

Palladium-Catalyzed One-Pot Stereospecific Synthesis of 2-Deoxy Aryl C-Glycosides from Glycals and Anilines in the Presence of *tert*-Butyl Nitrite

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The lay person generally understands carbohydrates as a source of energy, but these compounds are also an important class of biomolecules which have been investigated as drugs, vaccines, drug targets, diagnostic tools, and more.¹ Unlike other biomolecules, such as proteins and nucleic acids, carbohydrates are complex in nature not only because of their structure and stereochemistry, but also because of their manifold biological functions.² Complex carbohydrates such as polysaccharides are known as glycans, which can be broadly classified as *O*- and *C*-glycosides depending on their anomeric linkages. The group of Dr. Jeyakumar Kandasamy at the Indian Institute of Technology (Varanasi, India) has been studying these classes of molecules and recently published the title paper on the one-pot synthesis of 2-deoxy aryl *C*-glycosides.

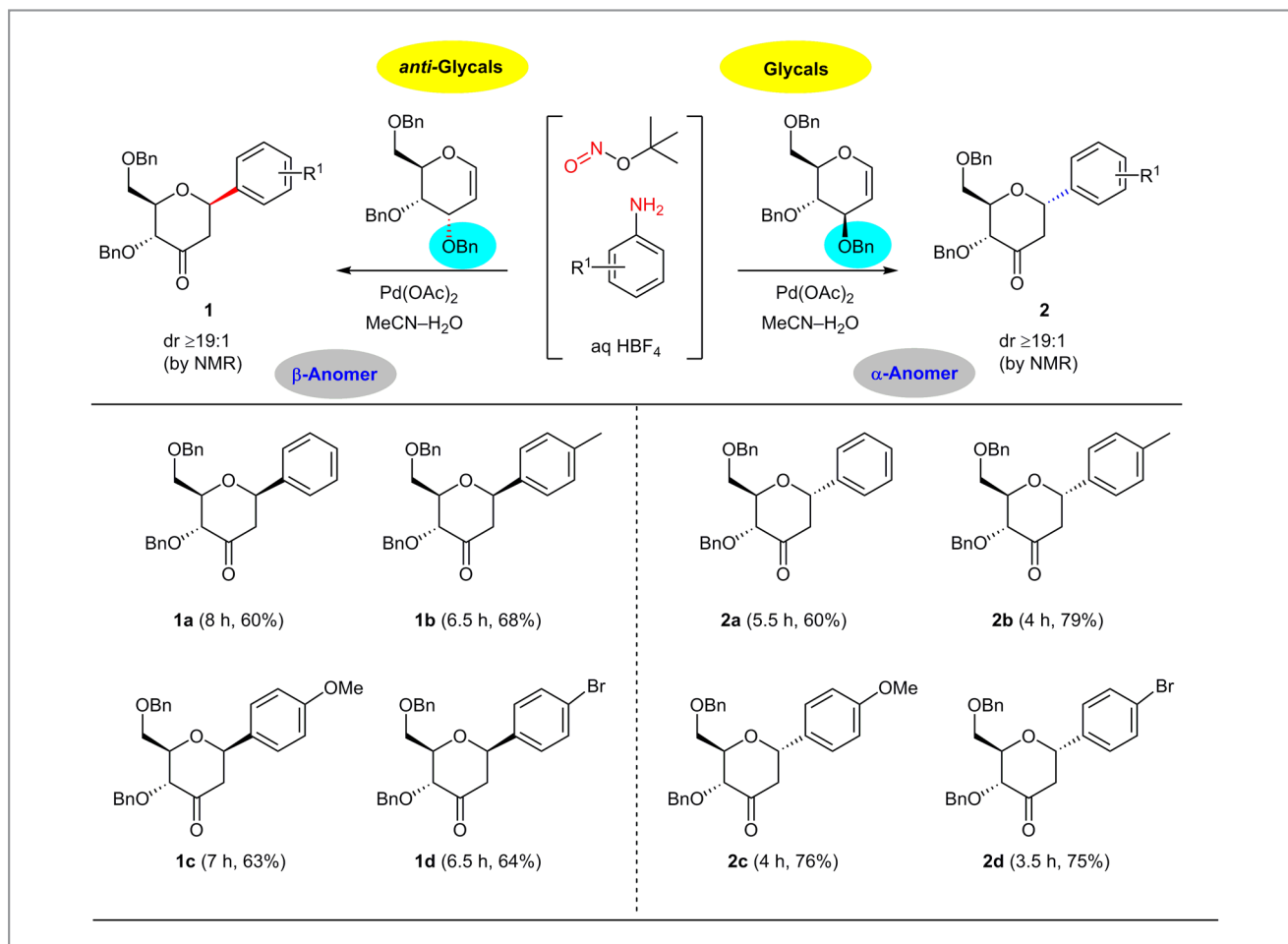
Aryl *C*-glycosides are compounds having direct C–C bonds between the sugar anomeric carbon and the aryl moiety, which are incorporated in various biologically active molecules and natural products.³ Dr. Kandasamy said: “Due to their potential bioactivity and medicinal significance, synthesis of aryl *C*-glycosides has attracted remarkable interest in synthetic organic chemistry.” He continued: “There are two types of aryl *C*-glycosides widely found in bioactive molecules, namely 2-hydroxy aryl *C*-glycosides and 2-deoxy aryl *C*-glycosides. Canagliflozin, dapagliflozin, bergenin, papulacandin, aspalathin, puerarin, mangiferin, cassialoin and ipragliflozin are some examples of bioactive molecules possessing 2-hydroxy aryl *C*-glycoside units.⁵ Angucyclines, marmycin A–B, urdamycinones A–D, kidamycin, pluramycin A, medermycin, saptomycin B and vineomycinone B₂ methyl ester are among the natural products having 2-deoxy aryl *C*-glycoside units.⁶”

