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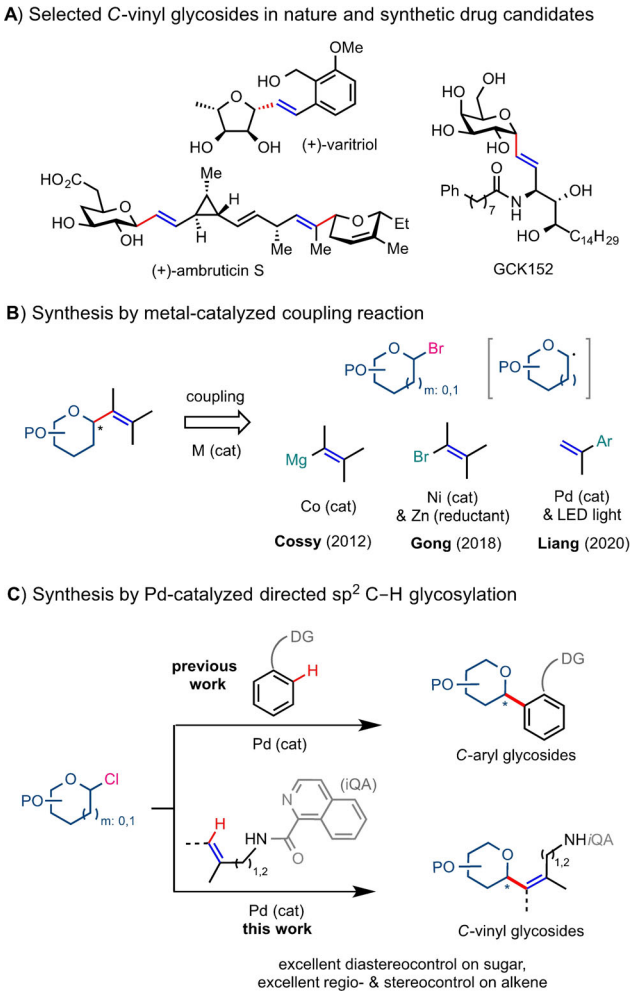
Stereoselective Synthesis of *C*-Vinyl Glycosides via Palladium-Catalyzed C–H Glycosylation of Alkenes

Qikai Sun, Huixing Zhang, Quanquan Wang, Tianjiao Qiao, Gang He, and Gong Chen**

Dedicated to Professor Christian Bruneau

Abstract: *C-vinyl glycosides are an important class of carbohydrates and pose a unique synthetic challenge. A new strategy has been developed for stereoselective synthesis of C-vinyl glycosides via Pd-catalyzed directed C–H glycosylation of alkenes with glycosyl chloride donors using an easily removable bidentate auxiliary. Both the γ C–H bond of allylamines and the δ C–H bond of homoallyl amine substrates can be glycosylated in high efficiency and with excellent regio- and stereoselectivity. The resulting C-vinyl glycosides can be further converted to a variety of C-alkyl glycosides with high stereospecificity. These reactions offer a broadly applicable method to streamline the synthesis of complex C-vinyl glycosides from easily accessible starting materials.*

C-vinyl glycoside motifs are found in many natural products and frequently used as mimics of *O*-glycosides in the design of glyco therapeutic agents (Scheme 1 A).[1–4] In addition to the higher metabolic stability over *O*-glycosides, the alkene linkages can enable unique structural tuning in the glycomimetic design. While considerable progress has been made for the synthesis of *C*-aryl glycosides over the past decade,[3,4] the synthesis of *C*-vinyl glycosides is more challenging and remains under-developed.[5,6] Metal-catalyzed cross coupling strategies have enjoyed the most success in constructing the *C*-vinyl glycosidic bonds (Scheme 1 B).[6] Notably, Cossy reported a cobalt-catalyzed coupling of glycosyl bromides and vinyl Grignard reagents.[6a] Gong reported a nickel-catalyzed reductive coupling of glycosyl bromides and vinyl chlorides using zinc reductant.[6b] More recently, Liang reported a palladium-catalyzed radical-mediated Heck coupling of glycosyl bromides and aryl olefins under visible light irradiated conditions.[6c] Glycosyl radical intermediates were invoked in the all above reaction systems. While useful, the requirement of pre-functionalized or aryl-activated olefin coupling partners limits synthetic utility. Recently, we developed a Pd-catalyzed *ortho*-directed C–H glycosylation of arenes and heteroarenes with glycosyl chloride donors to construct *C*-aryl glycosidic bonds (Scheme 1 C).[7] Herein, we



