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N-Heterocyclic Carbene Catalyzed *C*-Glycosylation: A Concise Approach from Stetter Reaction

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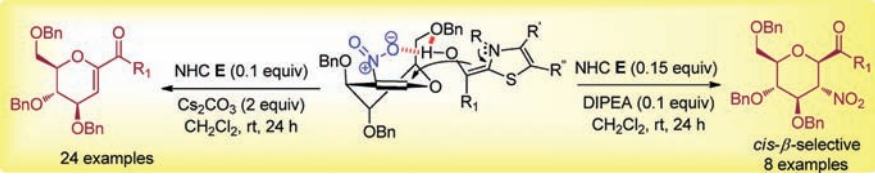
ABSTRACT



Described herein is the first example of an organocatalytic approach for acylanion addition to the anomeric carbon of 2-nitroglucal using an N-heterocyclic carbene catalyst. Control over the reaction conditions gives β-selective and nitro-eliminated *C*-glycosides, providing opportunities to produce new classes of *C*-glycoside.

Due to the fact that *C*-glycosides show attractive utility as potential drug candidates, their importance has grown over the years.[1] Therefore, the search for new methodologies for the expedient synthesis of *C*-glycosides has become of great interest to researchers. The development of new types of *C*-glycoside integrated with various heterocycles has gained much attention in recent times.[2] The potential pharmaceutical significance of this class of compounds has prompted various groups to develop different methodologies for *C*-glycosylation, including Lewis acid,[3a] metal-mediated,[3b] radical,[3c] and base-mediated glycosylation.[3d]

Recently, our group has actively investigated efficient and stereoselective *C*-glycosylation techniques, such as Lewis acid mediated glycosylation,[4a] Pd-catalyzed decarboxylative glycosylation,[4b] enol-triflate coupling glycosylation,[4c] and glycosidations based upon sulfur ylide cycloaddition reactions[4d] and sequential Rh-catalyzed aziridination/In-mediated Barbier allylation.[4e] In addition to these methodologies, we substantiated the importance of *C*-glycosides by demonstrating the high activities of certain *C*-glycosides toward biological systems.[5]

Some time ago, Schmidt, Vanker, and other groups devised a base-mediated glycosylation technique that used 2-nitroglucal derivatives.[6] Since 2-nitroglucal is a versatile Michael-type glycosyl donor under basic conditions, we envisioned that NHC catalyzed acylanion addition to

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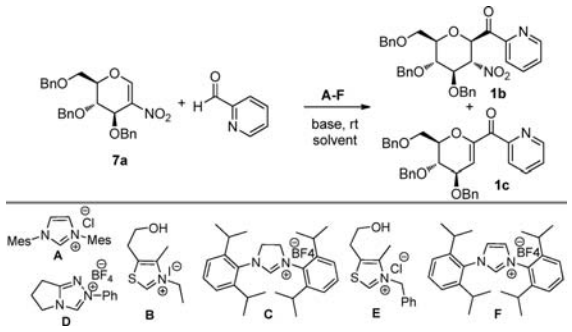
Table 1. Optimization of NHC Catalyzed *C*-Glycosylation



entry[a]	catalyst (equiv)	base (equiv)	solvent (0.05 M)	yield[b] **1b** (%)	yield[b] **1c** (%)
1	A (0.1)	DBU (0.1)	CH_2Cl_2	–	–
2	B (0.1)	DBU (0.1)	CH_2Cl_2	5	52
3	C (0.1)	DBU (0.1)	CH_2Cl_2	–	–
4	D (0.1)	DBU (0.1)	CH_2Cl_2	–	–
5	**E (0.1)**	**DBU (0.1)**	**CH_2Cl_2**	**10**	**59**
6	F (0.1)	DBU (0.1)	CH_2Cl_2	–	–
7	E (0.1)	Et_3N (0.1)	CH_2Cl_2	15	63
8	E (0.1)	DIPEA (0.1)	CH_2Cl_2	62	18
9	E (0.1)	Cs_2CO_3 (0.1)	CH_2Cl_2	20	68
10	**E (0.1)**	**Cs_2CO_3 (2)**	**CH_2Cl_2**	–	**87**
11	E (0.1)	Cs_2CO_3 (2)	CH_3CN	–	65
12	E (0.1)	Cs_2CO_3 (2)	THF	–	52
13	E (0.1)	Cs_2CO_3 (2)	dioxane	–	70
14	**E (0.15)**	**DIPEA (0.1)**	**CH_2Cl_2**	**77**	**5**
15	E (0.15)	DIPEA (0.1)	CH_3CN	30	20
16	E (0.15)	DIPEA (0.1)	THF	32	15
17	E (0.15)	DIPEA (0.1)	toluene	20	10

[a] Unless otherwise noted, all of the reactions were carried out using freshly distilled dry solvent at rt for 24 h. [b] Yield of isolated product.

