Iridium-Catalyzed Direct Hydroarylation of Glycals via C–H Activation: Ligand-Controlled Stereoselective Synthesis of α- and ß-*C*-Glycosyl Arenes

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Iridium-Catalyzed Direct Hydroarylation of Glycals via C–H Activation: Ligand-Controlled Stereoselective Synthesis of α- and β-*C*-Glycosyl Arenes

Kana Sakamoto,[†] Masaki Nagai,[‡] Yusuke Ebe,[‡] Hideki Yorimitsu,[‡] and Takahiro Nishimura[†,*]

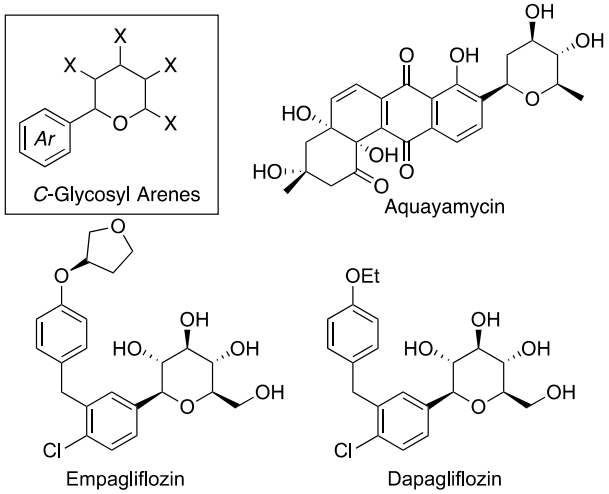
[†] Department of Chemistry, Graduate School of Science, Osaka City University, Sumiyoshi, Osaka 558-8585, Japan

[‡] Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

ABSTRACT: Diastereoselective direct hydroarylation of glycals with aromatic compounds was realized by use of an iridium/binap catalyst, giving the corresponding *C*-glycosyl compounds in high yields. The use of binap with the different absolute configuration enabled the stereoselective synthesis of α- or β-*C*-glycosyl arenes irrespective of the chirality of the glycals. The method showing the high functional group tolerance provides an atom-economical access to *C*-glycosyl arenes by way of C–H bond activation.
KEYWORDS: *iridium, hydroarylation, C–H activation, glycals, C-glycosyl arenes*

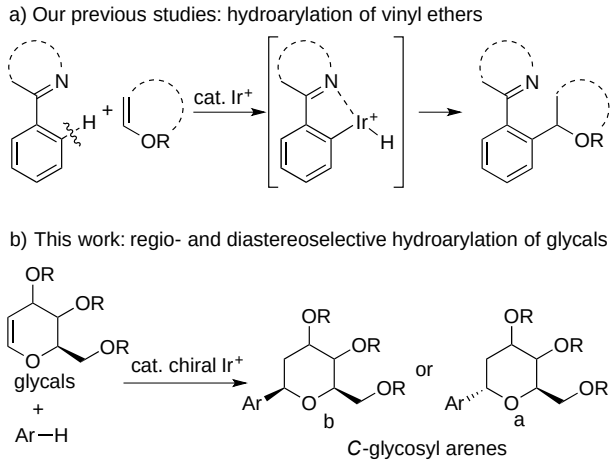
C-Glycosyl derivatives have attracted much attention due to the existence of a number of natural products and the significant biological properties (Scheme 1).[1] For example, some *C*-glycosyl arenes as inhibitors of renal sodium-dependent glucose cotransporter 2 (SGLT2) have been recently approved to be drugs targeting type 2 diabetes.[2] In this context, many efforts have been devoted to provide efficient methods of introduction of aryl moieties into sugars for the synthesis of *C*-glycosyl arenes.[1] Transition metal-catalyzed cross-coupling reactions have played important roles in the *C*-glycosylations because the reactions often display regio- and/or stereoselectivity.[3]