Scheme 1. Structure and synthesis of *C*-vinyl glycosides.

expand this Pd-catalyzed C–H glycosylation strategy to construct various *C*-vinyl glycosides from readily accessible alkene substrates using an easily removable auxiliary.[8–10] The method can glycosylate both γ and δ C–H bond of unactivated alkenes in high efficiency and with excellent regio- and stereoselectivity. Unlike the products from the *ortho* C–H glycosylation of arenes, the resulting *C*-vinyl glycosides can be easily converted to a variety of *C*-alkyl glycosides in high stereospecificity.

Metal-catalyzed directed C–H functionalization of alkenes has recently emerged as an effective strategy to synthesize complex alkenes from easily accessible precursors.[11–14] Bidentate directing groups have unique ability to

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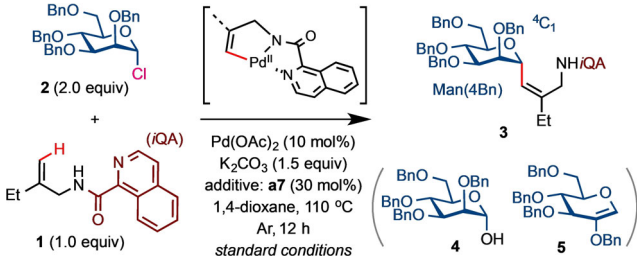
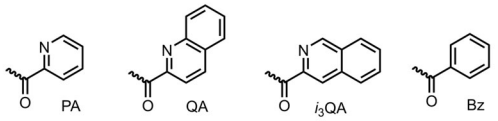
harness the reactivity of higher valent metal intermediates to form challenging chemical bonds.[15–17] In comparison to arenes, the π reactivity of alkene substrates might more strongly interfere with the C–H cleavage process, posing a challenge to reaction development. Encouraged by the success of Pd-catalyzed aryl C–H glycosylation and the recent advance of Pd-catalyzed directed C–H functionalization of alkenes, we wondered whether these chemistries could be merged to provide a useful method to synthesize *C*-vinyl glycosides.[13] As shown in Table 1, we were pleased to find the reaction of model substrate 3-ethyl vinylamine **1** bearing an amide linked isoquinolic acid (*i*QA) auxiliary with tetrabenzyl protected mannosyl chloride donor **2** (2.0 equiv) under the optimized conditions of 10 mol% of $Pd(OAc)_2$, 1.5 equiv of K_2CO_3, and 30 mol% of Boc protected valeric acid (Boc-Ava-OH, **a7**) as additive in dioxane at 110 °C for 12 hours gave the desired product **3** in 85% isolated yield and with exclusive α diastereoselectivity and *cis* stereoselectivity (entry 1). NMR analysis showed compound **3** adopts a $^4C_1$ conformation. Compounds **4** and **5** were obtained as the byproducts of **2** which was used in excess. Use of other solvents including 1,2-dichloroethane (DCE), CH_3CN and tetrahydrofuran (THF) gave considerably lower yield (entries 2–4). Replacement of K_2CO_3 with Na_2CO_3 or Ag_2CO_3 caused lower reactivity (entries 5, 6). Reaction at 80 °C gave lower conversion of **1** (entry 8). Notably, the reaction with 5 mol% of Pd catalyst on 1 mmol scale gave **2** in 92% isolated yield (entry 17). In comparison with *i*QA, the use of picolinic acid (PA) and other structural analogs gave considerably lower yields (entries 12–14). No product was formed when benzamide was used as the directing group (entry 15). The choice of carboxylic acid additive is also important to the reaction.[18] Screening of various alkyl, aryl carboxylic acids and α-amino acids showed that linear carbamate-protected aliphatic acids with four to five methylene units gave the optimal results.

