Stereospecific C-Glycosylation by Mizoroki-Heck Reaction A Powerful and Easy-to-Set-Up Synthetic Tool to Access α- and β-Aryl-C-Glycosides

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Stereospecific *C*-glycosylation via Mizoroki-Heck reaction, a powerful and easy-to-set-up synthetic tool to access α and β aryl-*C*-glycosides

Thibaud Mabit,[a,b], ⊥ Aymeric Siard,[a], ⊥ Frédéric Legros,[b] Stéphane Guillarme,[b] Arnaud Martel,[b] Jacques Lebreton,[a] François Carreaux,[c] Gilles Dujardin*[b] and Sylvain Collet*[a]

Abstract: A stereospecific Mizoroki-Heck cross-coupling of differently substituted glycals with haloarenes resulting in the exclusive formation of either α or β aryl-*C*-glycosides depending solely on the configuration at C3 is reported. The reaction is easy to set up as no specific precaution are required concerning moisture as well as oxygen, and proceeds by a chirality transfer from C3 to C1. After optimization of cross-coupling conditions, various prepared glycals (7 examples) and arenes (10 examples) have been tested leading stereospecifically to the corresponding aryl-*C*-glycosides with ketone at C3 and thus opening up new horizons for the total synthesis of glycosylated natural products.

C-glycosides[1] represent a class of compounds in which a glycon and an aglycon parts are linked together through an anomeric C-C bond. The strength of such linkage towards the hydrolysis (in comparison with their *O*-analogues) makes this latter family very attractive from a bioactive point of view. Consequently, many methods have been developed to achieve the formation of the anomeric C-C link of *C*-glycosides.[2] Among them, aryl-*C*-glycosides such as vineomycin B2 (**1**), hedamycin (**2**) (Figure 1), which exhibit a wide variety of biological activities, represent a large and well-studied class of compounds. [3] In this context, it is not surprising that latter family is considered as challenging target to synthetic chemists. The great scientific issue raised by these compounds can be evaluated by the wide literature on this topic. [4] While several strategies have been described to form the specific aryl-*C*-glycosidic linkage, two crucial challenges still persist: (1) the stereoselectivity of the reaction *i.e.* the α or β anomery of the product; (2) the regioselectivity of the reaction, keeping in mind the complexity of the targets which are typically mono- or polyglycosylated and highly functionalized polycyclic molecules.

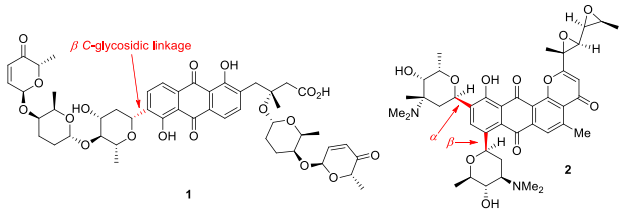

Figure 1 – Selected natural aryl-*C*-glycosides

Palladium cross-coupling reactions have been applied to synthesize *C*-glycosides since the mid-1970's.[5a] The major attention on this topic has been focused on the use of glycal as precursor for the formation of C-C bond which can be summarized according to three different approaches.[5b] (Figure 2)

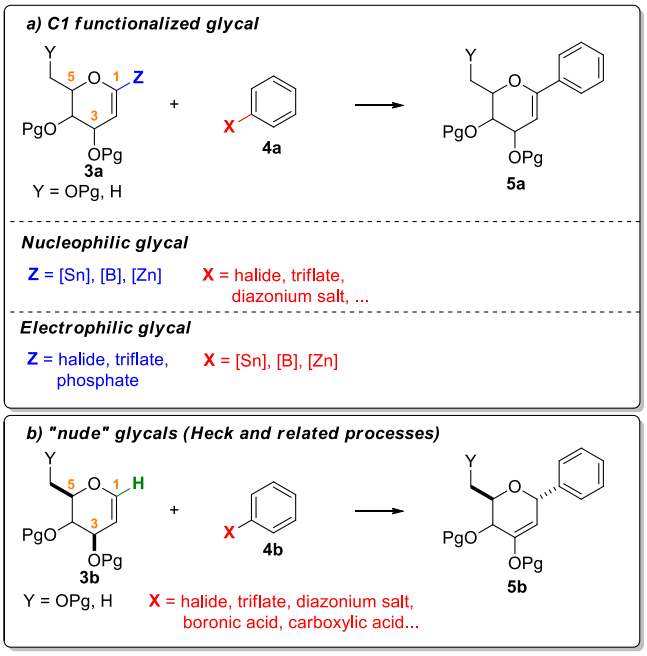

Figure 2. *C*-glycosylation reaction using a glycal as coupling partner

Although Stille, Suzuki-Miyaura and Negishi cross-couplings are effective to perform *C*-glycosylation reactions under mild