Glycals represent sugar derivatives having a double bond between carbon atoms 1 and 2 of the ring, which allows installation of many functional groups into the monosaccharide. Pd-catalyzed Mizoroki-Heck type arylation of glycals has been extensively studied for the synthesis of unsaturated *C*-glycosyl compounds, where, in most cases, aryl groups were introduced with α-selectivity.[4] Ni-catalyzed reaction of arylboronic acids with perbenzylated glycals involving regioselective β-*O* elimination of glycals was reported to give ring-opened products, which underwent the ring closure reactions leading to *C*-glycosyl arenes.[5] Pd-catalyzed addition/elimination reactions of acylated glycals with uracils, which involves C–H activation, was recently reported.[6] In this context, due to the growing medicinal importance of *C*-glycosyl arenes, a synthetic approach that uses the direct addition of arenes to glycals by C–H activation would be highly attractive from an atom-economical point of view.[7]



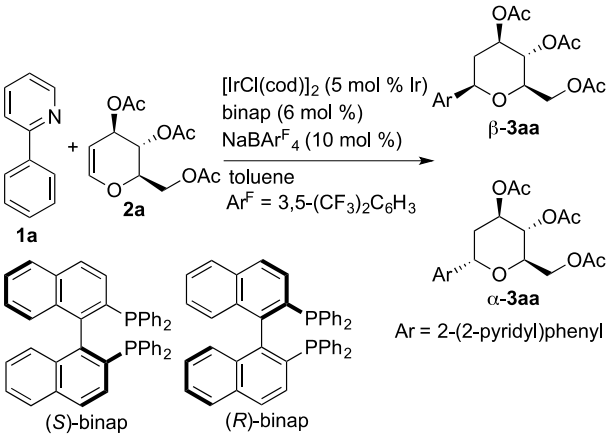
Scheme 1. Selected Biologically Active *C*-Glycosyl Arenes

Recently, we reported Ir-catalyzed directed hydroarylation of vinyl ethers (Scheme 2a),[8] where the aryl groups are selectively introduced into the α-carbon of the alkoxy group. The findings of the catalytic system of Ir prompted us to develop a new method for the synthesis of 2-deoxy aryl *C*-glycosyl derivatives in an atom-economical manner (Scheme 2b). Here we report the regio- and diastereoselective direct hydroarylation of glycals catalyzed by a chiral Ir complex.[9] The stereoselective synthesis of *C*-α- or β-glycosyl arenes was achieved



Scheme 2. Ir-Catalyzed Hydroarylation

Table 1. Ir/Binap-Catalyzed Stereoselective Hydroarylation of 2a with 1a[a]

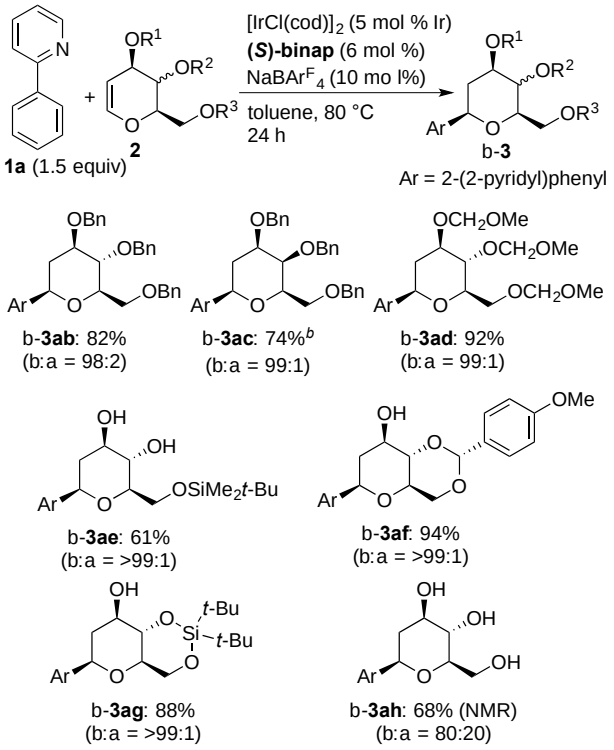


entry	ligand	temp. (°C)	yield (%)[b]	β:α[c]
1	(*S*)-binap	100	99	90:10
2	(*S*)-binap	80	90[d]	96:4
3[e]	(*S*)-binap	60	88	46:54
4	(*R*)-binap	100	84	12:88
5	(*R*)-binap	80	63	7:93
6[e]	(*R*)-binap	60	83[d]	5:95