Table 1: Optimization of the Pd-catalyzed C–H glycosylation of allylamine **1** with mannosyl chloride donor **2**.

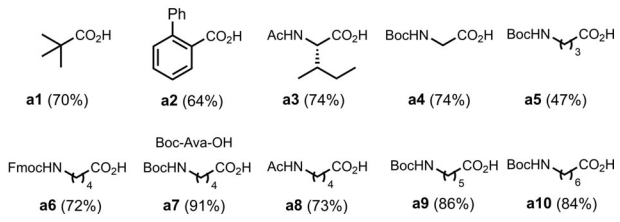


Entry	Change from standard conditions	Yield of **3** [%][a]
1	No change	91 (85[b])
2	DCE as solvent	25
3	CH_3CN as solvent	22
4	THF as solvent	56
5	K_2CO_3 replaced with Na_2CO_3	54
6	K_2CO_3 replaced with Ag_2CO_3	50
7	1.5 equiv of **2**	79
8	80 °C	42
9	Without Pd	ND
10	No additive added	45
11	$PdCl_2$ as cat	62
12	*i*QA is replaced with PA	44
13	*i*QA is replaced with i_3QA	53
14	*i*QA is replaced with QA	38
15	*i*QA is replaced with Bz	ND
16	5 mol% of Pd (0.1 mmol scale)	78
17	5 mol% of Pd, 24 h (1 mmol scale)	92[b]
18	2 mol% of Pd, 24 h (1 mmol scale)	70[b]