2-nitroglucal would afford a new class of *C*-glycosides. Our initial study commenced with the reaction of pyridine-2-carboxaldehyde (1 equiv) and tri-*O*-benzyl-2-nitro-D-glucal (**7a**, 1.3 equiv) using various NHC catalysts (**A**–**F**, 0.1 equiv) and 0.1 equiv of DBU in dichloromethane (0.05 M) at rt (Table 1, entries 1–6). We observed that only thiazolium salts **B** and **E** led to the formation of two products, namely, the Stetter type β-selective *C*-glycoside **1b** and the subsequent base-mediated nitro-eliminated[7] *C*-glycoside **1c** (entries 2 and 5). The reactions with other precatalysts including triazolium salts **D** and imidazolium salts **A**, **C**, **F** were found to be unsuccessful. To our delight, precatalyst **E** led to the formation of *C*-glycoside products **1b** and **1c** in yields of 10% and 59% respectively (entry 5) which prompted us to further investigate the conditions used in this reaction. The scope of this optimized reaction was subsequently explored by varying the catalyst and base loadings as well as subjecting the reaction to different bases. Employing precatalyst **E** (0.1 equiv), the scope of this transformation was evaluated with various bases (0.1 equiv) (Et_3N, DIPEA, Cs_2CO_3) (entries 7–9) at rt using dichloromethane as solvent. Compound **1b** was formed as the major product in a yield of 62% (entry 8) when DIPEA was used as the base (0.1 equiv) in CH_2Cl_2. Glycoside **1c** was formed in 68% yield when Cs_2CO_3 was used as the base in CH_2Cl_2 (entry 9). Therefore, we expanded our optimization studies for each glycoside, **1b** and **1c**. The increased loading of Cs_2CO_3 to 2 equiv under the same reaction conditions led to compound **1c** in a yield of 87% (entry 10). To favor product **1c**, we fixed the conditions to 2 equiv (< 2 equiv provides a minor amount of **1b**) of Cs_2CO_3 and 0.1 equiv of precatalyst **E** and then screened the various organic solvents (entries 11–13). The results showed that the reaction in dichloromethane produced the highest yield of 87% (entry 10). The *C*-glycoside **1b** was somewhat sensitive to basic conditions due to elimination of the nitro group to form **1c**. Indeed, usage of 2 equiv of DIPEA produced **1c** in a reasonable yield along with 10–20% of **1b** as a minor product, which was not found in the case of Cs_2CO_3. This prompted us to use DIPEA as a base to obtain Stetter type β-selective *C*-glycoside **1b**. Earlier, it was found that 0.1 equiv of DIPEA produced an optimal yield of 62% (entry 8). To avoid the conversion of compound **1b** to **1c**, the catalyst loading was increased to 0.15 equiv to trap any unused DIPEA (0.1 equiv); further, various solvents were screened to selectively obtain **1b** (entries 14–17). Similarly, the best result for obtention of **1b** resulted when dichloromethane was employed as the solvent, producing it in a yield of 77% along with small amounts of compound **1c** (5% yield) (entry 14).

The optimized conditions for the formation of **1b** involve the employment of 0.15 equiv of precatalyst **E** in the presence of 0.1 equiv of DIPEA in dichloromethane (0.05 M) and stirring at rt for 24 h (entry 14). On the other hand, the conditions for formation of the nitro-eliminated product **1c** involve employment of 0.1 equiv of precatalyst **E** in the presence of 2 equiv of Cs_2CO_3 in dichloromethane (0.05 M), at rt for 24 h (entry 10). With these optimized reaction conditions in hand, we began to explore the substrate scope (Figures 1 and 2).[8a] At the outset of this study, a few examples of N-containing heteroaromatic aldehydes and 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal were subjected to the Stetter type β-selective *C*-glycosidation (Figure 1), as we found that 2-formyl-N-containing heterocycles were competent substrates with good to moderate yields obtained for 2-quinoline (**2b**, 89%), 6-methyl-2-pyridine (**3b**, 82%), 6-hydroxymethyl-2-pyridine (**4b**, 75%), and 8-formylquinoline (**5b**, 75%). The formation of **4b** indicates that the reaction occurred specifically with the aldehyde functional group even in the presence of a hydroxymethyl group,

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(8) (a) See Supporting Information for experimental, spectral details and ORTEP drawings. (b) CCDC 823119 and 823120 (**2b** and **8c** respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

which proves that *C*-glycosylation is more facile than *O*-glycosylation. Concurrently, different sugars such as benzyl protected 2-nitro-D-galactal (**6b**, 84%), methyl protected 2-nitro-D-glucal (**7b**, 78%), and 3,4-di-*O*-benzyl-2-nitro-L-rhamnal (**8b**, 82%) also showed good yields. The base-mediated nitro-eliminated glycoside is a new class of *C*-glycoside, in contrast to a Michael addition type *C*-glycoside, which allows one to develop more diverse types of *C*-glycoside including various heteroaromatic, aromatic, and aliphatic aldehydes (Figure 2).