Importantly, the stereochemistry at the sugar anomeric carbon plays a key role in the biological activity. “It has been widely noted that most of the bioactive aryl *C*-glycosides (both natural and synthetic) exist as a β -anomer. However, creation of stereocentre at the anomeric centre is a challenging task which requires special care in terms of selection of substrate, protecting groups, reagents, reaction conditions, and so on,” Dr. Kandasamy explained. He continued: “2-Hydroxy aryl β -*C*-glycosides are typically obtained by Friedel–Crafts alkylation of electron-rich arenes with different glycosyl donors⁷ or by

the treatment of organometallic reagents such as aryllithium or aryl Grignard reagents to protected aldonolactones.⁸”

On the other hand, transition-metal-catalyzed cross-coupling reactions are well-established tools for the construction of 2-deoxy aryl *C*-glycosides. Dr. Kandasamy pointed out that Heck-type arylations of glycals with different aryl donors including aryl halides, arylboronic acids, arylzinc reagents, arylhydrazines, arylsulphinates, aryl carboxylic acids, etc. have been developed for the easy preparation of 2-deoxy aryl *C*-glycosides.⁴ “However, most of these methods have drawbacks, such as limited substrate scope, low yield, prolonged reaction time, etc.,” remarked Dr. Kandasamy. He continued: “Moreover, these reactions failed to generate 2-deoxy- β -*C*-aryl glycosides. Therefore, the development of a high-yielding stereochemical protocol for the preparation of 2-deoxy aryl *C*-glycosides remains a challenge in synthetic carbohydrate chemistry.”

Aryldiazonium salts are important synthetic intermediates that have been explored in different palladium-catalyzed cross-coupling reactions.⁹ In particular, as explained by the authors of this paper, aryldiazonium salt mediated Heck couplings of allyl alcohols, allyl ethers and vinyl ethers have received significant attention in organic synthesis, because such reactions take place under ligand-free conditions at room temperature. In this context, Dr. Kandasamy’s team has recently explored the synthesis of 2-deoxy α -aryl *C*-glycosides from aryldiazonium salts and glycals.¹⁰ “The reactions proceeded at room temperature without any additives and gave excellent yields of the desired products,” said Dr. Kandasamy. He continued: “However, to some extent, the extensive use of aryl diazonium salts has been limited in organic synthesis due to their instability and even explosive nature. Considering this fact, here we have developed a one-pot method to access both α and β anomers of 2-deoxy aryl *C*-glycosides stereospecifically from glycals and anilines in the presence of palladium acetate and *tert*-butyl nitrite (TBN) (Schemes 1 and 2). TBN has been used as an *in situ* diazotization reagent when isolation of the unstable aryldiazonium salt intermediate is not required.”



