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Palladium catalysed carbonylation of 2-iodoglycals for the synthesis of C-2 carboxylic acids and aldehydes taking formic acid as a carbonyl source†

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Pd catalyzed carbonylative reaction of 2-iodo-glycals has been developed taking formic acid as a carbonyl source for the synthesis of 2-carboxylic acids of sugars by the hydroxycarbonylation strategy. The methodology was successfully extended to the synthesis of 2-formyl glycals by using a reductive carbonylation approach. Both ester and ether protected glycals undergo the reaction and furnished sugar acids in good yield which is otherwise not possible by literature methods. The C-2 sugar acids were successfully utilized for the construction of 2-amido glycals, 2-dipeptido-glycal by Ugi reaction and C-1 and C-2 branched glycosyl esters.

Sugar acids constitute a diverse family of carbohydrates[1] which play a crucial role in cell–cell recognition, cellular adhesion, and virus–host recognition processes, for protection of cells from pathogen attachment, and in the synthesis of biologically active natural products.[2] α,β-Unsaturated sugar acids such as zanamivir and ianinamivir (Fig. 1) are subjects of particular interest because of their application as inhibitors of different glycoproteins such as hemagglutinin (HA) and neuraminidase (NA),[3] the major glycoproteins expressed by influenza viruses. While several reports dealing with the synthesis of carboxylic acids at C-6 and C-1 positions of sugars exist,[4a,b] there is no established procedure for the synthesis of C-2 carboxylic acids. In glycals accessing carboxylic group at C-1 position required *t*-butyl lithium and carbon dioxide treatment at −78 °C.[4c] There is only one report available in the literature in which carboxylic group was introduced to the C-2 position of glycals by Furstner *et al.*[4c,d] where the C-2 carboxylic acid was derived from the Pinnick oxidation of 2-formyl glycal obtained by classical Vilsmeier–Haack reaction[5] and thereafter utilized in the total synthesis of bioactive natural orevactaene (exhibits HIV-1 inhibitory property). This strategy has certain drawbacks like long reaction times with cocktails of oxidants and limited substrate specificity. For example, it works only with ether protected sugars like tri-*O*-benzyl-D-glycal and fails with other base labile and silyl protecting groups. Further, recovery of 2-formyl glycals after base workup is rather low in our hand. Our experience with glycals[6a–f] encouraged us to formulate an attractive way to launch carboxylic acid at C-2 position of glycals as shown in Scheme 1 and apply them in the synthesis of C-2 glycoconjugates.

This is pertinent to mention that carbonylation reactions of C-2 glycals have been successfully carried out by using metal carbonyl for the synthesis of C-2 branched glycoconjugates.[7a,b] In these reaction stoichiometric amount of costly $Mo(CO)_6$ is required for such transformation that too ends up with some non-carbonylative side products. CO surrogates[8,9] such as formic acid, formamide, chloroform and anhydride have been explored in recent times obviating metal carbonyls and CO gas. Among all formic acid is an attractive candidate for insertion of CO in an organic molecule,[10] because it liberates one water molecule after releasing one CO molecule thereby making the process environmentally benign. We felt that palladium catalyzed hydroxycarbonylation of stable glycal halides, which are conveniently accessed from glycals in good yield, may prove to be the most effective and environmentally benign method to prepare such molecules. With our continuous interest in synthesis of C-2 branched sugars,[11] this time we developed a reagent system for the direct synthesis of C-2 sugar

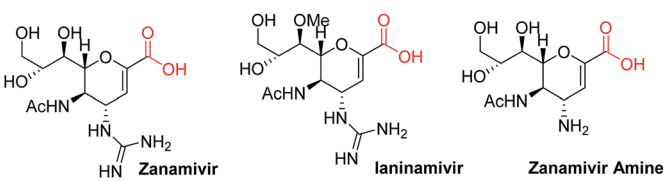

Fig. 1 Glycal based acids in drugs.