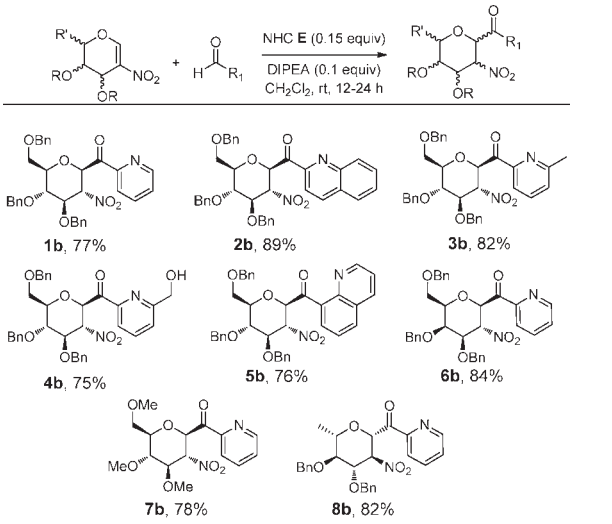


Figure 1. Scope of Stetter type β-selective *C*-glycosides.[8a] (a) For the enitre figure, unless otherwise noted all the reactions were carried out under standard optimized conditions. (b) Isolated yields are recorded above.

Pyridines with formyl groups at C-2, C-3, and C-4 (**1c**−**3c**) were screened, and the results showed that good to moderate yields were obtained (72−87%). 6-Methyl-2-pyridine (**4c**, 74%) and 6-hydroxymethyl-2-pyridine (**5c**, 83%) afforded the nitro-eliminated *C*-glycosides in good yield. By using 2.5 equiv of 2-nitroglucal (**7a**), a dimeric glucal type *C*-glycoside **6c** was produced in which two sugars were linked by 2,6-pyridinedicarboxaldehyde; it was formed in 74% yield. Next, we investigated the possibility of preparing *C*-glycosides from commercially available quinoline sources with formyl groups at C-2, C-3, and C-8. The reaction proceeded smoothly with yields of 74−79% (**7c**−**9c**). 2-Formylthiophene was also observed to give a moderate yield (64%) of product **10c**.

Subsequently, the reaction scope was investigated on 2-nitro-tri-*O*-benzyl-D-galactal (**11c**), 2-nitrodihydropyran (**12c**), and 2-nitro-di-*O*-benzyl-L-rhamnal (**16c**), and all were found to be viable substrates. Similarly, the reaction scope was evaluated with different protecting groups on the 2-nitroglucal (**13c**−**15c**), and it was found that a long chain alkyl substituent showed a moderate

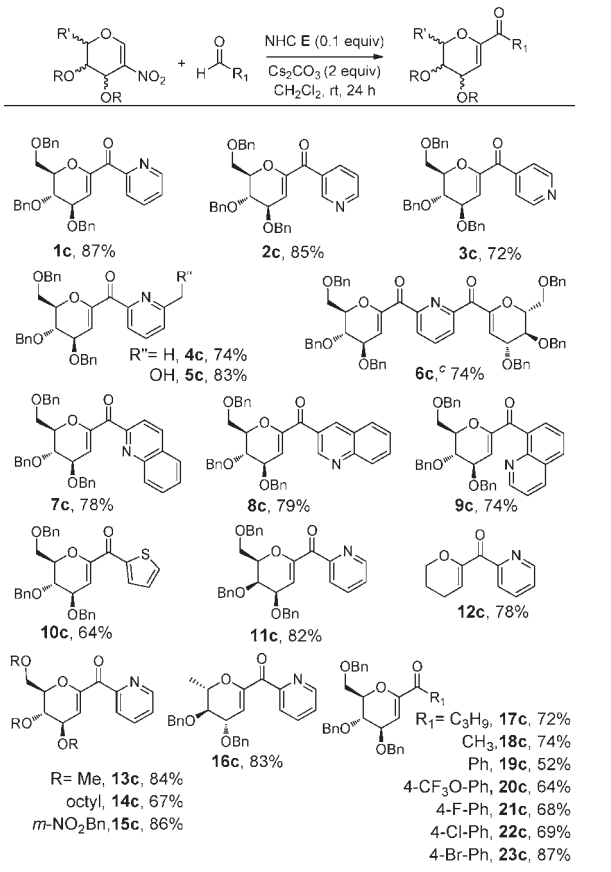


Figure 2. Scope of nitro-eliminated *C*-glycosides.[8a] (a) For the enitre figure, unless otherwise noted all the reactions were carried out under standard optimized condition. (b) Isolated yields are recorded above. (c) 2.5 equiv of tri-*O*-benzyl-2-nitro-D-glucal was used.

