C-Glycosylation

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Stereoselective β-*C*-Glycosylation by a Palladium-Catalyzed Decarboxylative Allylation: Formal Synthesis of Aspergillide A**

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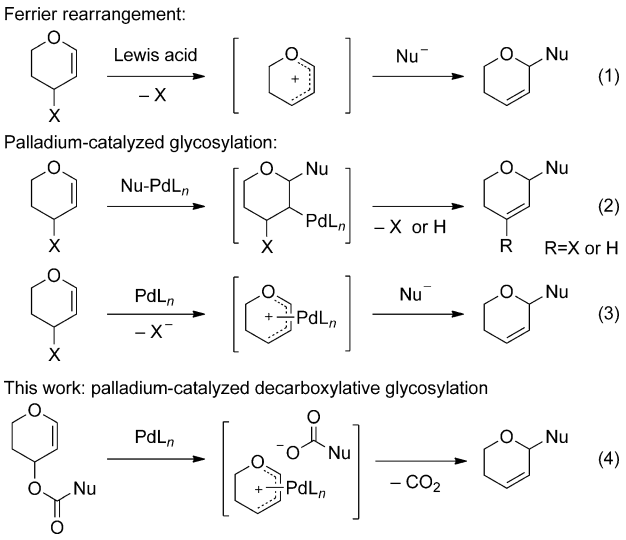
The efficient stereoselective construction of glycosidic linkages is indubitably a principal focus in carbohydrate chemistry because it is necessary for the construction of natural glycoconjugates.[1] Among the wide variety of glycosylation methods, the Ferrier reaction has received considerable attention as it provides convenient and direct access to 2,3-unsaturated glycosides from glycals.[2] However, the stringent requirement of glycosyl acceptors generally confines the reaction to specific nucleophiles with strong reactivity and the utilization of stoichiometric amounts of a Lewis acid is inevitable in some cases. In addition, the dominant anomeric effect leads to the stereoselective generation of α-glycosides for Ferrier-type *O*-glycosylation and therefore accents the rigidity of the reaction.[3] On the other hand, most results from Ferrier *C*-glycosylation reactions remain mediocre as only moderate α-selectivity has been achieved. The pursuit of high β-selectivity is also extremely challenging and judging from the lack of substantial reports, the barriers surrounding this problem has not been solved. [Scheme 1, Eq. (1)].[4] Consequently, the combination of limitations surrounding the Ferrier reaction prompted researchers to develop other methods to synthesize 2,3-unsaturated glycosides in exclusive selectivity, especially β-selectivity.

Recent demonstrations on the efficiency of palladium-catalyzed coupling reactions have stimulated considerable interest in applying this strategy to carbohydrates, particularly for the synthesis of 2,3-unsaturated glycosides. One of the successful and prominent examples is the Heck-type glycosylation of glycals with arylboronic acids or aryl halides by transition-metal insertion and reductive elimination [Scheme 1, Eq. (2)].[5] The allylic feature of glycals also encouraged chemists to pursue the applicability of palladium-catalyzed allylic alkylation[6] in glycosylation reactions [Scheme 1, Eq. (3)]. However, the formation of Pd π-allyl species in glycal systems has long been recognized as tedious and difficult.[7] To overcome this challenge, the more activated pyranone system was generated and additional activators were employed.[8] Following the removal of this hurdle, great strides were made in decarboxylative allylation (DcA).[9,10] In particular, intramolecular decarboxylative allylation has developed into an area of great potential among the transition-metal-catalyzed decarboxylative coupling reactions which have drawn considerable attention in the area of C–C bond formation.[11] The Tunge,[12] Trost,[13] and Stoltz groups,[14] for instance, have reported a series of catalytic decarboxylative allylation and benzylation reactions.[15] Inspired by these reports, we envisioned that the palladium-catalyzed decarboxylation of the C-3 ester of glycal would be helpful in the formation of a Pd π-allyl intermediate which might accomplish the desired *C*-glycosylation with high stereoselectivity [Scheme 1, Eq. (4)]. In a continuation of our work on developing efficient glycosylation methods,[5e,f,16] we report herein on a palladium-catalyzed stereo- and regioselective *C*-glycosylation by means of intramolecular decarboxylative coupling.



Scheme 1. Various types of glycosylation.

