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Note

Synthesis of 6-isopropoxy-2-phenyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine *via* palladium catalysed O-glycosylation

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One of the important and known processes in the chemistry of carbohydrates is the glycosylation reaction, in which C–O bonds are commonly used to join two different units. One of the most difficult but crucial aspects of glycochemistry to be addressed in the quest to advance this field is the design and development of sustainable catalytic methods for O-glycosylation. Herein, is described a straight forward and effective O-glycosylation technique using palladium as a catalyst, which involves triggering the activity of a phenylpropiolate glycoside donor.

Keywords: Palladium, Glycosylation, Donor, Intermolecular, Nucleophilic addition

In a vital class of biomolecules, oligosaccharides and glycoconjugates, where one sugar unit is coupled with another sugar unit or any other molecules (aglycons), the primary bond is the glycosidic connection. Since glycosidic bonds, which are abundant in natural biopolymers and play a crucial and important role in regulating a variety of biological processes, are made when one sugar unit is attached to another sugar unit or to any other molecule *via* a carbon-oxygen (C-O) bond, there has been a persistent interest in the developing a practical and effective synthetic method for creating these bonds[1]. Chemical glycosylation reactions heavily depended on fully or partially protected saccharides with a leaving group at the anomeric site, a glycosyl donor. Glycals, thioglycosides, glycosyl halides, glycosyl trichloroacetimidates, and others are a few of the well-known glycosyl donors[2]. However, these widely used glycosyl donors often have disadvantages such as limited donor stability, necessitating an equimolar quantity of promoters, requiring costly and toxic metal catalysts, and requiring the use of chemicals that smell bad[3,4]. Thus, glycochemists have been very interested in the creation of stable and effective glycosyl donors with a leaving group that may be quickly added and effectively glycosylated (Fig. 1, Fig. 2). In order to solve these problems, so many glycochemist introduced the bifunctional leaving group in past[5]. As a result, there is a constant need in the field of glycochemistry to develop an effective and adaptable glycosyl donor that can be prepared directly in one step and may regenerate an easily separated and reusable leaving group. Recently a group predicted that the bifunctional phenylpropiolate glycosides that result from combining lactose with phenylpropiolic acid that is readily available in the market would be ideal for use as a reliable and effective glycosyl donor. With the sole regeneration of phenylpropiolic acid and oxocarbenium ion, the alkyne group next to the ester moiety in may aid in the site-control activation with metal, which would lead to the breaking of the anomeric bond[6]. Numerous practical and effective techniques utilizing metal catalysts for the production of distinct glycosidic linkages with superior selectivity, have surfaced in recent times. However, Liu's group has reported using phenol type acceptors and a Pd-π-allyl intermediate as an effective glycosyl donor with activator in an electron-rich glycal system. Based on these circumstances, Liu's group's studies showed that the decarboxylative allylation, which has been thoroughly studied by numerous innovative groups, offered a feasible substitute for more active allylic carbonates[7]. It was discovered that the primary driving factor, the release of CO_2, accelerated and improved the formation of Pd-π-allyl species from carbonate

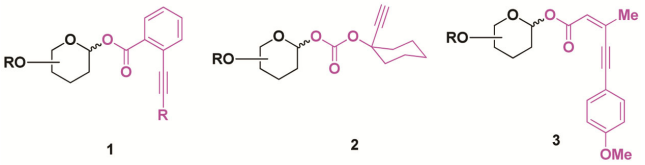


Fig. 1 — Stable Glycosyl donor with leaving group

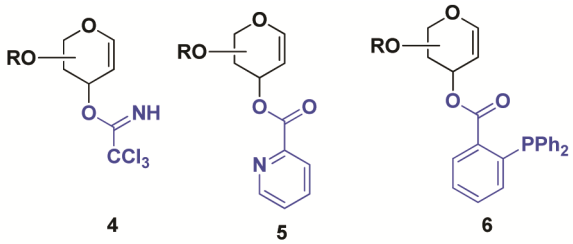
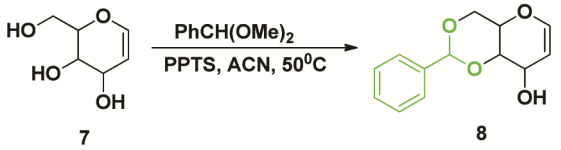


Fig. 2 — Stable protected glucal donor with leaving group

substrates. Furthermore, the resulting Pd-π-allyl intermediate is capable of effectively taking part in an intramolecular nucleophilic addition[8]. Herein, we first prepare the protected glycal with leaving group and followed by the intermolecular nucleophilic addition in the presence of palladium catalyst.



