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Palladium-Catalyzed Direct Cross-Coupling Reaction of Glycals with Activated Alkenes

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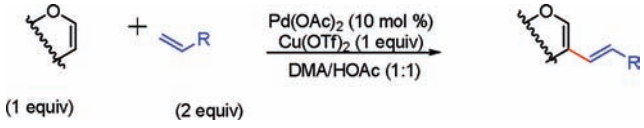
ABSTRACT



An efficient method for a $Pd(OAc)_2$-catalyzed cross-coupling reaction of glycals with activated alkenes under mild conditions has been developed. This transformation provides an expedient synthetic method to C(2)-functionalized glycals, which are common structural building blocks in natural products and other biologically active compounds. The reaction scope includes different kinds of carbohydrates, protecting groups and substituents on alkene. Moderate to excellent yields and pure *E* configuration selectivity were obtained.

The utility of saturated and unsaturated pyrans has increased enormously over the years; pyrans are also an important class of heterocycle which are widely found in natural products with various biological activities (Figure 1).[1] Consequently, a plethora of methods has been developed for the synthesis of multifunctionalized pyran rings. Popular methods include the Prins cyclization,[2] Lewis acid and transition metal promoted intramolecular cyclizations,[3] and hetero-Diels–Alder reactions.[4] Most of the reported methods focus on cyclization reactions to form the pyran rings from molecules with existing functional groups.[4]

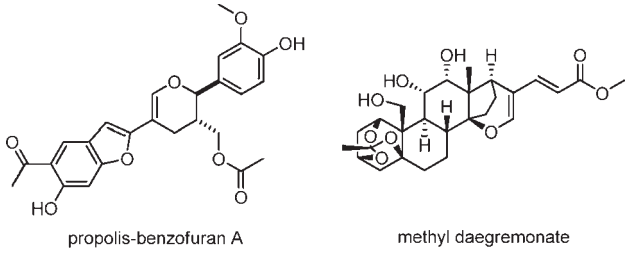


Figure 1. Pyran-containing natural products.

Sugar pyranoses are one of the most abundant pyrans that are fully substituted with specific chiral centers. Among the many sugar pyranose derivatives, glycals are preeminent. While in past decades, only reactions on the anomeric carbon of glycals have been intensively investigated;[5] to the best of our knowledge, there are only several reports of the addition of functional groups to C2

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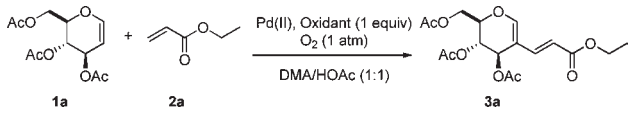
carbon of glycals.[6] C2-functionalized glycals could provide access to a large number of natural products and sugar derivatives. Among all the C2-functionalized glycals, formation of a diene moiety by the addition of an alkene to a glycal has attracted much attention because the diene moiety can serve as a potential building blocks for natural products such as Olivin,[7] Forslolin,[8] and Jamesoniellide[9] by Diels–Alder cyclization.

Recently, palladium-catalyzed C–H bond activation reactions have attracted considerable attention.[10] However, cross coupling reactions between alkenes to form dienes have been rarely reported due to the difficulty in activating the alkenyl carbon–hydrogen bond in contrast to the carbon–halogen bond. When the reactions are applied to alkenes such as acrylates, in the presence of common transition metals, dimerization often occurs to generate dicarboxylates.[11] In 2004, Ishii et al. reported an elegant oxidative coupling methodology of acrylates with vinyl carboxylates, catalyzed by $Pd(OAc)_2$.[12] Direct cross-coupling reactions between simple olefins and acrylates were also explored by Loh's group.[13] Recently, Yu et al. reported another direct alkene alkene coupling by terminal alkenes and functionalized 1,3-butadiene.[14] In continuation of our interest in functionalized sugar pyranose especially glycals,[15] herein we describe a simple and general method for functionalization of the C(2) position of glycals through a cross-coupling reaction.