In initial studies, the decarboxylative coupling reaction of compound **1a** was carried out in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ in DMF at 80 °C for 12 h. To our delight, the regiospecific coupling product **2a** was obtained in 50% yield with a β/α ratio of 6:1 (Table 1, entry 1). To improve the yield and selectivity, various Pd catalysts were screened with the 1,2-bis(diphenylphosphino)ethane (DPPE) ligand in DMF (Table 1, entries 2–4). We found that the reaction catalyzed by $Pd(OAc)_2$ gave better yield and

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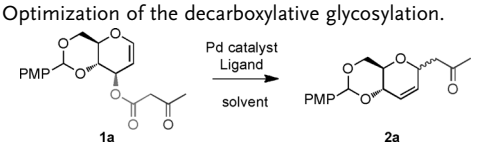
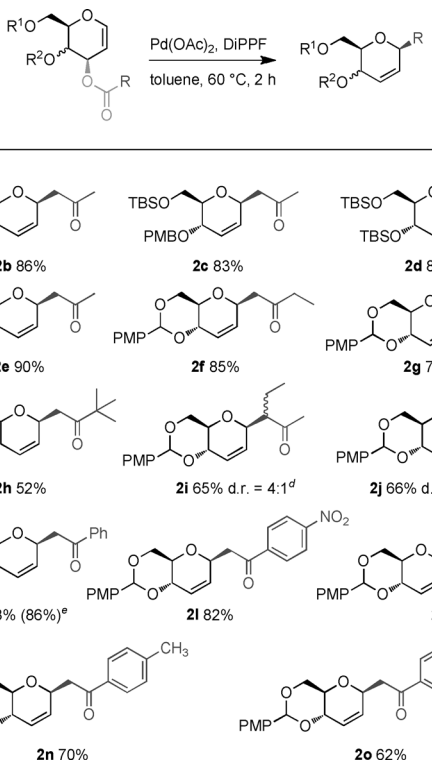
Table 1: Optimization of the decarboxylative glycosylation.



1a 2a

Entry	Cat./ligand	Solv.	*T* [°C]	Yield [%][a]	β/α
1	$[Pd(PPh_3)_4]$	DMF	80	50	6:1
2[b]	$[Pd_2(dba)_3]$/DPPE	DMF	80	38	20:1
3[b]	$Pd(OAc)_2$/DPPE	DMF	80	50	20:1
4[b]	$PdCl_2$/DPPE	DMF	80	–	–
5[b]	$Pd(OAc)_2$/DPPE	THF	80	51	>20:1
6[b]	$Pd(OAc)_2$/DPPE	toluene	80	58	>20:1
7[b]	$Pd(OAc)_2$/DPPE	CH_2Cl_2	40	–	–
8[b]	$Pd(OAc)_2$/DPPE	MeCN	80	55	>20:1
9[c]	$Pd(OAc)_2$/DPPE	toluene	80	68	>20:1
10[c]	$Pd(OAc)_2$/DPPE	toluene	60	80	>20:1
11[c]	$Pd(OAc)_2$/DPPE	toluene	40	trace	n.d.
12[c]	$Pd(OAc)_2/PPh_3$	toluene	60	70	5:1
13[c]	$Pd(OAc)_2$/DPPP	toluene	60	71	10:1
14[c]	$Pd(OAc)_2/PCy_3$	toluene	60	–	–
15[c]	$Pd(OAc)_2$/BINAP	toluene	60	15	β only
16[c]	$Pd(OAc)_2$/DiPPF	toluene	60	90	β only

[a] Yield of isolated product.[b] The reaction was conducted for 12 h. [c] The reaction was conducted for 2 h. BINAP = 2,2′-bis(diphenylphosphino)-1-1′-binaphthyl, n.d. = not determined, PMP = 4-methoxyphenyl.



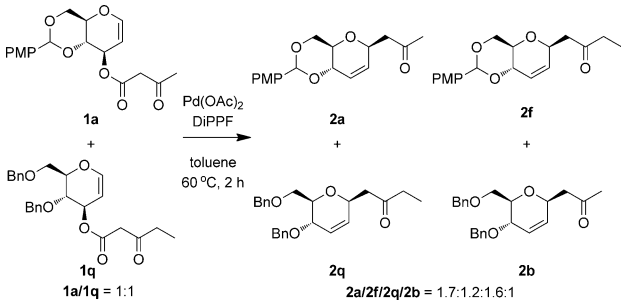
Scheme 2. Decarboxylative glycosylation of glycal-derived β-keto-esters.[a–c] [a] Reactions were carried out on a 0.2 mmol scale in the presence of 0.01 mmol $Pd(OAc)_2$ and 0.02 mmol DiPPF in 2 mL toluene at 60 °C for 2 h. [b] Yield of isolated product. [c] PMP = 4-methoxyphenyl. [d] d.r. was determined by ^{1}H NMR analysis. [e] Yield for a gram-scale reaction.