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conditions, the preparation of C1 functionnalized glycals remains a major drawback of these methods. Indeed, whether it is for the formation of nucleophilic or halogenated glycal, the first step corresponds to a tenuous lithiation at C1 position. Generally achieved by using an excess of *t*-BuLi or Schlösser's base,[6] these processes are not compatible with a wide range of functional groups, suffer from side reactions and could be difficult to handle. Another option is the use of ketene acetal triflates or phosphates as electrophilic glycals.[7] However, these highly unstable species cannot be purified and their syntheses are not easy, particularly on large scales. The direct use of "nude" glycals in Heck processes[8] seems to be a perfect compromise between a convenient preparation of coupling partners and a reaction carried out under mild conditions. This is probably the main reason explaining the developments[9] and applications[10] of these reactions to perform aryl-*C*-glycosylations.

Regarding the results described in the literature, two points can be emphasized: first, the double bond of the starting glycal always migrates from C1-C2 to C2-C3 on the coupled product. Secondly the only product isolated is the α anomer. The steric factors solely involved to rationalize this second point appears as an incomplete explanation. Indeed, modifying the bulkiness of the different substituents of the coupling partners have no effect on the stereoselectivity of the reaction.[9,11] The selectivity is probably a consequence of the inherent mechanism of the Mizoroki-Heck reaction.[12] (Figure 3)

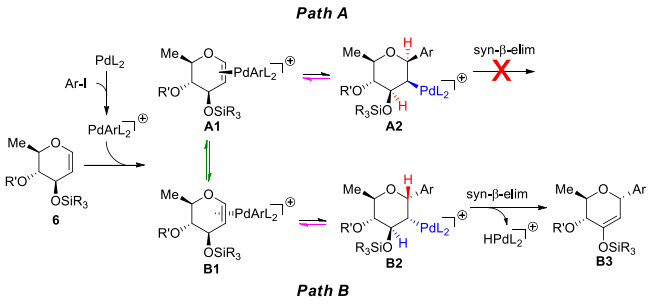


Figure 3. Plausible stereocontrol in Mizoroki-Heck reaction (in cationic conditions) involving a glycal as coupling partner

As depicted on Figure 3, two paths are envisioned. The first one, involving an approach of the aryl-palladium complex on the same face than the $OSiR_3$ group of the glycal. Path A would lead to the β-anomer but is not evolutive in terms of Mizoroki-Heck reaction. Indeed, **A2** intermediate does not provide any C-H bond in *syn* relation to C-Pd bond required for the elimination step. An approach on the other face of the glycal (path B) leads to **B2** intermediate which provides H3 as the only hydrogen available for *syn*-β-elimination step. We postulate that both the migration of the double bond and the stereochemistry at C1 position of the coupling product could be explained by the initial stereochemistry at C3 position of the glycal. At this stage, two hypotheses can be speculated. *Hypothesis 1* (green arrows): The equilibrium between **A1** and **B1** is entirely displaced in favor of **B1** due to the steric hindrance of C3 substituting group and conformational rigidity.[9a] Intermediate **A2** is thus never formed and that drives the selectivity observed. *Hypothesis 2* (pink arrows): The allylic oxy substituent (whether pseudoaxial or pseudoequatorial) is not enough discriminating to explain complete selectivities and carbopalladation may occur to lead to **A2**. As no H-*syn*-β-elimination can happen, an envisionable evolution for **A2** is the glycal extrusion. This kind of behavior is well-known with norbornene-Pd^{II} adducts in Catellani reaction[13] and has also been described with other alkyl-Pd^{II} lacking β-hydrogen for the elimination step.[14]

In the literature,[9] glycals used in Mizoroki-Heck reactions exhibit a *syn* relationship between C3 and C5 substituents (so called "*syn* glycals"), are easy to prepare from commercially available carbohydrates and lead exclusively to α-anomer products (Figure 4). In this work, we propose to use "*anti* glycals" as coupling partners expecting the formation of β-anomers.