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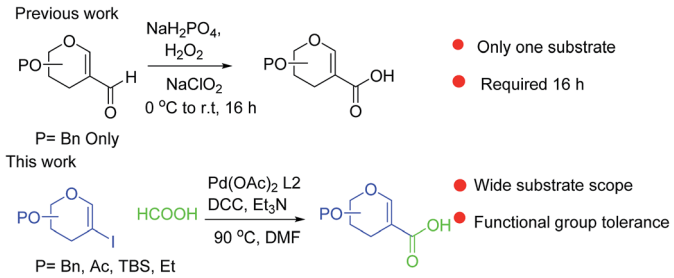


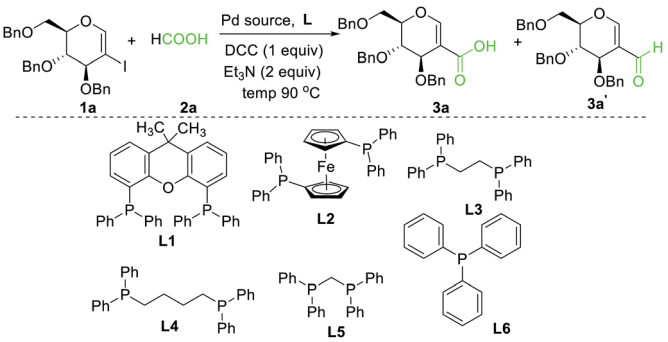
Scheme 1 Art of launching carboxyl group in sugars.

carboxylic acids from 2-iodo glycals using formic acid as carbonyl source. Further, we transformed the synthesized acid for the synthesis of different C-2 branched glycoconjugates.

Preliminary experiments were conducted by using 2-iodo-glycal **1a**, HCOOH as carbonyl source, *N*,*N*′-dicyclohexylcarbodiimide, (DCC) as an activator and xantphos as a ligand. When **1a** was reacted with 5 mol% $Pd(OAc)_2$, 10 mol% of xantphos, 1 equiv. of DCC, 2 equiv. of formic acid and 2 equiv. of triethyl amine as base in DMF at 90 °C for 16 h the desired product **3a** was obtained along with **3a**′ in 60 : 40 ratio with overall 63% yield (Table 1, entry 1). Perusal of the literature revealed that ligands play a crucial role in such carbonylation reactions. In order to synthesize selectively the desired product **3a**, we then decided to screen different ligands starting with the bidentate ligand **L2**, keeping other parameters as in entry 1. To our delight complete conversion of starting material was observed with **3a** as exclusive product in 72% yield (Table 1, entry 2). Encouraged with this result, we next reduced the reaction period to 6 h (Table 1, entry 3) to note that the yield went up to 80%. Further reduction of the time period to 1.5 h still enabled complete conversion along with improved yield (81%) of **3a** without any detrimental effect on selectivity (Table 1, entry 4), but reduction in reaction time to 1 h led to decrease in yield (Table 1 entry 5). Other ligands such as **L3**, **L4**, **L5** and **L6** produced mixture of both **3a** and **3a**′ along with poor overall yields (Table 1 entry 6–9). Next we investigated the role of different Pd catalysts such as $Pd(PPh)_3$, $Pd(TFA)_2$ and $PdCl_2$ (Table 1 entry 10–12) and found that $Pd(OAc)_2$ is the best catalyst for this transformation.

Utilising the optimised reaction condition (Table 1, entry 4), we then checked the substrate scope (Table 2) using different 2-iodo-glycals. Di-*O*-benzyl-2-iodo-L-rhamnal **1b** was tested to get a better yield of the product **3b**, (85%). The galactal substrate also furnished the desired 2-carboxyl galactal **3c** in good yield (76%). In order to broaden the substrate scope the reactivity of glycals protected with different protecting groups was next investigated. Gratifyingly, 2, 3-acetonide protected 2-iodo-D-

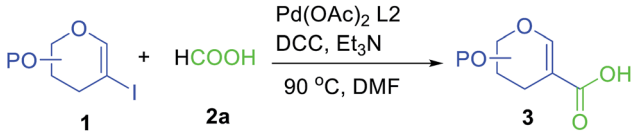
Table 1 Optimization of the reaction conditions[a]