diastereoselectivity (Table 1, entry 3) than those catalyzed by $[Pd_2(dba)_3]$ and $PdCl_2$ (Table 1, entries 2 and 4). The diastereoselectivity of the reaction catalyzed by $Pd(OAc)_2$ and DPPE in toluene is superior to that in DMF, THF, CH_2Cl_2,and MeCN (Table 1, entries 5–9). Decreasing the reaction temperature to 60 °C improved the yield to 80 % (Table 1, entry 10). This is because the sugar scaffold is prone to decompose at high temperatures. However, when the temperature was further decreased, the reaction was sluggish and only a trace amount of the product was obtained (Table 1, entry 11). In further ligand screening (Table 1, entries 12–16) excellent yield (90 %) and exclusive diastereoselectivity were obtained when the model reaction was carried out under the optimal conditions, which consists of $Pd(OAc)_2$ and 1,1′-bis(diisopropylphosphino)ferrocene (DiPPF) in toluene at 60 °C for 2 h. The stereoselective formation of compound **2a** was further confirmed by X-ray structure analysis (see the Supporting Information).

This result motivated us to continue our study of this decarboxylative glycosylation. Gratifyingly, similar results were obtained for substrates with other protecting groups and the results are summarized in Scheme 2. The protecting groups on glucal, such as benzyl, TBS, and PMB groups, did not have any undesirable effect on the reaction and similar yields and β-anomers were afforded exclusively (Scheme 2, **2b**–**2d**). Moreover, the decarboxylative glycosylation of the 4,6-benzyl galactal derivative gave pure β-anomer as well (Scheme 2, **2e**).

Subsequently, the various substituted ketones were used to investigate the scope of the decarboxylative glycosylation. γ-Aliphatic-substituted β-ketones were found to undergo the decarboxylative coupling under the optimized conditions in good to excellent yields (Scheme 2, **2f**–**2j**). It should be noted that sterically hindered substrates even with cyclic substituents were converted into the desired coupling products with exclusive β-selectivity (Scheme 2, **2h**–**2j**). However, the secondary substituted β-ketone substrates provided a mixture due to the prochirality of the α-carbon (Scheme 2, **2i** and **2j**). In view of these promising results, we directed our attention to ketones with aromatic substituents. An array of γ-aryl-substituted β-ketones were examined under the optimized conditions (Scheme 2, **2k**–**2o**). The coupling reactions proceeded well with aromatic ketones bearing electron-withdrawing groups, which had only a minor influence on the glycosylation. In contrast, the reactions of aromatic ketones possessing electron-donating groups required longer reaction times and gave lower yields. Because of the success of the β-ketone substrates, the reaction was scaled up to examine the possibility of commercial applications. Notably, the reaction could be conducted on a gram scale without a reduction of yield (**2k**, 86 %).

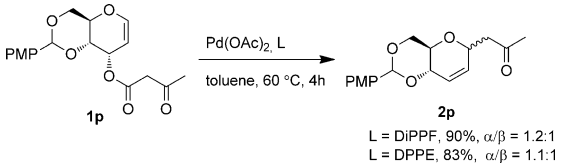
Although a palladium-catalyzed DcA mechanism is most feasible, an intramolecular rearrangement route (namely Carroll rearrangement) was also taken into account.[17] To identify this possibility, we carried out a crossover decarboxylative coupling reaction (Scheme 3). A 1:1 mixture of **1a** and **1q** was subjected to the optimized reaction conditions. Interestingly, we found that complete scrambling occurred, the products were formed in a ratio of 1.7:1.2:1.6:1 (**2a**/**2f**/**2q**/**2b**), and only β-products were observed. This result clearly



Scheme 3. Crossover decarboxylative coupling of **1a** and **1q**.

indicates that the palladium-promoted ionization occurs at the beginning of the reaction and an intramolecular rearrangement pathway is not involved.

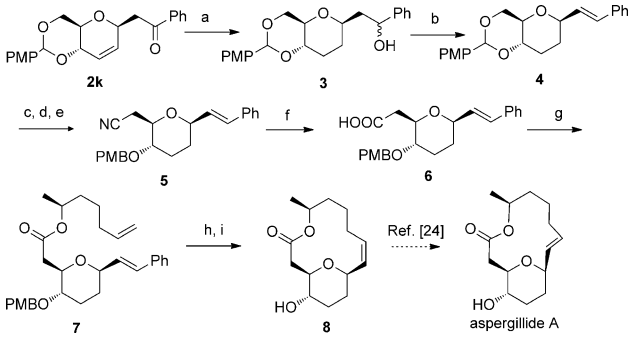
Interestingly, unlike the 3,6-*cis* substrates, the 3,6-*trans* substrate **1p** gave α/β mixtures with 1.2:1 and 1.1:1 ratios when DiPPFF and DPPE were used as the respective ligands (Scheme 4). This can be explained by the fact that formation