Structures of different directing groups on NH_2

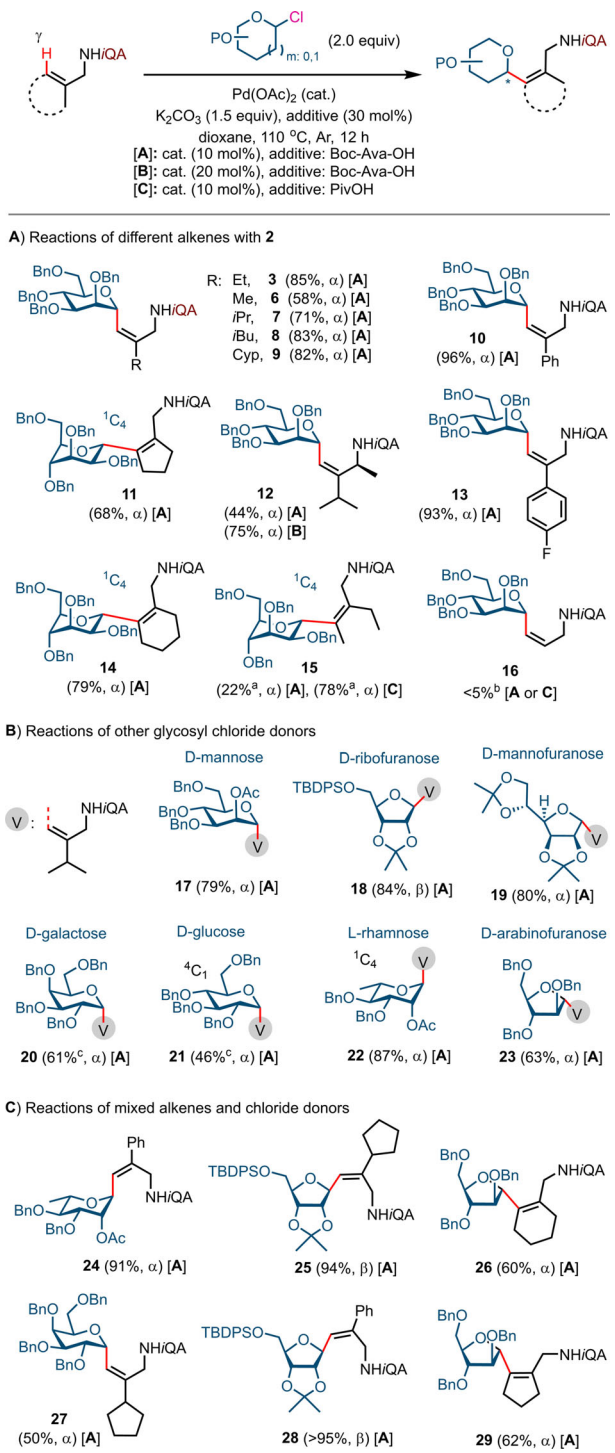


Yield of **3** using different additives under the standard conditions



[a] Yields are based on ^1H NMR analysis of the crude reaction mixture at a 0.1 mmol scale. [b] Isolated yield. ND: not detected.

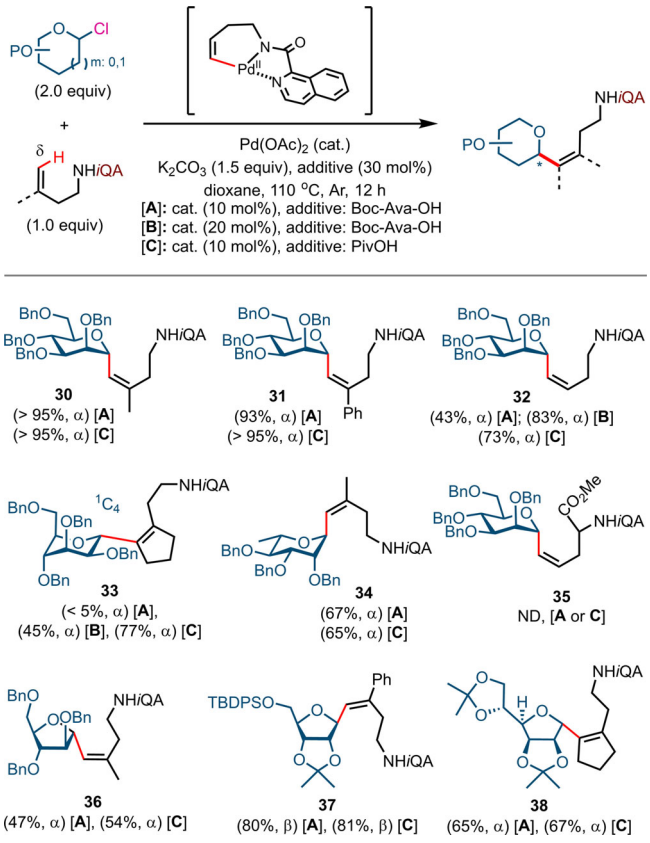
We next examined the scope of allylamines using their reactions with mannosyl chloride **2** under the optimized reaction conditions **A** (Scheme 2A). It was worth noting that excellent diastereoselectivity was observed in all successful reactions. Allylamines bearing various β-alkyl substituents worked well, giving the desired tri-substituted *C*-vinyl glycoside (**3**–**9**) in good to high yields and with exclusive *Z*-stereoselectivity.[19] β-Aryl-substituted allylamines (**10**, **13**) also showed excellent reactivity. In contrast, allylamines without β-substituents (e.g. **16**) gave little desired product under various reaction conditions. We suspect unsubstituted alkenes can form stronger π complexes with Pd, hampering the C–H palladation process. As seen in **12** (vs. **7**), allylamines bearing α-substituents showed lower reactivity. The yield of **12** can be improved to 75% using 20 mol% of Pd catalyst (conditions **B**). Cyclene substrates (e.g. **11**, **14**) worked well to give the tetra-substituted cyclic alkene products. Notably, acyclic tetra-substituted alkene product **15** can also be obtained in moderate yield from the corresponding acyclic tri-substituted allylamines. The yield of **15** was improved under conditions **C** in which Boc-Ava-OH additive was replaced with PivOH. In general, Boc-Ava-OH additive is more effective than PivOH in this γ C–H glycosylation. Tetra-substituted alkene products **11**, **14**, and **15** all adopt a $^1C_4$ conformation. As shown in Scheme 2B and C, both furanosyl and pyranosyl chloride donors can react with allylamine substrates to give the corresponding *C*-vinyl glycosides in good to excellent yields and with excellent stereoselectivity. Most of the glycosyl chloride donors were prepared in high α diastereoselectivity (α/β > 20:1), except for a 16:1 selectivity fora 5:1 selectivity for arabinose (see **23**). Notably, ribosyl chloride (see **18**) was obtained in high β selectivity (α/β = 1:16).[20] All glycosylation reactions proceeded in a stereoretentive fashion, forming predominantly *C*-α-vinyl glycosides except *C*-β-vinyl ribosides (see **18**, **28**). Overall, mannose (**17**, **19**), rhamnose (**22**, **24**) and ribose (**18**, **28**) exhibited highest reactivity; glucose (**21**) and galactose (**20**)