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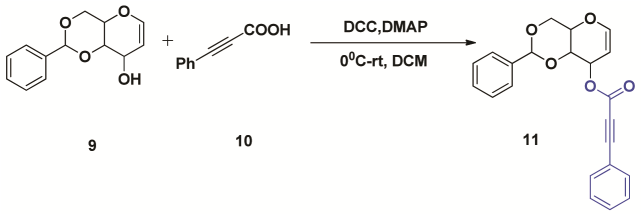
Scheme 1 — Synthesis of 2-phenyl-4,4a,8,8a-tetrahydropyrano [3,2-d][1,3]dioxin-8-ol



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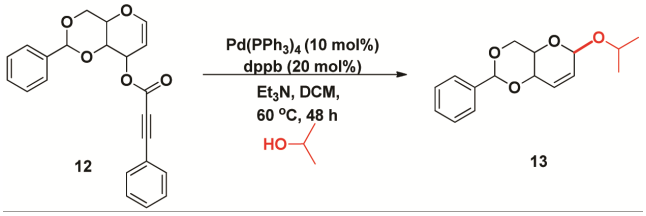
Scheme 2 — Synthesis of 2-phenyl-4,4a,8,8a-tetrahydropyrano [3,2-d][1,3]dioxin-8-yl 3-phenylpropiolate



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Scheme 3 — Synthesis of 6-isopropoxy-2-phenyl-4,4a,6,8a-tetrahydropyrano [3,2-d][1,3]dioxine

Results and Discussion

First 2-phenyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3] dioxin-8-ol was prepared (Scheme 1)[10]. Then the glucal donor was prepared from 2-phenyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-ol and phenyl-propiolic acid (Scheme 2)[9]. For the synthesis of 6-isopropoxy-2-phenyl-4,4a,6,8a-tetrahydropyrano[3,2-d] [1,3]dioxine (Scheme 3), the nucleophile 2-propanol was chosen as the acceptor. The reaction was expected to proceed through an intermolecular nucleophilic addition. Hence, the product was observed. We optimized reaction conditions at two different time with 10% $[Pd(PPh_3)_4]$ as a catalyst and 20% dppb as a ligand in CH_2Cl_2 at 60°C (Table 1).

Experimental Section

The glucal donor (12) (0.1 mmol), nucleophile (0.2 mmol), Et_3N (2.2 equiv), $[Pd(PPh_3)_4]$ (0.01 mmol) and dppb (0.02 mmol) were dissolved in CH_2Cl_2 (2 mL) in a sealed tube under a nitrogen atmosphere. The reaction mixture was heated at 60°C for 48 h. After that solvent was removed under reduced pressure and the residue was purified by the column chromatography to get the desired O-glycosides.

2-Phenyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3] dioxin-8-yl 3-phenylpropiolate (Fig. 3): ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.28− 7.60 (m, 10H), 6.44 (d, J = 8 Hz,

