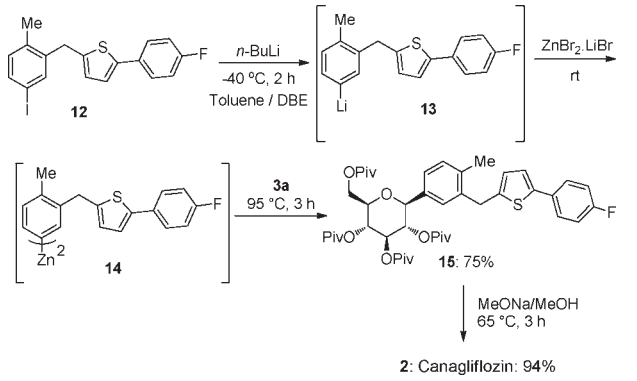
of the 2-pivaloyl group. Furthermore, direct evidence for a mechanistic pathway via **6** comes from the isolation of **11** when the tetra-benzoyl derivative **3b** was used as the substrate. In this case the oxonium carbon of **6** is less hindered and reacts directly with the arylzinc reagent. This result indirectly validates our choice of the pivaloyl group as a protecting group (Scheme 4).

With this methodology in hand, we turned our attention to the synthesis of Canagliflozin **2** starting from the aryl iodide derivative **12** (Scheme 5). The aryllithium reagent **13** was prepared in 1:1 toluene−DBE quantitatively at −40 °C. Transmetalation to the reactive Ar_2Zn species

Scheme 4. Mechanistic Experiments with Specific Probes



Scheme 5. Synthesis of Canagliflozin (**2**)

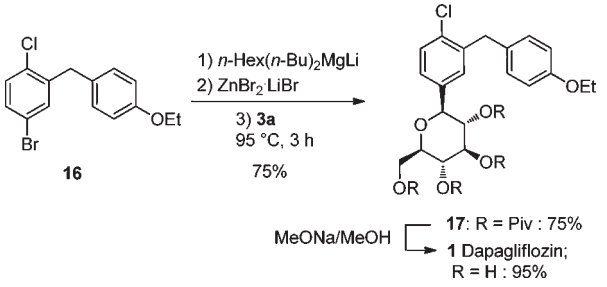


14 with $ZnBr_2$ took place upon warming to ambient temperature (to give back **12** in 96−98% yield by iodine quench). Addition of the bromo-sugar **3a** and heating to 90−100 °C produced the arylated glycoside **15** in 75% yield[14] which lead to Canagliflozin **2** by hydrolysis.

(14) The yield was determined by quantitative HPLC vs a highly purified external standard.

The synthesis of Dapagliflozin **1** was accomplished as well, starting from the bromide **16** (Scheme 6). Magnesate *n*-Hex(*n*-Bu)$_2$MgLi was used as the metalating agent,[15] to achieve selective Br/Mg-exchange, followed by Mg/Zn-exchange with $ZnBr_2 \cdot LiCl$ and finally coupling with **3a** to give the tetrapivaloyl intermediate **17** in 75% isolated yield. Smooth deprotection with MeONa in MeOH at rt afforded **1** in 95% yield.

Scheme 6. Synthesis of Dapagliflozin **1**



In conclusion, we have developed the first general, stereoselective, transition-metal-free approach to C-aryl glycosides by the direct coupling of glycosyl bromides with aryl and heteroaryl zinc reagents. The steric and electronic effects on the aryl component were studied, and evidence for an ionic mechanism involving anchimeric participation was provided. We are currently extending this methodology to other organozinc derivatives and carbohydrate substrates, and these results will be reported in due course.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) For references on the use of magnesates in metalation of aryl halides, see: (a) Harada, T.; Katsuhira, T. R.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958. (b) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733. (c) Kondo, Y.; Matsudaira, T.; Sato, J.; Murata, N.; Sakamoto, T. *Angew. Chem., Int. Ed.* **1996**, *35*, 736. (d) Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1996**, *37*, 5377. (e) Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 910. (f) Hojo, M.; Harada, H.; Ito, H.; Hosomi, A. *J. Am. Chem. Soc.* **1997**, *119*, 5459.

The authors declare no competing financial interest.