Scheme 2. Pd-catalyzed γ C(sp²)–H glycosylation of allyl amines. Isolated yield at a 0.1 mmol scale. The above reactions proceeded in excellent diastereoselectivity; <5% of the other diastereomer was detected by ^{1}H NMR or chromatographic analysis of the reaction mixture. a) An inseparable mixture of *Z* and *E* alkene starting material was used. *Z* isomer was unconsumed. Yield was based on the *E* isomer in starting material. b) The product was not isolated. c) About 30–40% of the alkene starting material was recovered. The stereochemistry of representative *C*-vinyl glycosides was assigned by NMR analyses, see SI for details.

were less reactive. Protecting groups such as benzyl, acetyl, silyl ether and acetonide were well tolerated.

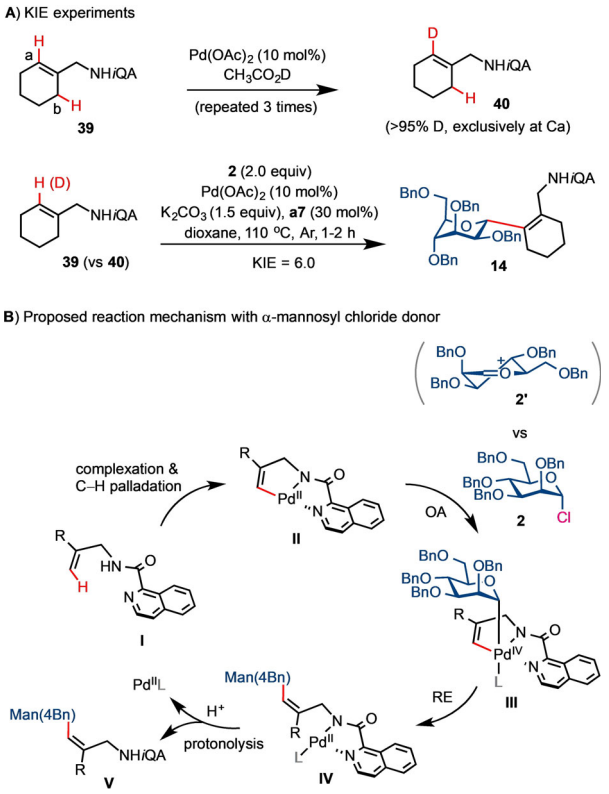
Following the success of γ C–H glycosylation of allylamines, we investigated whether the more remote δ C–H bond of homoallyamines can also be glycosylated via a 6-membered palladacycle intermediate (Scheme 3).[13g–i]



Scheme 3. Pd-catalyzed δ C(sp²)–H glycosylation of homoallylic amines. Isolated yield at a 0.1 mmol scale. <5% of the other diastereomer was detected by ^{1}H NMR or chromatographic analysis of the reaction mixtures.