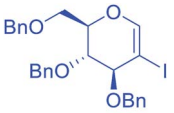
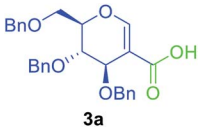
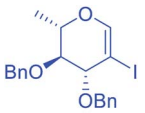
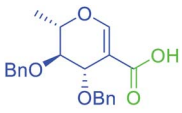
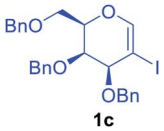
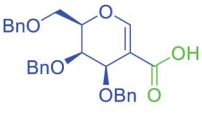
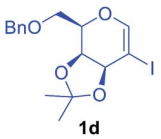
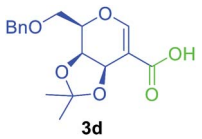
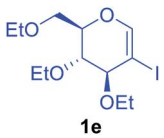
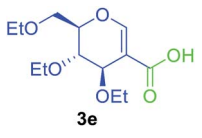
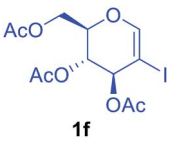
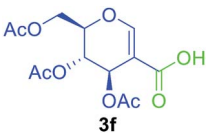
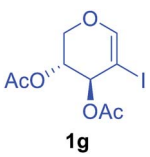
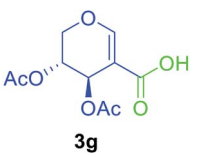
Entry	Pd source	Ligand	Time (h)	Conversion (%)	(**3a** : **3a**′)	Yield[b] (overall)%
1	$Pd(OAc)_2$	**L1**	16	90	60 : 40	63
2	$Pd(OAc)_2$	**L2**	16	99	>99 : 1	72
3	$Pd(OAc)_2$	**L2**	6	99	>99 : 1	80
4	**$Pd(OAc)_2$**	**L2**	**1.5**	**99**	**>99 : 1**	**81**
5	$Pd(OAc)_2$	**L2**	1	90	>99 : 1	73
6	$Pd(OAc)_2$	**L3**	16	40	45 : 55	23
7	$Pd(OAc)_2$	**L4**	16	30	30 : 70	15
8	$Pd(OAc)_2$	**L5**	16	10	—	Traces
9	$Pd(OAc)_2$	**L6**	16	10	—	Traces
10	$Pd(PPh)_3$	**L2**	2	75	>99 : 1	21
11	$Pd(TFA)_2$	**L2**	2	35	>99 : 1	27
12	$PdCl_2$	**L2**	2	23	>99 : 1	11

[a] Reaction conditions: **1a** (0.18 mmol), **2a** (0.36 mmol), $Pd(OAc)_2$ (0.009 mmol), **L2** (0.018 mmol), *N*,*N*′-dicyclohexylcarbodiimide (DCC) (0.18 mmol), triethylamine (0.36 mmol) at 90 °C for 2 h. [b] Yield of isolated product. Pd 5 mol% and ligand 10 mol% were used. Ratio of **3a** and **3a**′ and conversion were determined through ^{1}H NMR.

Table 2 Substrate scope[a]

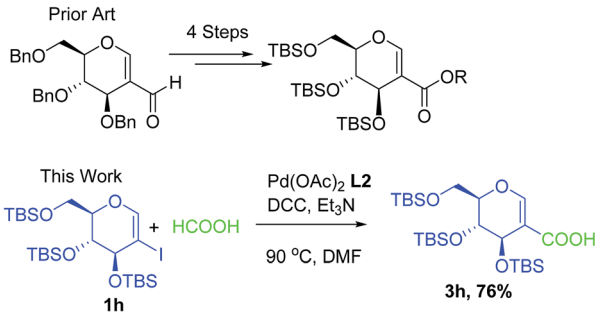


1 2a 3

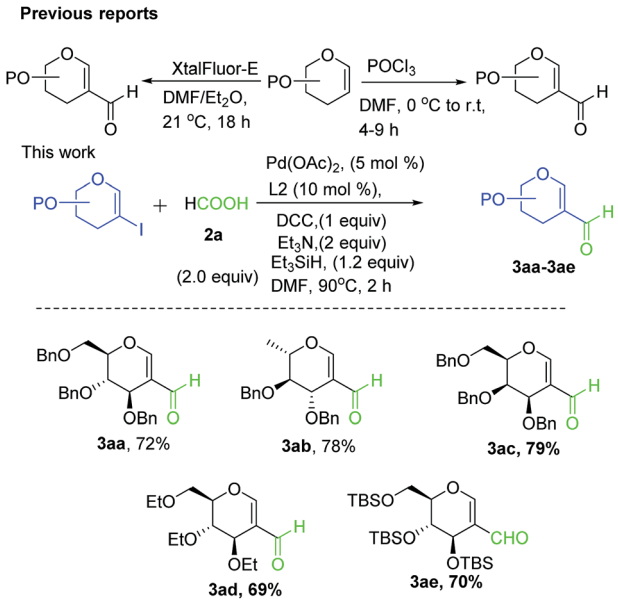
Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	 1a	 3a	1.5	81
2	 1b	 3b	1.5	85
3	 1c	 3c	1.5	76
4	 1d	 3d	1.5	75
5	 1e	 3e	2	76
6	 1f	 3f	2.5	73
7	 1g	 3g	2.5	75

