Title	One-pot synthesis of -N-glycosyl imidazole analogues via a palladium-catalysed decarboxylative allylation(Main article)
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Citation	Xiang, S., He, J., Ma, J., & Liu, X.-W. (2014). One-pot synthesis of -N-glycosyl imidazole analogues via a palladium-catalysed decarboxylative allylation. Chemical communications, 50(32), 4222-4224.
Date	2014
URL	http://hdl.handle.net/10220/24357
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One-pot synthesis of β-*N*-glycosyl imidazole analogues *via* a palladium-catalysed decarboxylative allylation

Cite this: DOI: 10.1039/xoxxoooooox

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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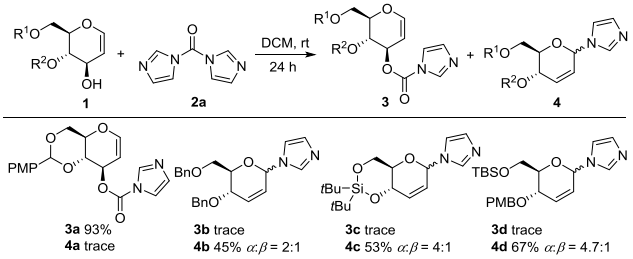
A concise and highly efficient strategy for the synthesis of *N*-glycosyl imidazole analogues is reported. This reaction is based on a palladium catalysed decarboxylative allylation and three steps, namely, carbamation, decarboxylation and allylation are involved. All the substrates can afford the desired products with excellent yields and selectivities.

N-Glycosides consist of a class of important structures in carbohydrate chemistry. They play significant roles in organism in the form of *N*-linked glycopeptides and glycoproteins,[1] and the *N*-glycoside scaffold possesses great potential in the field of medicinal chemistry.[2] Therefore, due to their unique characteristics, the synthesis of various *N*-glycosides has always been a popular topic in carbohydrate chemistry during the past few years.[3] However, compared to *O*-glycosides and *C*-glycosides, reports pertaining to the synthesis of *N*-glycosides, especially with high efficiency and stereoselectivity, are significantly fewer seen in literature.

Decarboxylative allylation has been widely used to form carbon-carbon and carbon-heteroatom bonds as established with the efforts of several pioneer groups.[4,5,6,7] Meanwhile, glycals are versatile intermediates and have been commonly employed in the formation of glycosidic bonds in our previous studies.[8] Considering the wide availablility of glycals, we endeavored to apply the strategy of decarboxylative allylation to the formation of glycosidic bonds. Gratifyingly, a wide variety of *C*- and *O*-glycosides were achieved with high regio- and stereo-selectivity in our previous work.[9,10] As a further expansion of this strategy, herein, we demonstrate its application to the synthesis of *N*-glycosyl imidazole analogues.

During the preparation of the carbamates **3** for the further study of palladium catalysed glycosylation, it was found that some of the carbamates were unstable and the decarboxylation occurred very fast during the reaction or the purification by column chromatography on silica gel, even after pre-treatment of the silica with Et_3N. The nucleophilic addition between the two active intermediates generated from the decarboxylation afforded *N*-glycosyl imidazole product. However, only moderate yields and poor selectivities were obtained.

Scheme 1. The decarboxylation of the carbamates without palladium catalyst[a,b]



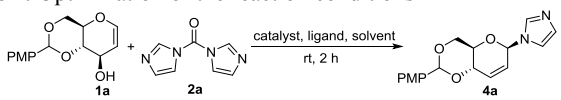
[a]Reaction conditions: glycal **1** 0.2 mmol, CDI **2a** (1,1'-carbonyldiimidazole) 0.3 mmol, DCM 4 mL; [b]The ratios were detemined by ^{1}H NMR.

Notably, as the results in Scheme 1 shows, the α-isomers were the major products and the ratios were determined by ^{1}H NMR spectra of crude products.