Initially, we examined the interaction of peracetylated glucal with ethyl acrylate in the presence of Pd(II) catalysts and 1 atm of oxygen (Table 1). It was observed that when the reaction was carried out in mixed DMA and acetic acid (v/v 1/1) with 10 mol % $Pd(OAc)_2$, the desired product was obtained in pure *E* form with an excellent isolated yield of 82%. Subsequently, when the catalyst loading was reduced to 5 mol %, a lower yield (53%) was obtained (Table 1, entry 10). On the other hand, further increase in the catalyst loading to 20 mol % did not have significant effect on increasing reaction yield (Table 1, entry 11). Screening of a variety of catalysts revealed that Pd complexes such as $PdCl_2$ (Table 1, entry 2), $Pd(TFA)_2$ (Table 1, entry 4), $Pd(PhCN)_2Cl_2$ (Table 1, entry 5), and $Pd(PPh_3)_2Cl_2$ (Table 1, entry 3) afforded much lower yields in contrast to Pd(OAc)2. After elucidating the optimal catalyst, the efficiency of different co-oxidants was examined. Intriguingly, the yield was much higher when the reaction was conducted in the presence of 1 equiv of $Cu(OTf)_2$ (Table 1, entry 8) as compared to 1 equiv of $CuSO_4$ (Table 1, entry 6), $Cu(OAc)_2$ (Table 1, entry 1) and Ag_2CO_3 (Table 1, entry 7). Presumably the ligand exchange between $Pd(OAc)_2$ and $Cu(OTf)_2$ made Pd (II) species more electrophilic and thus more prone to electrophilic substitution at C(2). In addition, adjusting reaction temperatures revealed that the reaction gave the best yield (82%) at 70 °C in a reasonable reaction time (24 h) (Table 1, entry 9).

With the optimized reaction conditions in hand, we proceeded to study the reaction with different alkene coupling partners (Scheme 1). The reactivities of an array of acrylates were first examined. To our delight, all the acrylate reagents used in the reaction gave the

Table 1. Direct Coupling Reaction of Peracetylated Glucal with Ethyl Acrylate[a]

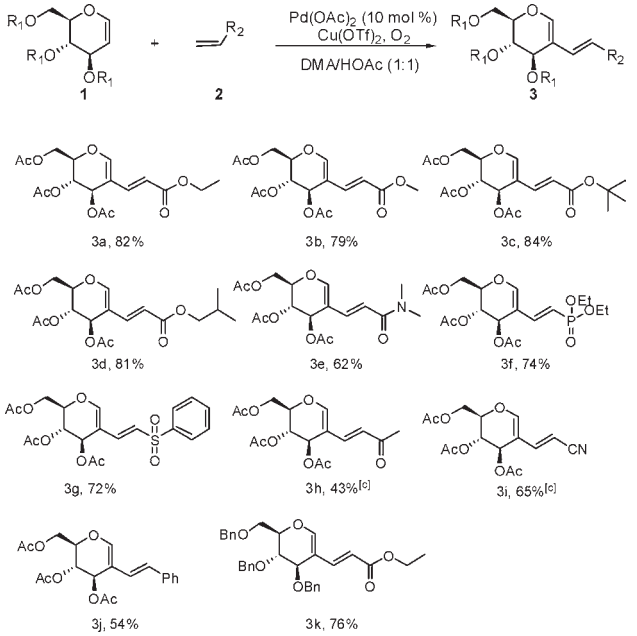


1a 2a 3a

entry	oxidant	catalyst (mol %)	temp (°C)	time (h)	yield[b] (%)
1	$Cu(OAc)_2$	$Pd(OAc)_2$ (10%)	60	24	61
2	$Cu(OAc)_2$	$PdCl_2$ (10%)	60	24	14
3	$Cu(OAc)_2$	$Pd(PPh_3)_2Cl_2$ (10%)	60	24	0
4	$Cu(OAc)_2$	$Pd(TFA)_2$ (10%)	60	24	56
5	$Cu(OAc)_2$	$Pd(PhCN)_2Cl_2$ (10%)	60	24	0
6	$CuSO_4$	$Pd(OAc)_2$ (10%)	60	24	36
7	Ag_2CO_3	$Pd(OAc)_2$ (10%)	60	24	23
8	$Cu(OTf)_2$	$Pd(OAc)_2$ (10%)	60	24	71
9	$Cu(OTf)_2$	$Pd(OAc)_2$ (10%)	70	24	82
10	$Cu(OTf)_2$	$Pd(OAc)_2$ (5%)	70	48	53
11	$Cu(OTf)_2$	$Pd(OAc)_2$ (20%)	70	24	85
12	$Cu(OTf)_2$	$Pd(OAc)_2$ (10%)	80	16	59