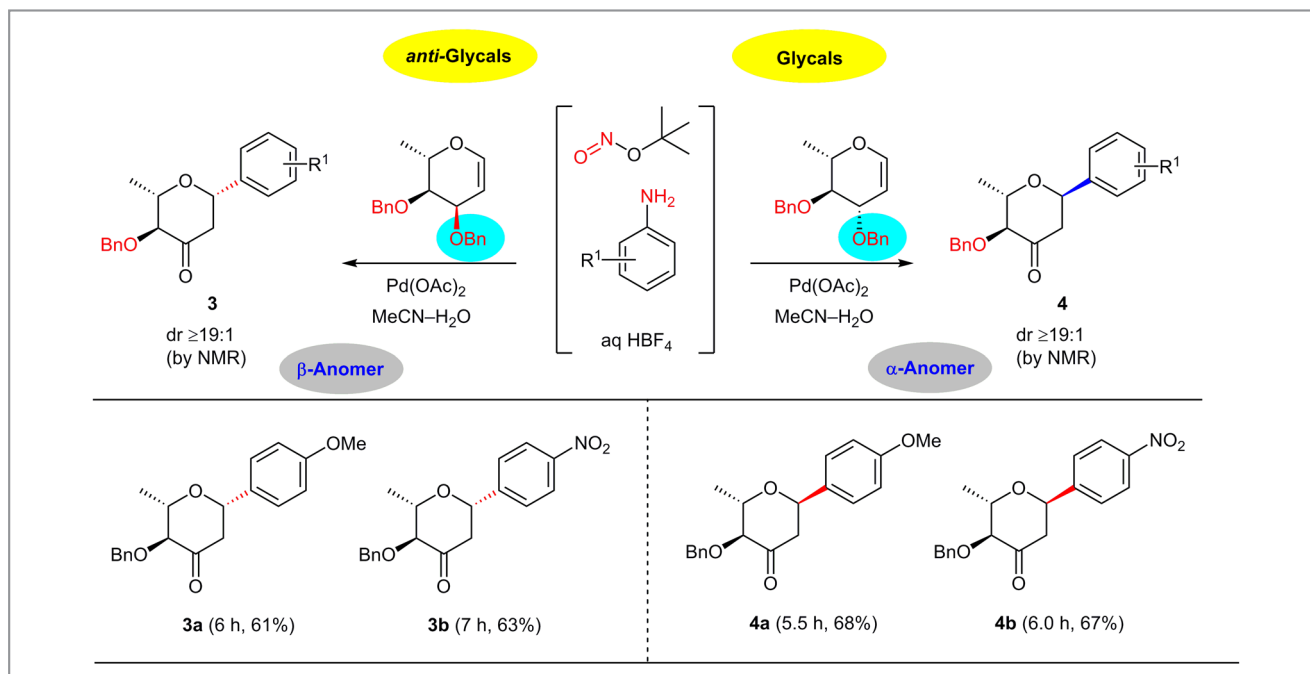
Scheme 1 Stereospecific reaction of tri-*O*-benzyl *D*-glucal and tri-*O*-benzyl *D*-altral (C-3 inverted *D*-glucal) with different anilines

“Basically, this one-pot method was optimized very carefully by changing the different reaction parameters including solvent, catalyst, acid additives, etc. to identify the best conditions that can provide a high yield,” explained Dr. Kandasamy. The team found that under optimized conditions, the glycals such as *D*-glucal, *D*-galactal, *D*-rhamnal, and *L*-rhamnal provided 2,3-deoxy 3-keto α -aryl C-glycosides stereospecifically in high yields. “From the proposed mechanism (Scheme 3), it is clear that the configuration at the C-3 position in the glycal dictates the α -anomeric selectivity through the β -syn-elimination process,” said Dr. Kandasamy. He explained: “One can easily achieve β -anomers of aryl C-glycosides stereospecifically by inverting the configuration at the C-3 position in the glycals. In order to prove that we have synthesized *anti*-glycals (i.e. C-3 inverted glycals) from *D*-glucal and *L*-rhamnal, these products were subjected to the Heck coupling reaction with anilines under optimized conditions. As expected, to our