This came as a surprise to us as from our previous studies,[9,10] excellent β-selectivities were observed when palladium catalysts were introduced in the decarboxylative glycosylation. Intrigued by these results, we postulated that if a palladium catalyst is employed in the reaction conditon, the carbamate intermediates could be readily converted to β-products once they were formed. We thus sought to confirm our hypothesis by carrying out the reaction of 4,6-*para*-methoxybenzylidene-glucal **1a** with CDI **2** in the presence of $Pd(PPh_3)_4$ in THF at room temperature for 2 h. To our delight, the desired product **4a** was afforded in 45% yield, with a conversion percentage of 60% of starting material **1a**. Thereafter, various catalysts, ligands, solvents were screened to optimize the reaction conditions. As shown in Table 1, the effect of the solvent was first studied. When CH_3CN was used as the solvent, only a trace amount of product was formed (Table 1, entry 2). However, the reaction did not proceed in DMF or toluene (Table 1, entries 3, 4). Interestingly, when this reaction was carried out in DCM, a product yield of 93% was obtained (Table 1, entry 5). Next we attempted to examine the effect of catalyst and ligand. It was discovered that $Pd(PPh_3)_4$ was

superior to any other catalyst and ligand systems tested (Table 1, entry 6-10). It is worth noting that all the reactions gave the products with excellent β-selectivity and the stereochemistry of the product was further confirmed by the X-ray diffraction crystallographic analysis of compound **4a**.[11] Thus, we concluded the optimized reaction conditions as following: the reaction was conducted with glucal **1a** (1.0 equiv) and CDI **2a** (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (0.05 equiv) in DCM at room temperature for 2 h.

Table 1. Optimization of the reaction conditions[a]

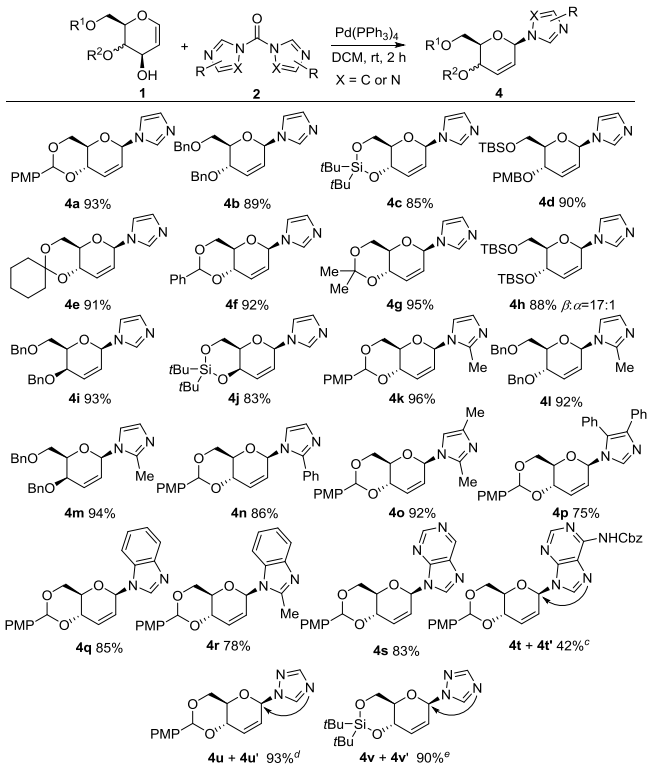


entry	catalyst	ligand	solvent	yield (%)[b]
1	$Pd(PPh_3)_4$	No	THF	45
2	$Pd(PPh_3)_4$	No	CH_3CN	trace
3	$Pd(PPh_3)_4$	No	toluene	NR[c]
4	$Pd(PPh_3)_4$	No	DMF	NR
5	$Pd(PPh_3)_4$	No	DCM	93
6	$Pd(OAc)_2$	PPh_3	DCM	30
7	$Pd_2(dba)_3$	PPh_3	DCM	41
8	$PdCl_2$	PPh_3	DCM	NR
9	$Pd(TFA)_2$	PPh_3	DCM	NR
10	$Pd(PPh_3)_2Cl_2$	PPh_3	DCM	NR

[a]Reaction conditions: 0.2 mmol glycal **1a**, 0.3 mmol CDI **2a**, 0.01 mmol Pd source, in 4 mL solvent at rt for 2 h; [b]Isolated yield; [c]NR = No reaction.