Gratifyingly, both 3-Me and 3-Ph substituted 3-butenylamines reacted with mannose donor **2** to give the desired products in excellent yields and with excellent stereoselectivity (**30**, **31**) under the standard conditions **A**. 3-butenylamine was glycosylated at the δ position to give **32** in moderate yield.[21] Interestingly, using PivOH additive increased the yield of **32** to 73% (condition **C**). Overall, PivOH additive was more effective for δ C–H glycosylation of homoallylamines (e.g. **33**). For unclear reasons, allylglycine bearing an α-CO_2Me group did not give any desired product **35** under various conditions (vs. **32**). In comparison to mannopyranose donor **2**, other glycosyl donors such as rhamnose (**34**), arabinose (**36**), ribose (**37**) and mannofuranose (**38**) showed lower reactivity in the δ C–H glycosylation reactions.

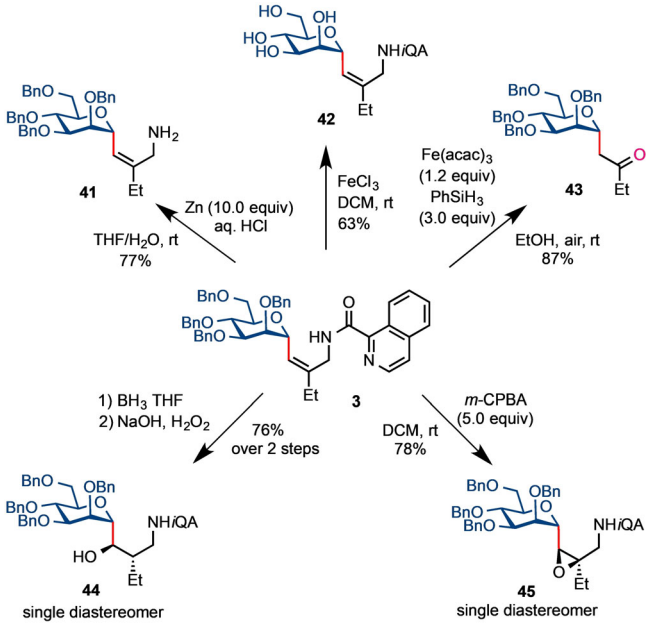
These Pd-catalyzed *i*QA-directed vinyl C–H glycosylation reactions with glycosyl chlorides likely follow a similar pathway of the *ortho*-directed aryl C–H glycosylation via the sequence of C–H palladation, oxidative addition (OA) and reductive elimination (RE).[7] As shown in Scheme 4A, Pd-



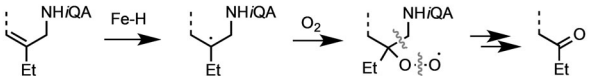
Scheme 4. Mechanistic considerations.