[a] Reaction conditions: **1** (1 equiv.), **2a** (2 equiv.), $Pd(OAc)_2$ (5 mol%), **L2** (10 mol%), DCC (1 equiv.), triethylamine (2 equiv.) at 90 °C for 1.5 to 2.5 h in 3 mL of DMF. [b] Yield of isolated product.

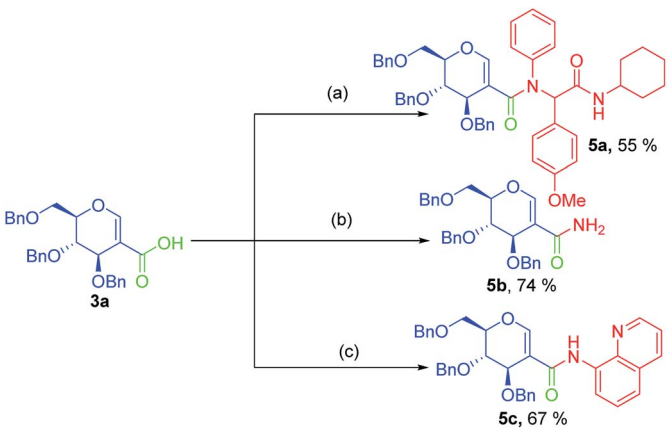
galactal **1d** survived under the reaction condition and yielded the product **3d** in good yield (75%). Tri-*O*-ethyl-2-iodoglucal **1e** also reacted well and formed the respective acid derivative **3e** in (76%) yield. Next we utilized different glycals having silicon based protection or ester protection. Tri-*O*-acetyl-2-iodoglucal **1f** and di-*O*-acetyl-2-iodoxylal **1g** were also well tolerated under the reaction condition and gave the desired products **3f–3g** in reasonable yields (73–75%). 2-Bromo-glucal was next tested under the optimized reaction condition and the desired



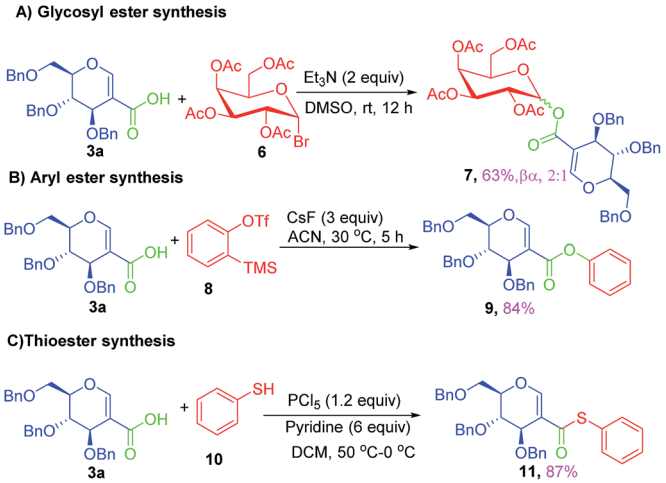
Scheme 2 Synthesis of silyl protected C-2 carboxylic acid.



Scheme 3 Synthesis of 2-formyl glycals.



Scheme 4 Synthesis of amides using **3a**. Reaction conditions: (a) **3a** (1.5 equiv.), aniline (1 equiv.), anisaldehyde (1 equiv.), cyclohexyl isocyanate (1 equiv.) in ethanol at rt for 48 h; (b) **3a** (1.0 equiv.), $SOCl_2$ (1.5 equiv.), NH_4OH (37%, 2 mL) in THF for 2 h; (c) **3a** (1.0 equiv.), PCl_5 (1.2 equiv.), pyridine (6 equiv.), 8-aminoquinoline (1.2 equiv.) in DCM for 5 h.



Scheme 5 Utilization of **3a** for establishing ester linkages.

compound **3a** was obtained in good yield although it takes 3 h to complete the reaction.