With the optimized reaction conditions in hand, we next investigated the scope and generality of this one pot reaction. As illustrated in Scheme 2, reactions involving glucals containing different kinds of protecting groups were performed first. It is apparent that the reactions proceeded smoothly and gave the desired products with 85%-96% yields (**4b**-**4h**). The substrates which gave mixtures of α- and β-anomers without palladium catalyst can afford pure β-products (**4b**-**4d**), further confirming our hypothesis. Exclusive β-selectivity was also obtained for most of the other substrates tested (**4e**-**4g**). However, a ratio of β:α = 17:1 mixture were obtained when *tert*-butylsilyl was selected as the protecting group of glucal (**4h**). Next, galactal substrates were employed for this reaction. Similarly, the desired products were obtained in high yields of 93% and 83% with exclusive β-selectivity (**4i**, **4j**). Subsequently, various CDI analogues were also screened to ascertain the substrate tolerance of the reaction. 2-Methyl and 2-phenyl substituted CDI analogues provided the corresponding products in excellent yields and exclusive β-selectivity (**4k**-**4n**). Disubstitued, such as 2,4-dimethyl or 4,5-diphenyl CDI analogues were then treated under the optimized reaction conditions, the desired products were furnished in 92% and 75% yields with β-selectivity (**4o**-**4p**). The corresponding β-type of benzimidazole and 2-methyl benzimidazole glycosides can also be prepared in 85% and 78% yields (**4q**-**4r**). Moreover, since hexopyranosyl nucleosides are present in various bioactive nature products, we then extended toward the preparation of this type of *N*-glycosides. Fortunately, purine and adenine type hexopyranosyl nucleosides were obtained successfully in 83% and 42% yields (**4s**-**4t**). Since both nitrogens are nucleophilic in the addition step, **4t** was afforded as a mixture while **4s** was obtained with good selectivity.[12] Similar results were obtained when 1,1'-carbonylbis(1,2,4-triazole) was utilized to furnish the desired *N*-glycosides with a ratio of 1:10 and 1:5 correspondingly (**4u**-**4v**).

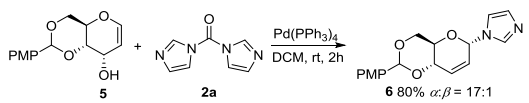
Scheme 2. The scope of *N*-glycosyl imidazole analogues[a,b]



[a]Reaction conditions: 0.2 mmol glycal **1**, 0.3 mmol **2**, 0.01 mmol $Pd(PPh_3)_4$, in 4 mL DCM at room temperature for 2 h; [b]Isolated yields; [c]Inseparable mixture with a ratio of 1:9 from ^{1}H NMR; [d]Inseparable mixture with a ratio of 1:10 from ^{1}H NMR; [e]Inseparable mixture with a ratio of 1:5 from ^{1}H NMR.

To investigate the mechanism of this decarboxylative reaction, compound **5** with a 3,5-*trans* structure was then prepared. When compound **5** was treated with CDI under the optimized reaction conditions, α-isomer was obtained as the major product as expected, with a ratio of α:β = 17:1.[13]

Scheme 3. The reaction of compound **5**[a,b,c]