[a]Reaction conditions: **1a** (0.11 mmol for entries 1–3, and 0.15 mmol for entries 4–6), **2a** (0.10 mmol), $[IrCl(cod)]_2$ (5 mol % Ir), binap (6 mol %), and $NaBAr^F_4$ (10 mol %) in toluene (0.40 mL) for 24 h. [b]Combined yield of the products determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard. [c]Determined by ^1H NMR of the crude mixture. [d] Isolated yield of the major product. [e]For 48 h.

by use of binap with the different absolute configuration.[10]

Initially, we selected glucal **2a** as an accepter of the addition of a C–H bond of 2-phenylpyridine (**1a**) as shown in Table 1. After an optimization of the reaction conditions of the Ir catalysis being effective in our previous studies,[8a] it was found that the diastereoselectivity in hydroarylation of glycals via C–H activation of aromatic compounds was controlled by changing the absolute configuration of a chiral ligand under the optimized reaction temperature. Thus, treatment of tri-*O*-acetyl-D-glucal (**2a**) with 1.1 equivalents of 2-phenylpyridine (**1a**) in the presence of $[IrCl(cod)]_2$ (5 mol % Ir, cod = 1,5-cyclooctadiene), (*S*)-binap[11] (6 mol %), and $NaBAr^F_4$ [Ar^F = 3,5-$(CF_3)_2C_6H_3$] (10 mol %) in toluene at 80 °C for 24 h gave *C*-glycosyl derivative β-**3aa** as a major product (β:α = 96:4, Table 1, entry 2).[12] Analytically pure β-**3aa** was isolated in 90% yield by preparative TLC. The high β-selectivity was observed at the high reaction temperature: the reaction at 60 °C gave an almost 1:1 mixture of the isomers (entry 3).[13] The ligand-controlled β-selectivity of the present Ir catalysis is different from the selectivity observed in the reported Pd-catalysis of the addition/elimination reactions, which show α-selectivity significantly influenced by the stereochemistry of the glycals.[4] In contrast, the use of (*R*)-binap enabled highly α-selective hydroarylation of D-glucal **2a** (entries 4–6), where the lower reaction temperature improved the α-selectivity. Thus, the reaction of **1a** (1.5 equiv.) with **2a** in the presence of the cationic Ir/(*R*)-binap catalyst at 60 °C for 48 h gave α-**3aa**

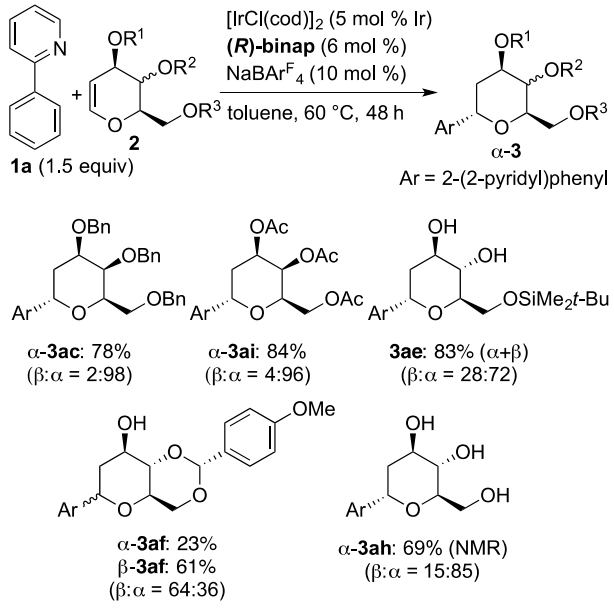


[a]Isolated yield of the major product is shown unless otherwise noted. The diastereomeric ratio in the parenthesis was determined by ^1H NMR of the crude mixture. [b]At 100 °C.

