Rh(III)-catalyzed direct access to 2,3-substituted β-*N*-glycosyl indoles through C-H activation/annulation coupling of β-*N*-aryl glycosides with substituted internal alkynes

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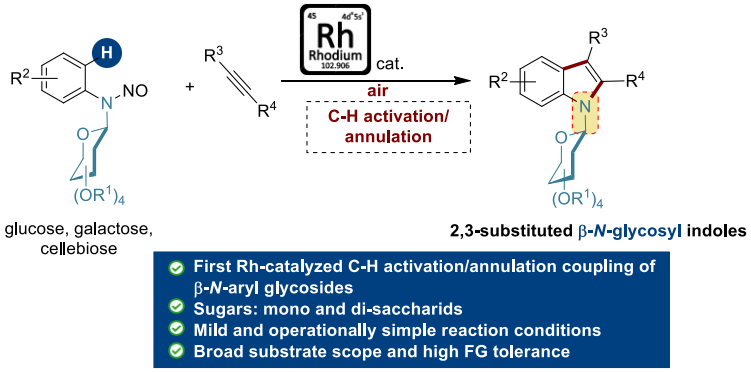


ABSTRACT: An efficient and selective C-H activation/annulation of readily available β-*N*-aryl glycosides with various alkynes has been established. Using $[Cp^*RhCl_2]_2$ as a catalyst and $AgSbF_6$ in DCE, this protocol proved to be general to prepare a variety of 2,3-substituted *N*-glycosyl indoles in good yields with exclusive β-selectivity.

β-*N*-glycosyl indoles are of high importance in medicinal chemistry and commonly found in many compounds of practical importance, ranging from natural compounds to pharmaceutical agents[1] (Figure 1). While these derivatives clearly hold a great potential in medicinal chemistry, relatively little attention has been devoted to their syntheses (Figure 1-B), since the stereoselective induction of a nitrogen indole scaffold at the anomeric position remains as a particularly difficult task. From a synthetic point-of-view, 2,3-substituted β-*N*-glycosyl indoles **3** (Figure 1) were prepared through multi-steps syntheses by treating indoline derivatives with sugars lactols[1i,2] followed by (*i*) oxidation of the indoline into indole and (*ii*) functionalization of the C-2 and C-3 positions (Figure 2, Path A). The synthesis of 2,3-substituted β-*N*-glycosyl indoles is also possible *via* a β-glycosylation of indoles through a SN_2 Mitsunobu reaction[1k, 1l, 3] followed by the functionalization of the indole nucleus (Figure 2, Path B). However, the reaction necessitate the use of a well-defined α-sugar lactols which are difficult to synthesize through multisteps sequences.[4] Moreover, a mixture of α- and β-anomers was obtained in most cases. Another way to prepare stereoselectively β-*N*-glycosyl indoles is the use of Danishefsky α-1,2-anhydro sugars (Figure 2, Path C).[5] While this method is efficient, beside the necessary of C2- and C3 functionalization,

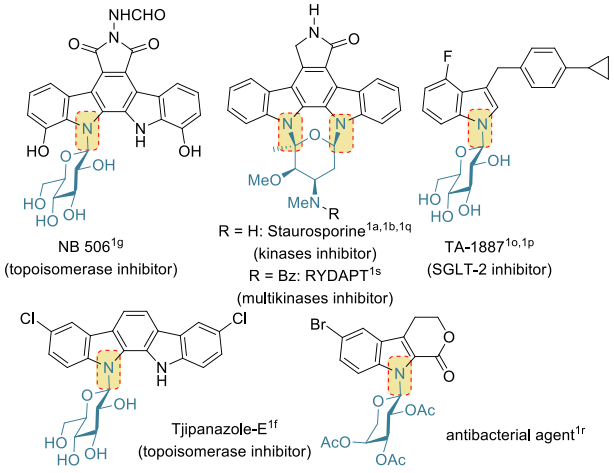


Figure 1. Heteroaryl *N*-glycoside-based bioactive molecules

access to α-1,2-anhydrosugars (epoxides) remain no trivial. Indeed, their synthesis from epoxidation of the corresponding glycals is inherently relies on the use of the Murray's reagent[6] (DMDO) which is an instable volatile peroxide not easy to prepare and manipulate. Despite these advances, the absence of a general and predictable