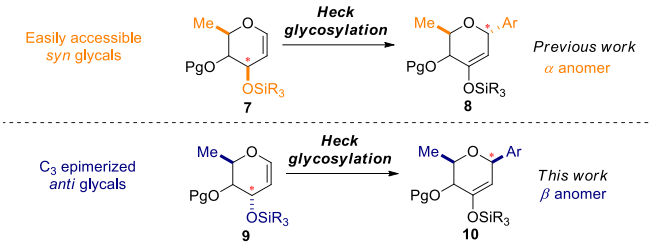


Figure 4. Stereochemical relationship between coupling product and starting glycal

We began studying the equilibrium between **A1** and **B1** π-complexes by DFT calculations (Ar = Ph, R = R' = Me. For computational details see Supporting Information). The results are presented for *D*-rhamnal and 6-deoxy-*D*-allal which are supposed to lead respectively to α and β anomers after coupling. The less energetic conformers are represented [15] in Figure 5 and the computed energies (at 328.15 K) of subsequent π-complexes are depicted in Figure 6. As presented in the literature,[16] functionalized *D*-rhamnal **11** and 6-deoxy-*D*-allal **12** adopt preferentially a $^4H_5$ conformation. All substituents in **11** happen to be in pseudo-equatorial position in the less energetic conformer. OTMS group at C3 in **12** is in pseudo-axial position when other substituents remain the same as **11**.

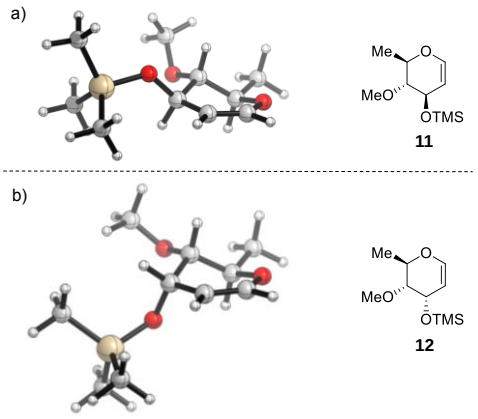


Figure 5. a) 4-OMe-3-OTMS-*D*-rhamnal **11** b) 6-deoxy-4-OMe-3-OTMS-*D*-allal **12**

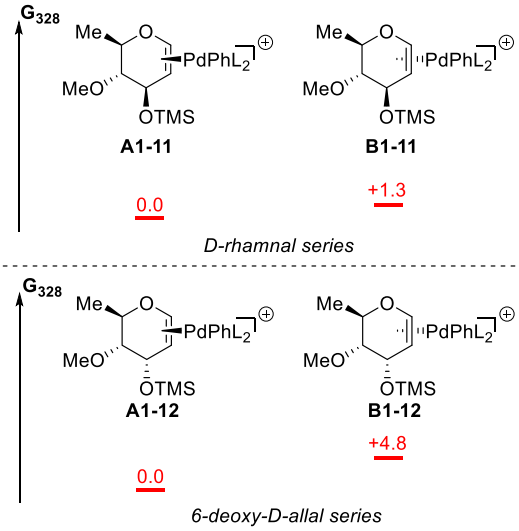


Figure 6. Four π-complexes with free energies (given at reaction temperature 328.15 K) in kcal.mol^{-1}. L=PPh_3

Considering allal series, the energetic gap between **A1-12** and **B1-12** is significant (4.8 kcal.mol^{-1}). This could be explained by the pseudoaxial position of OTMS group which hinders *Re* face of the glycal (Figure 5b). This result appears encouraging to synthetize the β anomers through Mizoroki-Heck cross coupling but is not consistent to rebut any hypothesis. As expected, the gap between **A1-11** and **B1-11** is low (1.3 kcal.mol^{-1}) certainly due to the pseudoequatorial position of OTMS group which has no effect on the stereochemical outcome (Figure 5a). Interestingly, **A1-11** appears to be the favored complex which tends to invalidate the steric bulk at C3 invoked in *hypothesis 1.* Usually, the subsequent *syn*-β-H-elimination energetic barrier is too low to allow reversibility in the carbopalladation step.[17] That is why *hypothesis 2* is rarely formulated even if reversible carbopalladations have been observed.[13,14] These theoretical results in hands, we decided to confirm experimentally expectations toward stereospecificity of the reaction.