Scheme 3. Ir-Catalyzed β-Selective Hydroarylation of Glycals[a]

as a major product (β:α = 5:95), which was isolated in 83% yield (entry 6).[14]

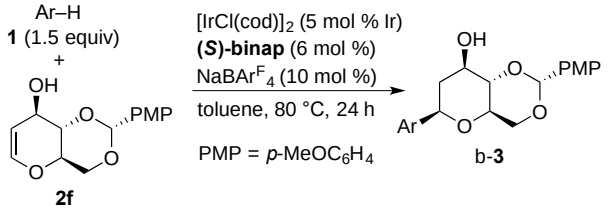
The protecting groups employed in the chemistry of sugars are highly important towards the preparation of complex oli-

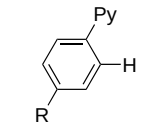
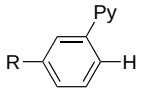
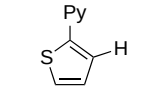
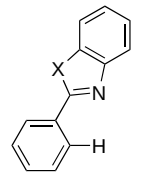


[a]Isolated yield of the major product is shown unless otherwise noted. The diastereomeric ratio in the parenthesis was determined by ^1H NMR of the crude mixture.

Scheme 4. Ir-Catalyzed α-Selective Hydroarylation of Glycals[a]

Table 2. Ir/(*S*)-Binap-Catalyzed β-Selective Hydroarylation of 2f with 1[a]



entry	1		yield (%)[b]	ratio (b:a)[c]
1		R = Me (**1b**)	86 (b-**3bf**)	>99:1
2		MeO (**1c**)	83 (b-**3cf**)	>99:1
3		F (**1d**)	72 (b-**3df**)	>99:1
4		Br (**1e**)	73 (b-**3ef**)	>99:1
5	Py = 2-pyridyl	Ph (**1f**)	87 (b-**3ff**)	>99:1
6		R = OMe (**1g**)	66 (b-**3gf**)	>99:1
7		Br (**1h**)	73 (b-**3hf**)	>99:1
8		**1i**	77 (b-**3if**)	>99:1
9		X = O (**1j**)	71 (b-**3jf**)	>99:1
10[d]		O (**1j**)	72 (b-**3jg**)	>99:1
11		NMe (**1k**)	71 (b-**3kf**)	>99:1

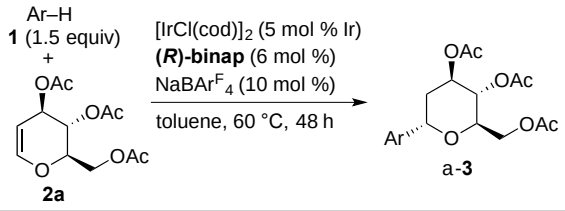
[a]Reaction conditions: **1** (0.15 mmol), **2f** (0.10 mmol), $[IrCl(cod)]_2$ (5 mol % Ir), (*S*)-binap (6 mol %), and $NaBAr^F_4$ (10 mol %) in toluene (0.40 mL) at 80 ºC for 24 h. [b]Isolated yield. [c]Determined by ^1H NMR of the crude mixture. [d]**2g** (0.10 mmol) was used instead of **2f**.

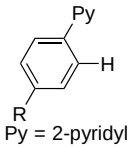
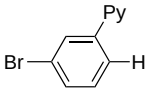
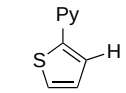
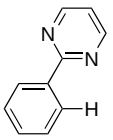
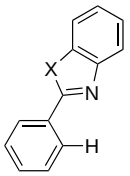
gosaccharides. Therefore, a high functional group tolerance in the functionalization of sugars is desirable. Under the present catalytic conditions, diverse glycals **2b**–**h** participated in the β selective hydroarylation using (*S*)-binap to give high yields of the corresponding *C*-glycosyl arenes **3ab**–**ah** (Scheme 3). In the reaction of tri-*O*-benzyl-D-glucal (**2b**) and tri-*O*-benzyl-D-galactal (**2c**), a high β-selectivity was observed. Glucal **2d** having methoxymethyl groups reacted with **1a** to give **3ad** in 92% yield. Partially protected glucals **2e**–**g** can also be applied to the reaction to give the corresponding *C*-glycosyl arenes **3ae**–**ag** in high yields. Non-protected D-glucal (**2h**) also underwent the hydroarylation, but a slightly low diastereoselectivity was observed (β:α = 80:20).