catalyzed C–H deuteration of **39** in CH_3CO_2D selectively took place at the alkenyl C–H bond, forming **40** in good yield after three rounds of reaction. A kinetic isotope effect (KIE = 6.0) for the reactions of **39** vs. **40** with **2** indicated that the C–H palladation is the rate-limiting step. As outlined in Scheme 4B, the C–H glycosylation reaction starts with the *i*QA-directed C–H palladation of the alkene substrate **I** to form the palladacycle intermediate **II**. OA of mannosyl chloride donor **2** to **II** gives the Pd^{IV} intermediate **III**, which then gives the Pd^{II}-bound glycosylated product **IV** upon RE. The details of the OA step have not been firmly established. Our previous computational studies of the related Pd-catalyzed aryl C–H mannosylation system supported a concerted OA mechanism with the α mannosyl chloride donor.[7b] However, a stepwise OA of a glycosyl oxocarbenium intermediate to **II** cannot be ruled out. The stereochemical outcome of the glycosylation is probably controlled by both steric and stereoelectronic effects as both 1,2-*trans* (e.g. **3**) and 1,2-*cis* (e.g. **20**) configured products can be formed in high selectivity for different glycosyl donors. In comparison to aryl C–H glycosylation, the alkene moiety in both starting material and glycosylated product might be able to form a π complex with Pd^{II}. Such complexation could interfere with the C–H palladation and hamper the dissociation of Pd catalyst from the glycosylated product (from **IV** to **V**). The role of carboxylic acid additives is unclear at the moment. While their involvement in the C–H palladation step cannot be ruled out, they could also facilitate the Pd^{II} dissociation from the product to speed up catalyst turnover.[18]

As shown in Scheme 5, the *i*QA auxiliary of compound **3** was removed under mild conditions via treatment of Zn powder at rt to give free amine **41** in 77% yield.[22] Treatment of **3** with excess amount of anhydrous $FeCl_3$ (8.0 equiv) in



Proposed mechanism for the formation of **43** via oxidative cleavage of Cα-Cβ of **3**:



Scheme 5. Facile removal of *i*QA auxiliary and stereospecific conversions of *C*-vinyl glycoside **3** to *C*-alkyl glycosides.

DCM at rt gave debenzylated product **42** in good yield.[23] Hydroboration of **3** with BH_3THF followed by H_2O_2 oxidation gave **44** in 76% yield as a single diastereomer. Epoxidation with *meta*-chloroperbenzoic acid (*m*-CPBA) gave the epoxide product **45** as a single diastereomer. Interestingly, treatment of **3** using a modified procedure of Baran's method with stoichiometric $Fe(acac)_3$ and $PhSiH_3$ under air atmosphere gave the unexpected ketone product **43** in high yield.[24] We suspect that a Fe–H species first adds to the alkene to generate an alkyl radical, which reacts with O_2 to give the ketone product following cleavages of the O–O and C–C bonds.

In summary, we have developed a new method for stereoselective synthesis of *C*-vinyl glycosides via Pd-catalyzed C–H glycosylation of unfunctionalized alkenes with glycosyl chloride donors using an easily removable auxiliary. The glycosyl groups can be installed on both γ C–H bond of allylamines and δ C–H bond of homoallylamines in high efficiency, regio- and stereoselectivity. Moreover, the resulting *C*-vinyl glycosides can be easily converted to various *C*-alkyl glycosides with high stereospecificity. Overall, this C–H glycosylation strategy provides a streamlined and versatile method to synthesize a variety of *C*-vinyl and *C*-alkyl

glycosides that can be difficult to access by other means from readily available precursors.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: alkene functionalization · auxiliary · C–H glycosylation · *C*-vinyl glycoside · palladium

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Communications

Synthetic Methods

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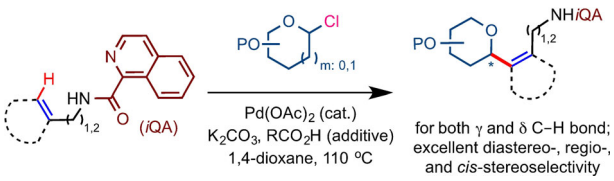
Stereoselective Synthesis of *C*-Vinyl Glycosides via Palladium-Catalyzed C–H Glycosylation of Alkenes



A new strategy has been developed for stereoselective synthesis of *C*-vinyl glycosides via Pd-catalyzed directed C–H glycosylation of alkenes with glycosyl chloride donors using an easily removable bidentate auxiliary.