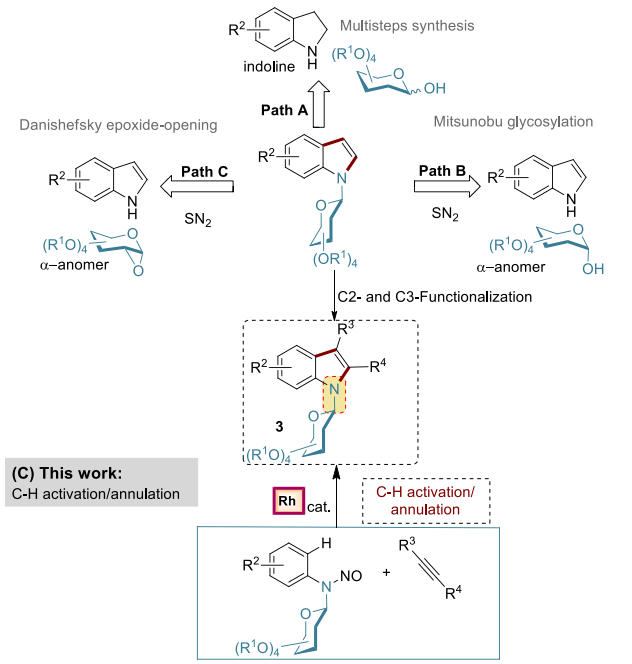


Figure 2 Strategies to access to 2,3-substituted β-*N*-glycosyl indoles

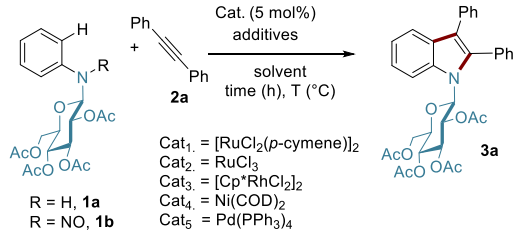
method for the direct synthesis of 2,3-substituted β-*N*-glycosyl indoles with a minimum of steps remains a major gap in glycochemistry preventing greater investigation of the biology and applications of these compounds.

Recently, our group reported an efficient protocol for the synthesis of β-*N*-aryl glycosides *via* a copper-catalyzed Chan-Lam-Evans *N*-arylation of aryl boronic acids.[7] As part of our continued efforts to functionalize sugars under transition-metal catalysis to access complex glycosides,[8] we envisioned whether β-*N*-aryl glycosides could be utilized as building blocks in the synthesis of β-*N*-glycosyl indoles through a transition-metal-catalyzed activation/annulation reaction in the presence of various alkynes (Figure 1-C). This modular strategy is conceptually attractive in terms of diversifying the *N*-glycosyl indoles frameworks with the aim to identify novel scaffolds of biological interest. In this work, we showed for the first time, that β-*N*-aryl glycosides and alkynes were successfuly joined together through a C-H activation/annulation process[9] to afford in a single step stereoselectively, a variety of substituted β-*N*-glycosyl indoles (Figure 1-C).

To achieve successfully our goal, initial investigations focused on identifying optimal conditions for the coupling of β-*N*-phenyl glucopyranoside **1a** with 1,2-diphenylethyne **2a** as models study (Table 1). In preliminary experiments, the C–H activation/annulation reaction was examined under various conditions in the presence of different catalysts such as Ru,[10] Rh,[11] Ni,[12] and Pd,[13] but unfortunately, β-*N*-glycosyl indole **3a** was not detected under these conditions.