Scheme 4 summarizes the results obtained for the α-selective hydroarylation of glycals using (*R*)-binap as a ligand. The hydroarylation of tri-*O*-benzyl-D-galactal (**2c**) and tri-*O*-acetyl-D-galactal (**2i**) took place with high α-selectivity. A good α-selectivity was also obtained in the reaction of mono-*O*-silylated **2e**. In contrast, α-selective reaction was not possible for **2f** giving β-**3af** as a major product probably due to the rigid conformation induced by a cyclic acetal moiety.[15] The reaction of D-glucal (**2h**) also proceeded to give **3ah** in good yield and selectivity.

As shown in Schemes 3 and 4, the present catalytic system can be applied to a protecting group-free gulcal **2h**. However,

Table 3. Ir/(*R*)-Binap-Catalyzed α-Selective Hydroarylation of 2a with 1[a]

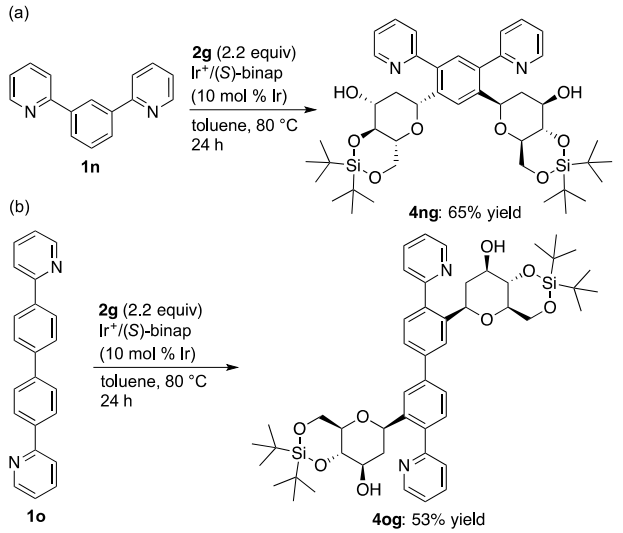


entry	1		yield (%)[b]	ratio (b:a)[c]
1[d]		R = Me (**1b**)	79 (a-**3ba**)	4:96
2		MeO (**1c**)	91 (a-**3ca**)	2:98
3		F (**1d**)	97 (a-**3da**)	2:98
4	Py = 2-pyridyl	Br (**1e**)	84 (a-**3ea**)	2:98
5		**1h**	67 (a-**3ha**)	7:93
6[d]		**1i**	67 (a-**3ia**)	7:93
7		**1l**	65 (a-**3la**)	12:88
8		X = O (**1j**)	53 (a-**3ja**)	1:99
9		S (**1m**)	56 (a-**3ma**)	1:99

[a]Reaction conditions: **1** (0.15 mmol), **2a** (0.10 mmol), $[IrCl(cod)]_2$ (5 mol % Ir), (*R*)-binap (6 mol %), and $NaBAr^F_4$ (10 mol %) in toluene (0.40 mL) at 60 ºC for 48 h. [b]Isolated yield. [c]Determined by ^1H NMR of the crude mixture. [d]For 72 h.

the diastereoselectivity of the reaction is not enough high to obtain the pure isomers considering the difficulty of the purification. The problem was readily solved by deprotection of tri-*O*-acetyl groups in α- and β-**3aa** obtained in pure form. The deacetylation of α- and β-**3aa** in the presence of K_2CO_3 in methanol thus gave the corresponding unprotected *C*-glycosyl arenes α-**3ah** and β-**3ah** in 90% and 93% yields, respectively.

The present catalytic system can be applied to β-selective hydroarylation of glucal **2f** with several aromatic compounds **1** using (*S*)-binap (Table 2). 2-Phenylpyridines substituted with functional groups, Me (**1b**), MeO (**1c**,**g**), F (**1d**), Br (**1e**,**h**), and Ph (**1f**) are all good substrates to give the corresponding addition products **3bf**–**hf** with high diastereoselectivity (entries 1–7). An installation of a 3-thienyl group was also possible to give β-**3if** in 77% yield (entry 8). As directing groups, benzoxazolyl **1j** and benzimidazolyl **1k** functioned and the addition reactions of them gave the corresponding adducts in good yields (entries 9–11). Unfortunately, however, other aromatic compounds such as acetophenone, acetophenone *O*-methyl oxime, and *N*-(4-methoxyphenyl)-1-phenylethan-1-imine, which were good substrates for Ir-catalyzed *ortho*-C–H alkylation,[8a,b] were inert under the present reaction conditions.