[a] Reaction conditions unless otherwise specified: **1a** (1 equiv), **2a** (2 equiv), oxidant (1 equiv), O_2 (1 atm) in the mixture of HOAc and DMA. [b] Isolated yields. Key: HOAc, acetic acid; TFA, trifluoroacetate; DMA, dimethylacetamide.

Scheme 1. Direct Coupling of Protected Glucals with Activated Alkenes[a,b]



[a] Reaction conditions unless otherwise specified: **1** (1 equiv), **2** (2 equiv), $Cu(OTf)_2$ (1 equiv), O_2 (1 atm) at 70 °C in the mixture of AcOH and DMA for 24 h. [b] All yields in Scheme 1 are isolated yields. [c] Reactions were carried out at 45 °C for 72 h.

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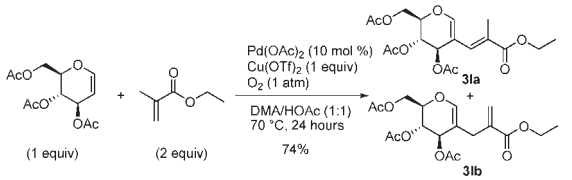
corresponding (*E*) products (**3a**−**g**) in good to excellent yield (62−84%). Besides acrylates, alkenes such as methyl vinyl ketone (**3h**) and acrynitrile (**3i**) provided pure *E*-alkenes in moderate yield as well. Relatively electron-rich alkenes such as styrene also afforded the desired product (**3j**) in moderate yield. Subsequently, the effect of various protecting groups on the glucal substrate was examined. Glucal substrates with acid tolerant protecting groups such as acetyl (**3a**) and benzyl (**3k**) gave good yields. On the contrary, unprotected glucal substrates and glucals with acid-sensitive protecting groups of the (trimethylsilyl or isopropylidene) failed to afford any desired product.

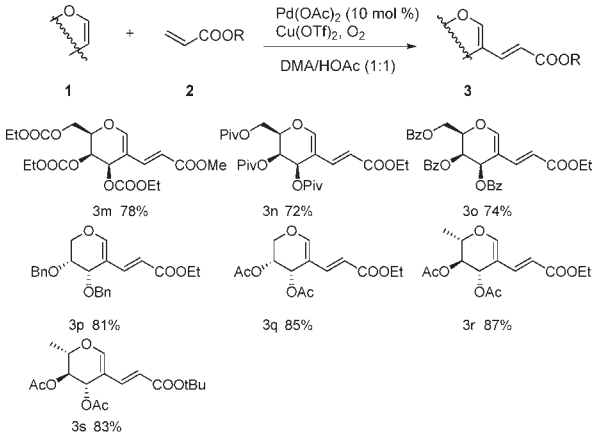
Interestingly, we found that the reaction of glucal and ethyl methacrylate afforded a mixture of compounds **3la** and **3 lb** with a ratio of 1:2.5 in 74% total yield (Scheme 2).

Scheme 2. Direct Coupling of Peracetylated Glucal with Ethyl Methacrylate



Investigation of the reactivities of different carbohydrate moieties was next carried out, and the reaction was tested with a wider range of protecting groups. The results are summarized in Scheme 3. Interestingly, substrates derived from D-galactose (**3m**−**o**), D-ribose (**3p**−**q**), and L-6-deoxyl-3,4-diacetyglucal (**3r**−**s**) also afforded the desired products in good to excellent yields. On top of that, other acid tolerant protecting groups such as ethoxycarbonyloxyl (**3m**), pivaloyl (**2n**), and benzoyl (**3o**) gave the desired products in good yields too. In the case of **3q**, X-ray crystallography (Figure 2) further comfirmed the product structure.