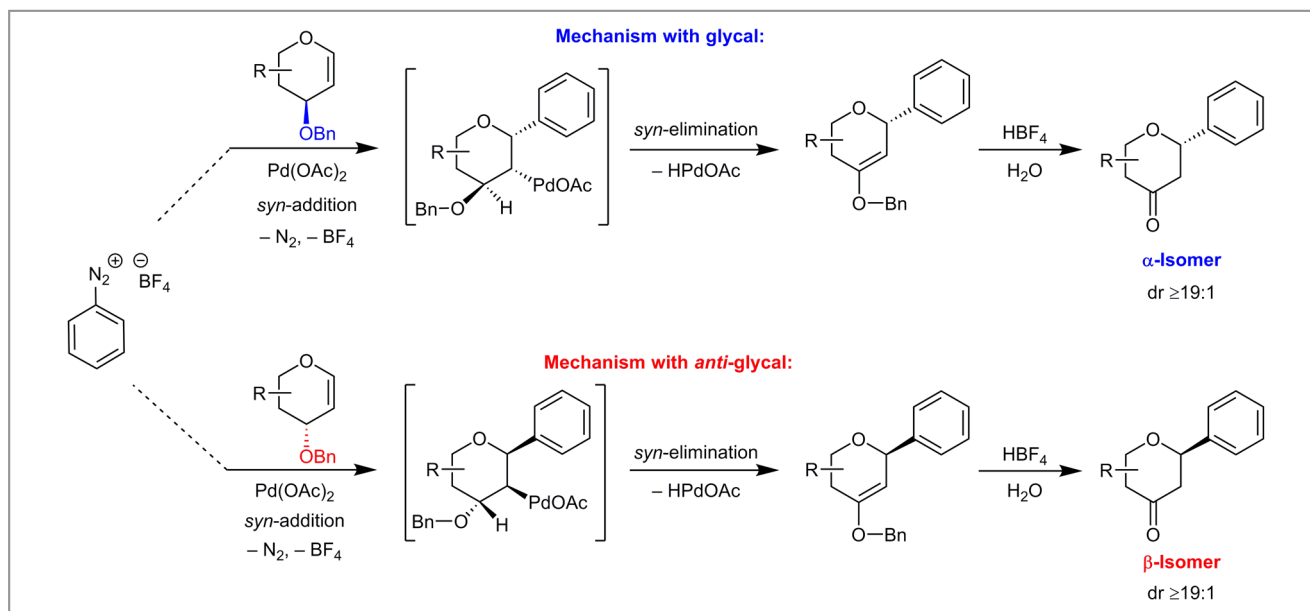
delight, the reactions provided 2,3-deoxy-3-keto β -aryl C-glycosides in good to excellent yields.”

“Overall, the developed protocol provides simple and easy access to α - and β -anomers of 2-deoxy aryl C-glycosides in good yields at room temperature with high stereospecificity,” said Dr. Kandasamy. He concluded: “The current methodology appears to be quite general from a synthetic viewpoint, therefore we hope it will find broad applications for the preparation of biologically relevant aryl-C-glycosides.”

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Scheme 2 Stereospecific reaction of di-O-benzyl L-rhamnal and di-O-benzyl 6-deoxy-L-allal (C-3 inverted L-rhamnal) with different anilines



Scheme 3 Plausible mechanisms for the C-arylation of glycals and anti-glycals

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Dr. J. Kandasamy

Jeyakumar Kandasamy was born in Tamil Nadu, India. He obtained his B.Sc. and M.Sc. from the University of Madras (India) in 2000 and 2003, respectively. In 2008, he obtained his PhD from the Department of Chemistry, Indian Institute of Technology Madras (India) under the supervision of Prof. Dillip Kumar Chand. After his PhD, he worked with Prof. Timor Baasov in Technion-Israel (2008–2011) and Prof. Peter H. Seeberger in Max-Planck Institute of Colloids and Interfaces, Berlin, Germany (2012–2013) as a postdoctoral fellow. In June 2014, he joined the Department of Chemistry, Indian Institute of Technology (BHU), Varanasi (India) as an Assistant Professor. In August 2019, he was promoted to Associate Professor in the same institute. His research focus is organic synthesis covering catalysis, synthetic methodology, and carbohydrate synthesis.

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