Further, inspired by the recent work described by Zhu[14a] and Fan[14b] whose reported the cyclization of *N*-nitrosoanilines under Rh(III)-catalysis, we evaluated the influence of a nitroso-substituent on the phenyl glucopyranoside nitrogen atom (compound **1b**). When we used β-*N*-nitrosophenyl glucopyranoside **1b** with [(Cp*RhCl$_2$)$_2$] (5 mol%), AgSbF$_6$ (20 mol%), and diphenylacetylene (**2a**, 2

Table 1 Survey of reaction conditions for the C-H activation/annulation of **1a,b** with **2a**[a]



entry	R	Cat.	additive	solvent	Temp (°C)	Time (h)	yield **3a** (%)[b]
1	H	Cat$_1$	AgNO$_3$	*t*-AmOH	120	12	0
2	H	Cat$_1$	Ag$_3$PO$_4$	*t*-AmOH	120	12	0
3	H	Cat$_1$	MeCO$_2$Ag	*t*-AmOH	120	12	0
4	H	Cat$_1$	CF$_3$CO$_2$Ag	*t*-AmOH	120	12	0
5	H	Cat$_1$	AgSbF$_6$	*t*-AmOH	120	12	0
6	H	Cat$_1$	AgSbF$_6$	dioxane	120	12	0
7	H	Cat$_1$	AgSbF$_6$	DCE	120	12	0
8	H	Cat$_1$	AgSbF$_6$	Acetone	120	12	0
9	H	Cat$_1$	AgSbF$_6$	DMF	120	12	0
10	H	Cat$_1$	AgSbF$_6$	Toluene	120	12	0
11	H	Cat$_2$	AgSbF$_6$	*t*-AmOH	120	12	0
12	H	Cat$_3$	AgSbF$_6$	*t*-AmOH	120	12	0
13	H	Cat$_4$	AgSbF$_6$	*t*-AmOH	120	12	0
14	H	Cat$_5$	AgSbF$_6$	*t*-AmOH	120	12	0
18	NO	Cat$_3$	AgSbF$_6$	DCE	100	3	38
19	NO	Cat$_3$	AgSbF$_6$	DCE	120	3	25
20	NO	Cat$_3$	AgSbF$_6$	DCE	rt	15	trace
21	NO	Cat$_3$	AgSbF$_6$	DCE	60	15	31
22	NO	Cat$_3$	AgSbF$_6$	DCE	100	5	55[c]
23	NO	Cat$_3$	AgSbF$_6$	DCE	90	5	70
24	NO	Cat$_3$	--	DCE	90	5	0
25	NO	--	AgSbF$_6$	DCE	90	5	0
26	NO	Cat$_3$	AgSbF$_6$	DCE	90	5	72[d]

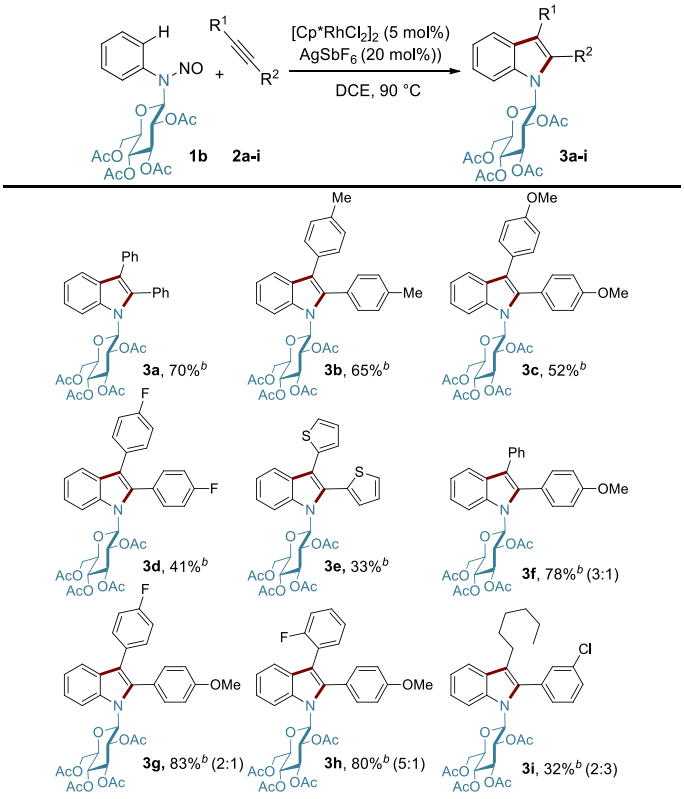
[a] Reactions were conducted with substrate **1a** or **1b** (0.10 mmol), alkyne (0.2 mmol), catalyst, additive, and solvent (1.0 mL). [b] Yield of isolated product **3a**. [c] **1b** was completely consumed. [d] 0.4 mmol of **2a** were used.