The conditions described by Ye[9d] are effective to perform the coupling reactions with simple iodoarenes but are not adapted to more sophisticated coupling partners. Thus, we decided to develop a more versatile and robust catalytic system. After investigations on precatalyst source, ligands, base and additives (See Supporting Information), using $Pd(TFA)_2$ (0.1 eq.), PPh_3 (0.2 eq.), and Ag_2CO_3 (2 eq.) turned out to be the most powerful system, easy to set-up as it is neither moisture nor air sensitive.

The latter in hands, it has been decided to apply these newly optimized conditions to perform *C*-glycosylation reactions between 3-OTBS protected glycals and a first set of iodoarenes. Unfortunately, it appears that: (1) the ratio silyl enol ether/ketone differs following both the glycal and the aromatic core, without clear rationalization; (2) the silyl enol ethers cannot be columned as a retro-Michael reaction occurs on silica or in acidic medium; (3) the crude mixture cannot be converted into ketone by using fluoride anions as a retro-Michael also occurs, followed by a ring closure into pyrane which induces a loss of the stereogenic information at the anomeric position. (Figure 8)

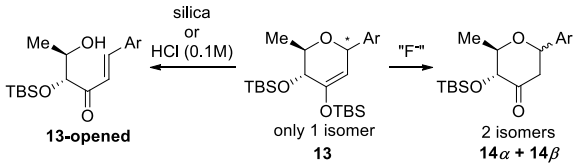


Figure 8. Reactivity of the enol silyl ethers in acidic or basic fluoride media

To overcome these problems, the TBS protecting group has been replaced by a more labile TMS group. Using this suitable protecting group, all silyl enol ether is converted *in situ* into functionalizable ketone. Several glycals with either a *syn* or *anti* C3-C5 relationship were coupled to **15a** to prove the expected total stereospecificity of the reaction. (See Figure 9, Table 2)

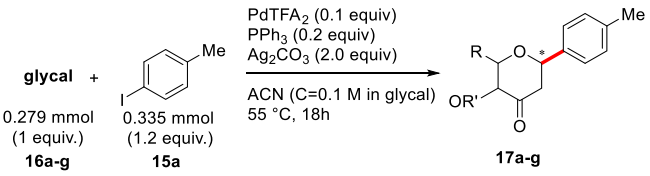
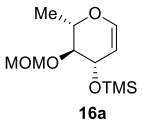
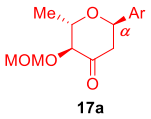
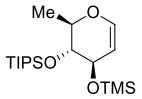
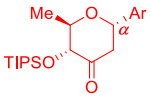
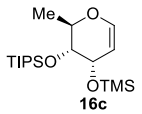
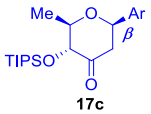
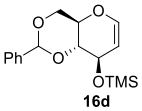
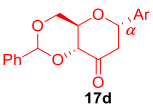
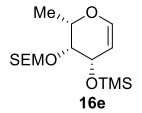
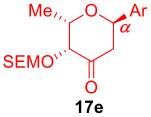
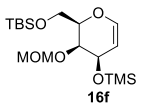
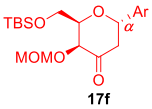
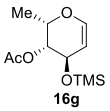
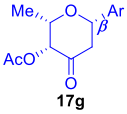


Figure 9. General procedure for glycal scope

Table 2. Scope of glycals

Entry	Glycal	Product[a]	Conv[b]	Yield[c]

a	 **16a**	 **17a**	95	80
b	 **16b**	 **17b**	> 99	87
c	 **16c**	 **17c**	> 99	86
d	 **16d**	 **17d**	77	68
e	 **16e**	 **17e**	86	80
f	 **16f**	 **17f**	95	83
g	 **16g**	 **17g**	20	15

Stereochemistries at C1 have been assigned by NOESY experiments (See SI). [a] Ar = *p*-tolyl. [b] In molar percentage. Based on the analysis of ^{1}H NMR spectrum. [c] Isolated yield after column chromatography