TBS protected sugars acids are used in the total synthesis of various bioactive natural products by activating the anomeric carbon which is otherwise not possible with other protecting groups. In the literature in order to get such types of acids multiple steps are required along with poor overall yield. By utilizing carbonylation strategy under Pd catalysis we were able to synthesis the TBS protected acids in just 2 h when substrate **1h** was reacted with HCOOH under Pd catalysis to generate product **3h** in good yield.

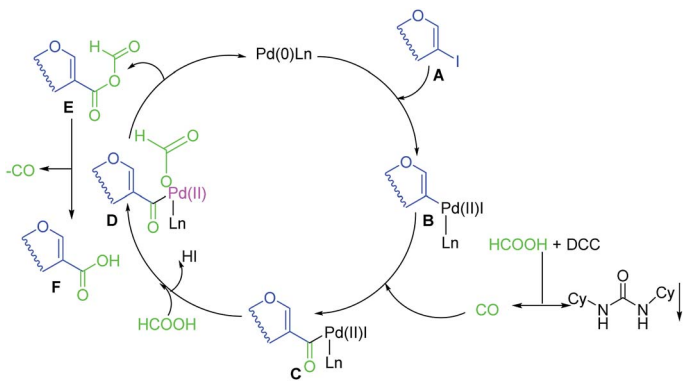
After successful execution of our strategy for hydroxycarbonylation of 2-iodoglycals, we became interested to apply the same carbonylative approach for the synthesis of 2-formyl glycals. In the literature formylation at C-2 of glycals has been carried out either by Vilsmeier–Haack or XtalFluor-E catalyzed reactions (Scheme 3).[5,12] We utilized the reductive carbonylation approach employing triethylsilyl hydride (1.2 equiv.) as a hydride source keeping other reagents same as for acid synthesis. To our delight, the required 2-formyl glycals were obtained in good to excellent yields (Scheme 3, **3aa–3ae**).

To test the utility of sugar acids in the synthesis of C-2 glycoconjugates, sugar acid **3a** was successfully utilized for the synthesis of C-2 linked dipeptides *via* Ugi reaction (Scheme 4, **5a**). The simple amide **5b** was also synthesised from **3a** using thionyl chloride and ammonium hydroxide; the product is otherwise difficult to synthesize *via* the existing methods. Where substituted amides are synthesized. The acid chloride of **3a** could be successfully coupled with 8-aminoquinoline, leading to the amide **5c** in good yield. In order to test the reactivity of the acid **3a**, we used it as a glycosyl acceptor in glycosylation reaction by treating with a suitable glycosyl donor like **6**, when the pseudodisaccharide **7** was isolated in good yield (63%) with a mixture of anomers. On the other hand, treatment with aryne precursor **8** resulted in the formation of compound **9** in excellent yield (84%) *via* coupling of aryne with the sugar acid. When sugar acid **3a** was treated with thiophenol thioester **11** was isolated in excellent yield (Scheme 5).

A plausible reaction mechanism has been proposed for hydroxycarbonylation of 2-iodoglycals (Scheme 6). Initially Pd(0) is generated *in situ* in the presence of ligand L*n*. The catalytic cycle then starts with oxidative addition of Pd(0) to 2-iodoglycal **A** which produces the pallado complex **B**.

Coordination and insertion of carbon monoxide generated *in situ* by the combination of DCC and formic acid leads to the formation of acyl Pd(II) complex **C**. Formic acid attack on complex **C** *via* transmetallation affords the intermediate **D** with release of HI. Pd(0) could be regenerated for the next catalytic cycle after reductive elimination from complex **D** with formation of anhydride **E**. Decomposition of the anhydride with release of one molecule of CO generates the desired sugar acid **F**.

In conclusion we have developed an efficient and mild Pd catalysed synthetic strategy for hydroxycarbonylation of 2-iodoglycals using the cheap reagent formic acid as CO source and 1 equiv. of DCC as an activator. The methodology was successfully extended to various glycals with different protecting groups like acetonide, ether, ester and silicon based ones. 2-Formyl glycals were also synthesised by using reductive carbonylation approach. The synthesised sugar acid could be used in the synthesis of glycoconjugates, pseudodisaccharides, for aryl ester and thioester.



Scheme 6 Plausible mechanism of hydroxycarbonylation reaction.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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