Scheme 1. *C*-Glycosylation on Disaccharide

yield of 67% while the rest showed good yields (84−86%). This organocatalytic *C*-glycosylation protocol was further extended to aliphatic aldehydes such as butyraldehyde and acetaldehyde (**17c** and **18c**), and the corresponding *C*-glycosides were obtained in moderate yields of 72% and 74% respectively. Various benzaldehyde derivatives were employed as glycosyl acceptors, and they produced moderate yields of the product (52−69%). However, 4-bromobenzaldehyde was able to achieve a good yield (**23c**, 87%). Finally, this reaction pattern was applied to disaccharide **18a** and a moderate yield was obtained for **24c** (Scheme 1, 69%) showing that this glycosylation is

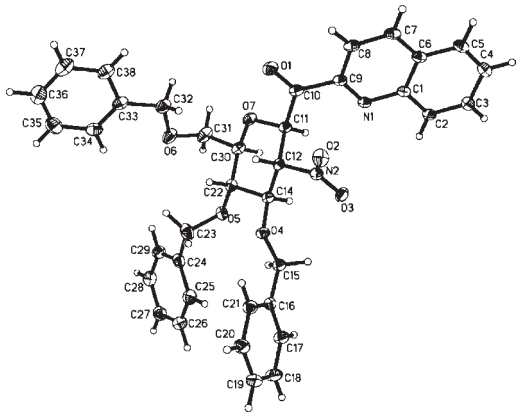


Figure 3. X-ray structure of compound **2b**.

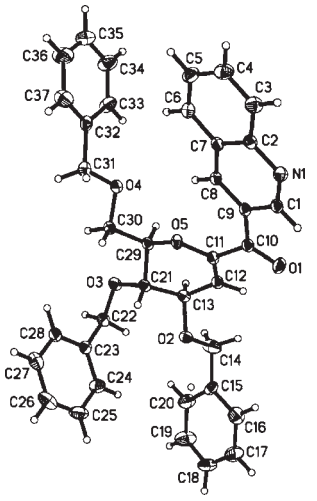
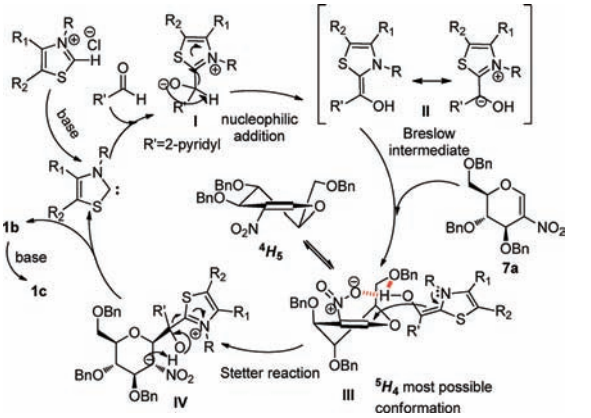


Figure 4. X-ray structure of compound **8c**.

tolerant to a wide range of substrates. All the products were well characterized,[8a] and the structures of **2b** and **8c** were confirmed by X-ray crystallography[8b] (Figures 3 and 4).

Scheme 2. Plausible Reaction Mechanism



The possible catalytic cycle for this reaction is depicted in Scheme 2. Presumably, the reaction proceeds through the nucleophilic addition of carbene to aldehyde (**I**), forming the Breslow intermediate **II**, which then attacks the more favored $^5H_4$ conformation (**III**) of **7a** to form **IV**, which then undergoes a proton shift followed by NHC ejection to form *C*-glycoside **1b**. The Schmidt group[3d] explained that 2-nitroglucal may favor the $^5H_4$ conformation as opposed to the $^4H_5$ conformation due to the allylic strain. This would favor the acyl anion preferentially adding from the β-side of **III**.

In conclusion, we have developed a new method for an organocatalytic *C*-glycosidation, which is the first example of acylanion equivalent addition to the anomeric carbon of sugars.

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Supporting Information Available. Experimental procedures and compound characterization data of all the unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.