Scheme 4. Decarboxylative coupling of compound **1p**.

of π-allyl Pd complexes from both α and β faces of **1p** by ionization are close in energy. Given the experimental result of selectivity differentials, we hypothesized that the ketone enolate anion resulting from ionization may attack the allyl group from the face opposite to the Pd complex; thus, the reaction might proceed through an outer-sphere mechanism.[18,19]

The synthetic utility of this transformation was further demonstrated by the formal total synthesis of aspergillide A (Scheme 5).[20] The synthesis started from the decarboxylative coupling product **2k**. Treament of **2k** with Raney Ni and H_2 reduced the alkene and carbonyl group. Elimination of the newly formed hydroxy group of **3** generated the disubstituted alkene **4** in 83% yield. Reduction of acetal group with DIBAL-H freed the primary alcohol, which was further transformed to a nitrile group in good yield. Further hydrolysis of the nitrile group of **5** under basic conditions produced carboxylic acid **6** in 87% yield. Coupling of acid **6** with (*S*)-hept-6-en-2-ol under Yamaguchi esterification conditions[21] gave diene **7** in excellent yield. Treatment of diene **7** with the 2nd generation Grubbs catalyst (Ru-II) and 1,4-benzoquinone (BQ)[22]furnished the *Z* alkene which was further deprotected by DDQ to produce the known compound **8**.[23] Thus, starting from commercial available glucal, we accomplished the formal synthesis of aspergillide A in 11 steps and 16% overall yield. Following the literature procedures,[24] *Z* alkene **8** could be isomerized to give the *E* alkene aspergillide A in one step.



Scheme 5. Formal total synthesis of aspergillide A. Reagents and conditions: a) Raney Ni, H_2, EtOH/EtOAc 2:1, RT, 95%; b) DTBMP, Tf_2O, CH_2Cl_2, RT, 83%; c) DIBAL-H, CH_2Cl_2, −15 °C, 82%; d) TsCl, Et_3N, DMAP, RT, 91%; e) KCN, DMSO, 50 °C, 79%; f) KOH, EtOH/H_2O 1:1, 80 °C, 87%; g) (*S*)-hept-6-en-2-ol, Yamaguchi esterification, 94%; h) Ru-II, BQ, toluene, 100 °C, 71%; i) DDQ, aq CH_2Cl_2, 90%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine, DTBMP = 2,6-Di-tert-butyl-4-methylpyridine, Ru-II = 2nd generation Grubbs catalyst, Tf = trifluorosulfonyl, Ts = *p*-toluenesulfonyl.

In conclusion, we have developed a mild Pd-catalyzed decarboxylative *C*-glycosylation of readily available glycal derivatives. Essentially, this transformation is a tandem sequence of rearrangement and decarboxylation on the sugar scaffold. The versatility and flexibility of this method is evident from its extensive substrate scope. Remarkably, high yields and exclusive regioselectivity and diasteroselectivity were obtained, demonstrating that the reaction tolerates a wide range of substituents. In addition, the reaction could be conducted on a gram scale, highlighting its possible industrial application. The potential of employing this method to access natural products is intriguing, as *C*-glycosides constitute a major component of many natural glycoconjugates. We aslo applied this strategy to achieve the concise formal synthesis of aspergillide A.

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Communications

C-Glycosylation

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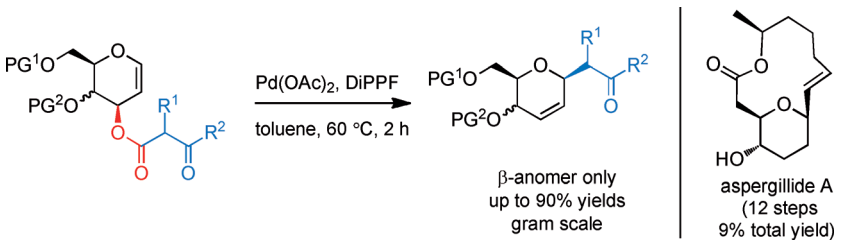
Stereoselective β-*C*-Glycosylation by a Palladium-Catalyzed Decarboxylative Allylation: Formal Synthesis of Aspergillide A



Mild and sweet: The title reaction proceeds under mild conditions with high regio- and diastereoselectivity (see scheme, PG = protecting group, DiPPF = 1,1′-bis(diisopropylphosphino)ferrocene). This reaction is suitable for a wide range of glycal-derived γ-ketone esters and affords *C*-glycosides with exclusive β-selectivity. The method was further applied to a concise formal synthesis of aspergillide A.