equiv.) in 1,2-dichloroethane (DCE) at 100 °C for 3 h, we obtained *β*-*N*-glucosyl indole **3a** ($J_{1,2}$ = 9.3 Hz) in 38% yield (entry 18). After screening several parameters, we finally found that the C-H annulation between **1b** and **2a** occured smoothly with 70% yield in the presence of [(Cp*RhCl2)2] (5 mol%), AgSbF$_6$ (20 mol%), in DCE at 90 °C for 5 h without adding any external oxidant (Table 1, entry 23). It should be noted that the Rh-catalyst and AgSbF$_6$ were necessary to achieve this transformation since no reaction occur when the coupling was conducted in the absence of [(Cp*RhCl$_2$)$_2$] or AgSbF$_6$ (entries 24 and 25).

Motivated by these results, we next explored the scope of the coupling reaction of **1b** with a variety of internal alkynes and we are gratifyingly pleased with the generality of this method. Various internal alkynes reacted smoothly to afford the desired 2,3-disubstituted *N*-glucosyl indoles **3a-i** in satisfactory yields. A variety of symmetric diaryl alkynes were efficiently converted into the corresponding products and electron-donating substituents on the aromatic rings had a positive electronic effect on yield than electron-withdrawing substituents (Table 2, **3a–d**). The coupling reaction with 1,2-di(thiophen-2-yl)ethyne was also efficient to afford **3e** in a moderate yield. Moreover, unsymmetrically substituted alkynes **2f-i** were converted with variable yields and moderate regioselectivities (**3f-i**).

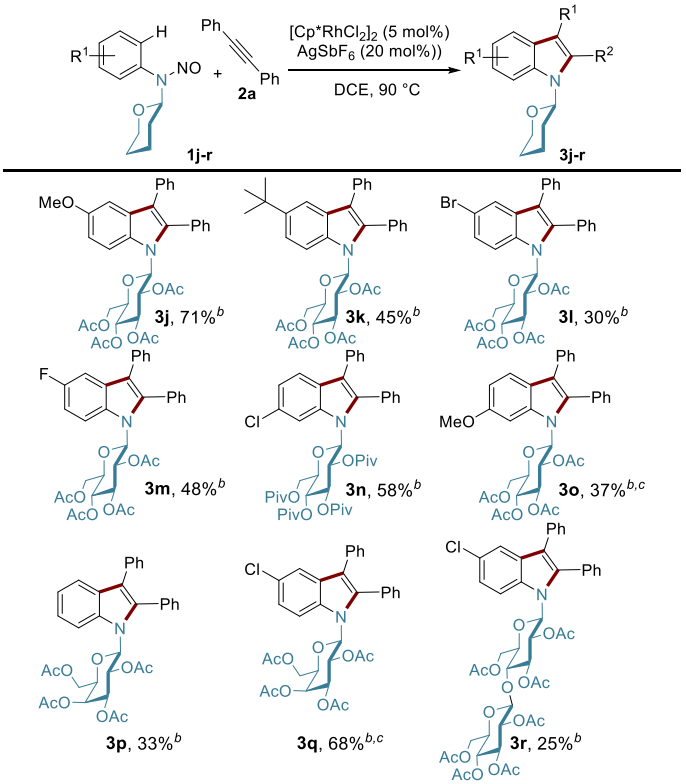
In a further set of experiments, we investigated the scope and generality of the method with respect to β-*N*-aryl glycosides **1j-r**. As depicted in Table 3, the protocol tolerated different β-*N*-aryl glucosides and a multitude of 5- and

Scheme 1 Scope of alkynes coupling with tetraacetyl β-*N*-nitrosophenyl glucopyranoside **1b**



Reaction conditions: reactions were performed in a flame dried re-sealable Schlenk tube using 1b (0.30 mmol), alkynes 2 (2 equiv), [RhCp*Cl2]2 (5 mol%), AgSbF6 (20 mol%), in 1,2-DCE (0.1 M) at 90 °C for 5 h. b Yield of isolated product 3.