Scheme 5. Introduction of Two Sugar Units

α-Selective addition of a variety of aromatic groups to **2a** can be achieved using (*R*)-binap as the chiral ligand (Table 3). Aromatic compounds having a 2-pyridyl group (**1b**–**e**,**h**,**i**), 2-pyrimidyl (**1l**), 2-benzoxazolyl (**1j**), and benzothiazolyl (**1m**) were introduced into **2a** to give the corresponding α-*C*-glycosyl arenes in good yields (entries 1–9).

Finally, we conducted the installation of two sugar units into an aromatic molecule (Scheme 5). Thus, 1,3-di(2-pyridyl)benzene (**1n**) reacted with 2.2 equiv of glucal **2g** to give **4nf**, which involves two sugar units in the benzene ring (Scheme 5a). It should be noted that the *ortho*-C–H bond between two pyridyl rings, which is often metalated to give pincer metal complexes, is inert in the present reaction. The reaction of 4,4'-di(pyridin-2-yl)-1,1'-biphenyl (**1o**) was selectively alkylated by 2.2 equiv of glucal **2g** to give **4og** in 53% yield (Scheme 5b). The structure of **4og** was clarified by X-ray crystallographic analysis (Figure 1). These compounds are potential materials for multivalent glycoconjugates[16] and further studies on the transformation of these compounds are underway.

In summary, we have developed the iridium-catalyzed regio- and diastereoselective hydroarylation of chiral glycals with aromatic compounds. The reaction proceeded via *ortho*-C–H activation of an aromatic ring and the subsequent regio- and stereoselective addition to glycals gave the hydroarylation products. The aryl groups were selectively introduced into the anomeric carbon and the stereoselectivity of the addition was controlled by the ligand. Thus, the use of binap with the different absolute configuration enabled the stereoselective synthesis of α- or β-C-glycosyl arenes irrespective of the chirality of the glycals. The present method provides an atom-economical access to *C*-glycosyl arenes via C–H bond activation.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

* Email: tnishi@sci.osaka-cu.ac.jp

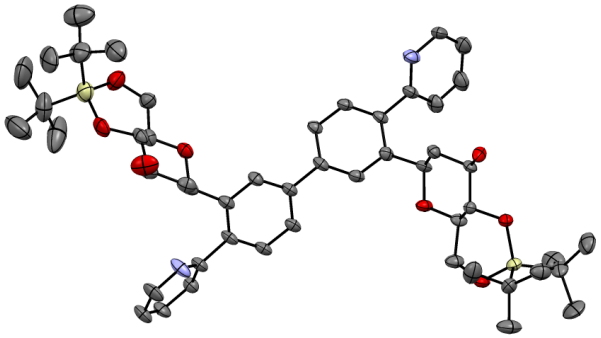


Figure 1 ORTEP illustration of **4og** with thermal ellipsoids drawn at 30% probability level. Solvent molecules and hydrogen atoms are omitted for clarity. One of two independent molecules is shown.

Notes

The authors declare no competing financial interest.

Supporting Information

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

Experimental procedures and compound characterization (PDF and cif)

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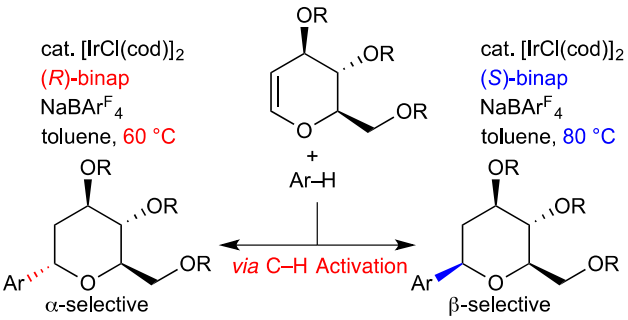

Regio- and Stereoselective Synthesis of C-Glycosyl Arenes