All the "*syn* glycals" (entries **a**, **b**, **d**, **e**, **f**), commonly used in this type of reaction, lead to the formation of α-aryl-*C*-glycosides with very high conversions and yields. In contrast, and as predicted, "*anti* glycals" (entries **c** and **g**) are converted exclusively into β-aryl-*C*-glycosides. To the best of our knowledge, these results are the first examples of completely selective β-aryl-*C*-glycosylations described in the literature *via* Mizoroki-Heck cross-coupling. Comparison between entries **b** and **c** clearly emphasizes the crucial importance of the stereochemistry at C3 on stereogenic information at the anomeric position in coupled product. Moreover, while all the stereocenters are inverted except C3 (entries **f** and **g**), the aromatic core is bound on the same face of the glycal, which implies the formation of an α anomer and a β anomer as the stereochemistry has been modified at C5. The low conversion observed entry **g** could be explained by the steric hindrance induced by both methyl and acetate groups on the approach face. Remarkably, even if the conversion is low, only β anomer product was obtained, reinforcing *hypothesis 2* based on a reversible carbopalladation. The lower conversion observed with **17d** can be explained by the constrained *trans* decaline system that can be deleterious on the syn-β-elimination step. This methodology is compatible with a wide panel of protecting groups but deprotection and degradation problems have been encountered with poly-TMS protected glycals.

These encouraging results in hands, several arenes have been tested. Considering total conversion of **16c** (Table 2), it has been decided to use this entry as a reference. (Figure 10, Table 3)

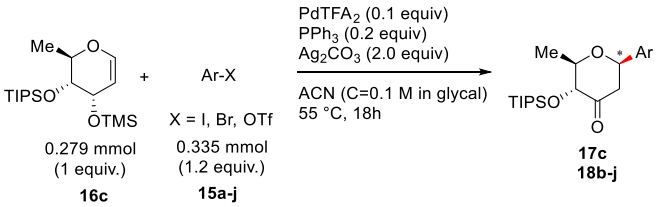
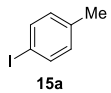
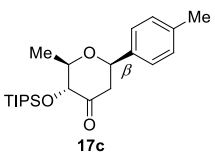
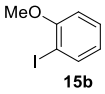
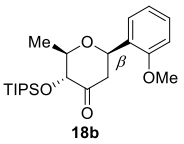
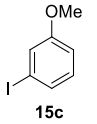
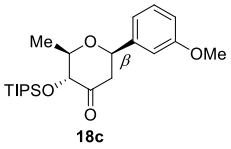
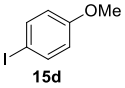
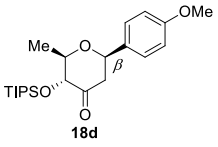
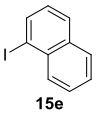
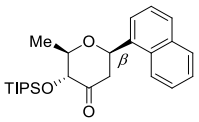
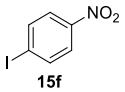
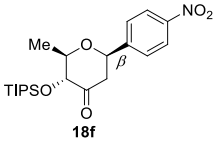
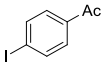
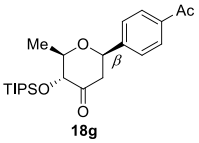
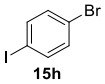
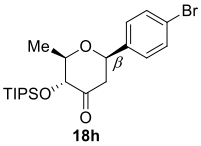
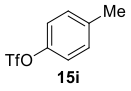
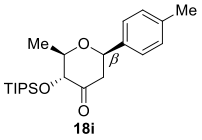
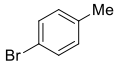
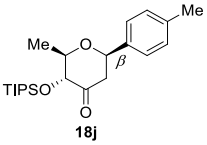


Figure 10. General procedure for aromatic partner scope

Table 3. Aromatic partner scope

Entry	Haloarene	Product	Conv[a]	Yield[b]
a	 **15a**	 **17c**	> 99	86

b	 **15b**	 **18b**	72	68
c	 **15c**	 **18c**	52	48
d	 **15d**	 **18d**	> 99	88
e	 **15e**	 **18e**	75	71
f	 **15f**	 **18f**	-	-
g	 **15g**	 **18g**	54	52
h	 **15h**	 **18h**	52	48
i	 **15i**	 **18i**	20	15
j	 **15j**	 **18j**	-	-

Stereochemistries at C1 have been assigned by NOESY experiments (See SI). [a] In molar percentage. Based on the analysis of ^{1}H NMR spectrum. [b] Isolated yield after column chromatography

As expected, only β-aryl-*C*-glycosides have been obtained. It appears that electron-rich iodoarenes are more prompt to react in such couplings (**15a**, **15d**). **15b** conducted to more modest yield certainly due to the formation of a palladacycle. Under these conditions **15c** gave lower yield which confirm that electron-rich iodoarenes are more efficient. Entries **f** to **h** are consistent with the previous observations. Thus, **15g** and **15h** gave a 50% conversion when **15f** presented a lack of reactivity.