Scheme 2 Scope of β-*N*-nitroso-aryl glycosides **1j-r** coupling with **2a**

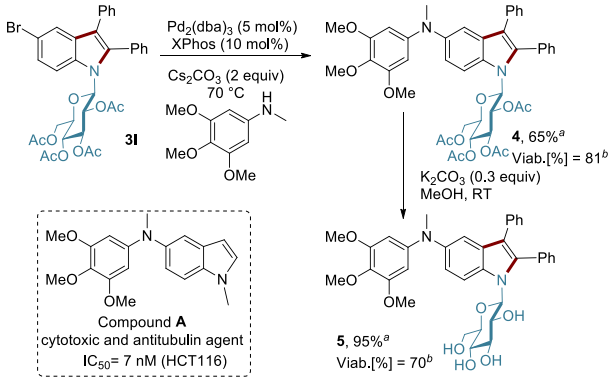


Reaction conditions: reaction were performed in a flame dried re-sealable Schlenk tube using **1j-r** (0.30 mmol), alkyne **2a** (2 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), in 1,2-DCE (0.1 M) at 90 °C for 5 h. [b] Yield of isolated product **3**. [c] The reaction was achieved at 80 °C

6-substituted indoles **3j-o** were readily prepared using this reaction. 5-Substituted β-*N*-aryl glycosides bearing elec tron-donating or electron-withdrawing groups afforded the corresponding 5-substituted β-*N* glucosyl indoles **3j-m** in acceptable yields. In addition, meta-substitution was tolerated furnishing 6-disubstituted β-*N*-glucosyl indoles **3n** and **3o** in 58% and 37% yields, respectively. Interestingly, this cross-coupling tolerated the presence of C–halogen bonds (*e.g.*, F, Cl, Br) which offers a platform for further metal-catalyzed cross coupling reactions (compounds **3l**, **3m** and **3n**). Moreover, the C-H activation/annulation process is not limited to β-*N*-aryl glucosides but also works successfully with β-*N*-aryl galactosides **1p,q** and the peracetylated β-D-disaccharide **1r** derived from D-β-cellobiose octaacetate, however only 25% isolated yield of the disaccharide **3r** was obtained probably due to its intrinsic instability of **3r**. Of note, the stereochemistry of the 1→4' glycosidic bond remained intact. It is noteworthy that the coupling of unprotected β-*N*-nitrosophenyl glucoside with 1,2-diphenylethyne **2a** under the above experimental conditions failed, as only starting materials were recovered unchanged.

With substantial amounts of **3l** in hand (Table 2), we focused our attention on demonstrating whether our method could be employed for molecular diversity. As shown in Scheme 1, β-*N*-glucosyl indole **4**, which is an analogue of compound **A**, a highly promising cytotoxic and antitubulin agent developed in our group,[15] was easily prepared *via* a Pd-catalyzed coupling reaction of **3l** with 3,4,5-trimethoxy-*N*-methylaniline. Compound **5** was obtained from **4** by deprotection of the acetates groups under Zemplen's conditions using a catalytic amount of potassium carbonate in methanol.[16]

Scheme 1 Application of this methodology the synthesis of bioactive compounds **4** and **5**



The *in vitro* activity of derivatives **4** and **5** was evaluated by their growth-inhibitory potency against HCT-116 cancer cells (human colon carcinoma) at the concentration of 10^{-6} M. The quantification of cells survival in this cell line was established by using MTT assays after 72 h of exposure. We found that analogues **4** and **5** displayed a mod-

erate effect in the growth of HCT-116 (81% and 70% survival, respectively) compared to the reference compound **A** (IC_{50} = 7 nM) (Scheme 1).

In conclusion, we successfully developed an efficient and practical method based on Rh(III)-catalyzed C-H activation/annulation process of various β-*N*-nitroso-aryl glycosides with alkynes. The protocol exhibited a broad substrate scope with respect to the coupling partners, thus providing an attractive access to a large molecular diversity of 2,3-disubstituted *N*-glycosyl indoles **3**. This protocol developed is stereoretentive, functional-group tolerant, and proceeds in good yields. We believe that this methodology will find broad applications in organic synthetic chemistry as well as in combinatorial and pharmaceutical sciences.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectroscopic data and NMR spectra of new compounds.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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