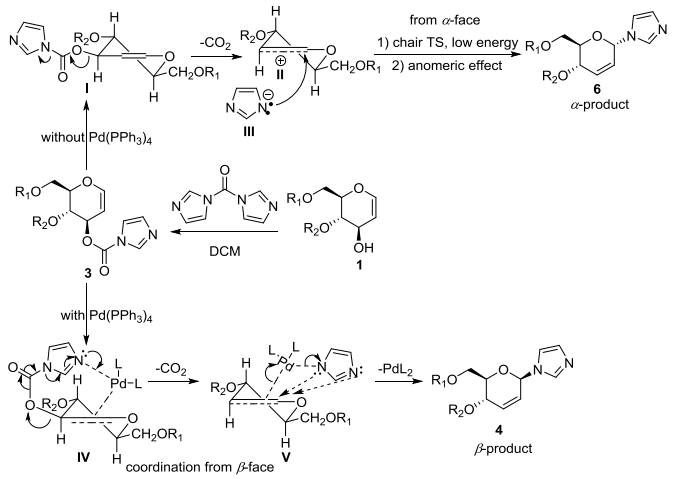
[a]Reaction conditions: 0.2 mmol glycal **5**, 0.3 mmol CDI, 0.01 mmol $Pd(PPh_3)_4$, in 4 mL DCM at room temperature for 2 h; [b]Isolated yield; [c]The ratios were detemined by ^{1}H NMR.

Furthermore, to confirm that the reaction indeed involves a carbamate intermediate, compound **3a** was prepared and subsequently treated with $Pd(PPh_3)_4$ in DCM for 2 h. The reaction gave pure β-product **4a** in 95% yield. Meanwhile, the reaction of **1a** and CDI in the presence of $Pd(PPh_3)_4$ in $CDCl_3$ monitored by ^{1}H NMR showed the existence of the carbamate intermediate **3a** (for details, see supporting information).

After that, we turned to examine the syntheses of *N*-furanosides with this method since nucleosides, the most important *N*-glycosides, exist as *N*-furanosides. Initially, the desired product was obtained under the same conditions.[14] However, poor stereoselectivity as compared to *N*-pyranosides was observed, possibly due to the difference in conformation and reactivity of intermediates. Although the result is less than satisfactory, it may provide an access to the formation of *N*-furanosyl linkage and the further investigation is currently ongoing in our laboratory.

To explain the selectivities of palladium catalysed glycosylation, the steric effect of the C3 substituent was always mentioned.[15] However, this hypothesis does not match the results from our previous studies in a few cases.[9,16] Recently, a double coordination effect was introduced which provided a more reasonable explanation.[17] Based on the above results, a double coordination effect mechanism is therefore proposed as following: the first step involved the formation of the carbamate intermediate **3** from the reaction of glycal **1** and CDI analogues. Without any catalyst, an allylic cation **II** and an imidazole anion **III** were then generated *in situ* through the decarboxylation of unstable intermediate **I**. Under this set of conditions, the α-isomer was furnished as the major product due to anomeric effect, which made the heteroatomic substituent **III** prefer axial orientation. Meanwhile, the lower energy chair-form transition state of nucleophilic addition from α-face may further enhance α-selectivity. On the other hand, in the presence of $Pd(PPh_3)_4$, double coordination of palladium catalyst involving the double bond of glycal and the lone pair of nitrogen atom resulted in the formation of key intermediate **IV** with the palladium species on the β-face. Subsequently, intermediate **V** was generated through a decarboxylative reaction promoted by the palladium catalyst. Thereafter, nucleophilic addition gave compound **4** with β-selectivity and the elimination of palladium catalyst completed the catalytic cycle. For asymmetric CDI analogues, since both of the nitrogen can be worked as a nucleophile in the next step, so two different products can be obtained.

Scheme 4. Plausible reaction mechanism



In conclusion, we have developed a concise and highly efficient strategy for the synthesis of *N*-glycosyl imidazole analogues. This reaction was based on a palladium catalysed decarboxylative allylation and three sequential steps of carbamation, decarboxylation and allylation were involved in this one-pot reaction. Different kinds of protecting groups, glycals and various CDI analogues were screened for this reaction and all the substrates gave the desired products with excellent yields and stereoselectivities. By varying the chirality of the C3 position of the glycal substrates, both α- and β-isomers can be obtained with high stereoselectivites.

We gratefully acknowledge the support by Nanyang Technological University (RG50/08) and support by an NMRC grant (H1N1 R/001/2009) from Ministry of Health, Singapore. We thank Yong-Xin Li and Dr. Ganguly Rakesh for X-ray analysis.

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization of new compounds are detailed. See DOI: 10.1039/c000000x/

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