Interestingly, as shown by entry **j**, coupling in these conditions is not successful with bromoarenes. This observation has also been confirmed by entry **h** as only coupled product at iodinated position has been obtained. It is therefore easy to discriminate between different halides and to couple selectively on iodide aromatic derivatives. This remarkable result shows that this easy-to-set-up methodology can be used in elaborated syntheses. To extend this significant outcome, a triflate arene has been tested. Nevertheless, a low conversion has been observed (entry **i**). Byproducts due to degradation of starting aryltriflate were also detected in the crude material.

We described here an easy-to-set-up and robust methodology that overcomes recurring issues encountered in syntheses of α and β aryl-*C*-glycosides. The coupling is fully regioselective at C1 position of the glycal and iodinated position of functionalized aromatic cores. This reaction is very powerful as the stereochemistry at the anomeric position is directly controlled by a strict *anti* chirality transfer from the initial stereocenter C3 (Figure 11).

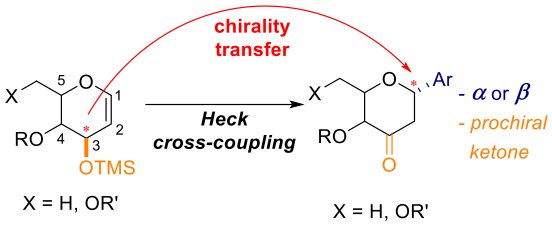


Figure 11. Formation of aryl-C-glycosides through Heck cross-coupling

The carbonyl group obtained at C3 should enable numerous reactions with a relative control of the stereochemistry. Configurations at C4 and C5 are set by the starting carbohydrate and have no effect on the stereospecificity of the reaction. As a conclusion, using the appropriate starting glycal, our methodology permits the access to aryl-*C*-glycosides with a control of stereochemistry at C1 and paves the way to numerous functionalizations at C3, the main source of chemical diversity in this family of products.

Even if several hypotheses are emitted, experimental proofs and DFT investigations are currently ongoing to fully understand the stereospecificity of the reaction. We are also working on applications of this powerful methodology to the syntheses of natural products.

Acknowledgements

We fully acknowledge Prof. Cyril Bressy, Prof. François-Xavier Felpin and Cloé Azarias for fruitful discussions.

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Keywords: Mizoroki-Heck reaction; *C*-glycosides; α-glycosylation; β-glycosylation

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[11] With peracetylated glycals, a mixture of anomers is sometimes obtained with the loss of the acetate leaving group at C3 position. This is certainly the consequence of a very different mechanism passing through a Ferrier/Tsuji-Trost-like mechanism as this mixture of anomers has never been observed without departure of a leaving group at C3 position.

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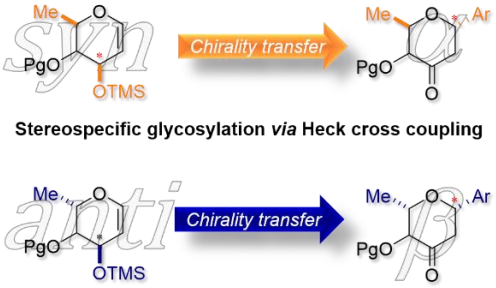
Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

α or β ? This is no longer a question to ask with this stereospecific aryl-*C*-glycosylation system. An easy-to-set-up Mizoroki-Heck cross coupling between diversely substituted glycals and haloarenes has been studied, leading exclusively either to α or β aryl-*C*-glycosides depending on the relative configuration at C3 and C5 and thanks to a chirality transfer from C3 to C1.



Stereospecific glycosylation *via* Heck cross coupling

Thibaud Mabit, Aymeric Siard, Frédéric Legros, Stéphane Guillarme, Arnaud Martel, Jacques Lebreton, François Carreaux, Gilles Dujardin and Sylvain Collet**

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Stereospecific *C*-glycosylation via Mizoroki-Heck reaction, a powerful and easy-to-set-up synthetic tool to access α and β aryl-*C*-glycosides