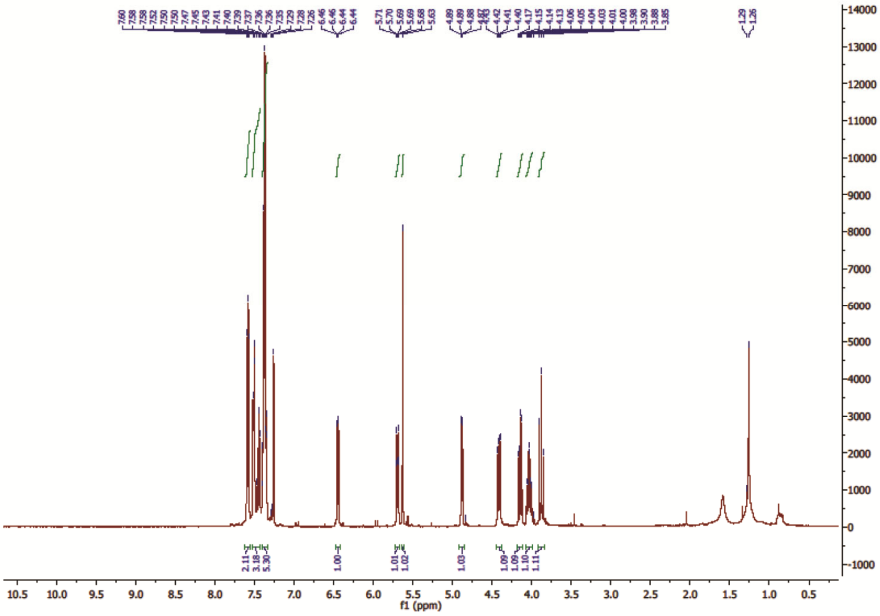

Fig. 3 — ^{1}H NMR of 2-phenyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl 3-phenylpropiolate

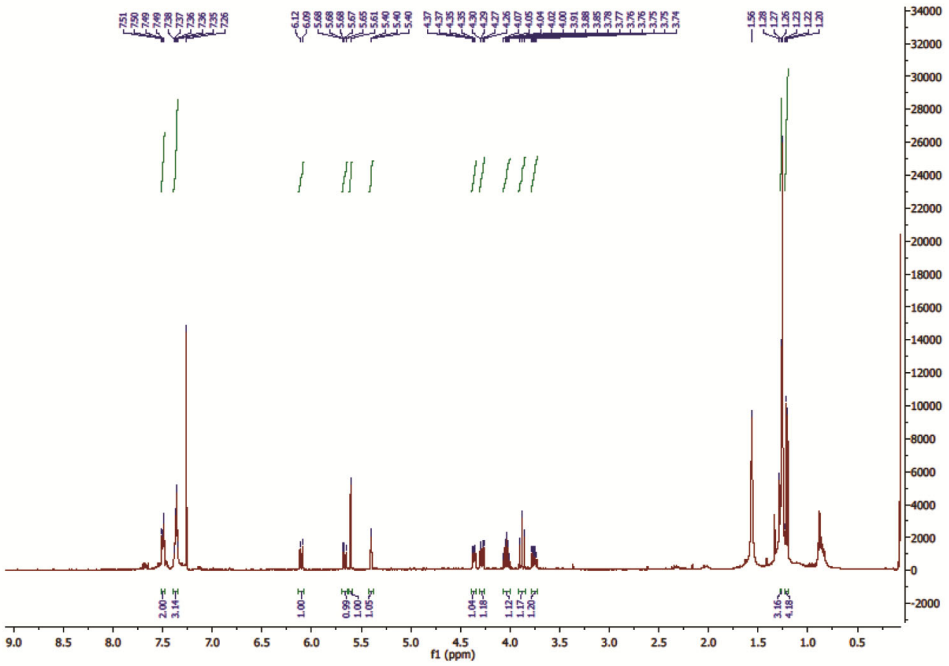

Fig. 4 — ^{1}H NMR of 6-isopropoxy-2-phenyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine

Table 1 — Optimization table of compound **13**

S. No.	Time (h)	Yield (%)
1	12	–
2	24	35
3	48	60

1H), 5.68− 5.71 (m, 1H), 5.63 (s, 1H), 4.87(d, J = 8 Hz, 1H), 4.40 (m, 1H), 4.13-4.17 (m, 1H), 3.98-4.06 (m, 1H), 3.85−3.90 (m, 1H).

6-Isopropoxy-2-phenyl-4,4a,6,8a-tetrahydropyrano [3,2-d][1,3]dioxine (Fig. 4): ^{1}H NMR (400MHz, $CDCl_3$): δ 7.36− 7.55 (m, 5H), 6.09 (d, J = 12 Hz, 1H), 5.67− 5.68 (m, 1H), 5.40 (s, 1H), 4.35−4.37 (m, 1H), 4.26−4.30 (dd, 1H), 4.00-4.07 (p, 1H), 3.85-3.87 (t, J = 12 Hz, 1H), 3.74−3.78 (m, 1H), 1.26 (d, 3H), 1.20 (d, 3H).

Conclusion

In conclusion, we have reported a palladium-catalyzed intermolecular glycosylation and we get the desired with good yields.

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Conflict of interest

The authors declare no conflict of interest.

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