Scheme 3. Direct Coupling of Protected Glycals with Acrylates[a−c]



[a] All reactions were carried out with **1** (1 equiv), **2** (2 equiv), $Cu(OTf)_2$ (1 equiv), O_2 (1 atm) for 24 h. [b] All yields in Scheme 3 are isolated yields. [c] All of the products are in an *E* configuration.

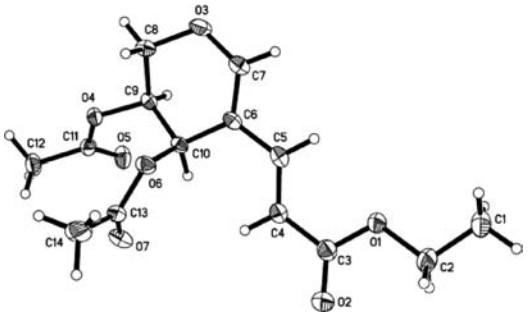
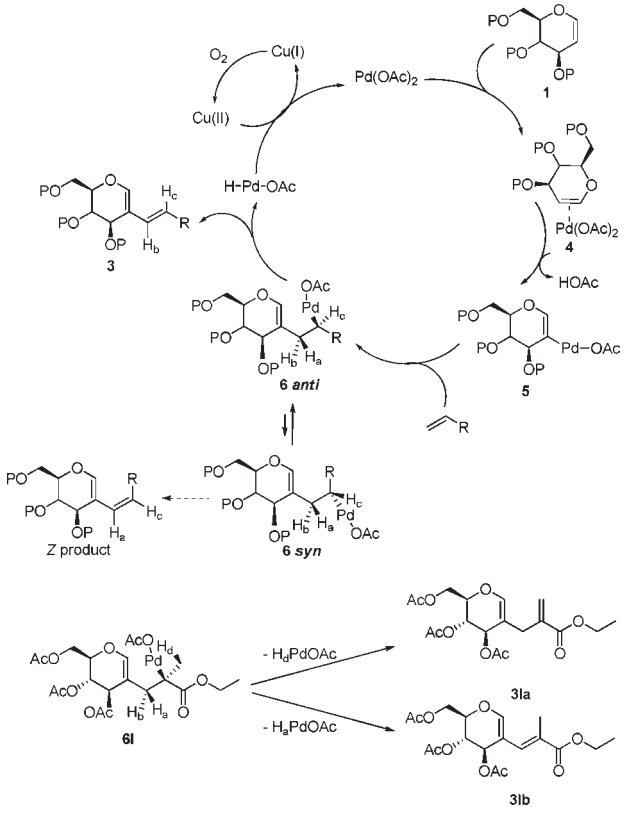


Figure 2. X-ray structure of compound **3q**.

Scheme 4. Plausible Mechanism for the Coupling Reactions Observed



A plausible mechanism of this reaction is depicted in Scheme 4. The Pd complex **5** is formed by electrophilic substitution on the glycal at C(2) due to the latter being

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electron rich. Carbopalladation of the acrylate then occurs to give **6**. The conformation **6** ***anti*** of complex **6** is relatively more stable than conformation **6** ***syn*** as the two bulky groups in **6** ***anti*** are situated at *anti* positions. The formation of this intermediate justifies the observation that only *E* configuration products were afforded from all of the substrates. Through β-hydride elimination, final compounds are dissociated from the Pd complex. Both products **3la** and **3lb** were formed due to the fact that β-hydride elimination could take place on any of the two β carbons of **6l**. Pd(0) generated from reductive elimination is then oxidized by Cu(II) to form the active Pd(II) catalyst species once more.

In conclusion, we have developed an efficient $Pd(OAc)_2$-catalyzed coupling reaction of glycals with activated alkenes under mild conditions. The reactions display high tolerance to a vast scope of substrates, including glycals protected by various protecting groups and a diversified range of activated alkenes. Pyran derivatives were obtained in moderate to excellent yields with pure *E* selectivity. It is noteworthy that the functionalized pyran products potentially provide entries to many pyran-containing natural products, signifying their immense potential in the synthetic field.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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