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Synthesis of Aryl C-Glycosides via Iron-Catalyzed Cross Coupling of Halosugars: Stereoselective Anomeric Arylation of Glycosyl Radicals

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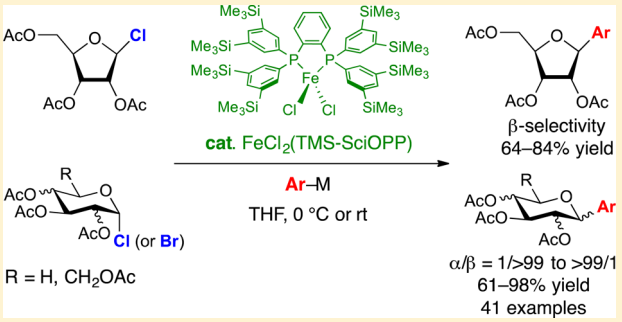
Supporting Information

ABSTRACT: We have developed a novel diastereoselective iron-catalyzed cross-coupling reaction of various glycosyl halides with aryl metal reagents for the efficient synthesis of aryl C-glycosides, which are of significant pharmaceutical interest due to their biological activities and resistance toward metabolic degradation. A variety of aryl, heteroaryl, and vinyl metal reagents can be cross-coupled with glycosyl halides in high yields in the presence of a well-defined iron complex, composed of iron(II) chloride and a bulky bisphosphine ligand, TMS-SciOPP. The chemoselective nature of the reaction allows the use of synthetically versatile acetyl-protected glycosyl donors and the incorporation of various functional groups on the aryl moieties, producing a diverse array of aryl C-glycosides, including Canagliflozin, an inhibitor of sodium-glucose cotransporter 2 (SGLT2), and a prevailing diabetes drug. The cross-coupling reaction proceeds via generation and stereoselective trapping of glycosyl radical intermediates, representing a rare example of highly stereoselective carbon−carbon bond formation based on iron catalysis. Radical probe experiments using 3,4,6-tri-O-acetyl-2-O-allyl-α-D-glucopyranosyl bromide (**8**) and 6-bromo-1-hexene (**10**) confirm the generation and intermediacy of the corresponding glycosyl radicals. Density functional theory (DFT) calculations reveal that the observed anomeric diastereoselectivity is attributable to the relative stability of the conformers of glycosyl radical intermediates. The present cross-coupling reaction demonstrates the potential of iron-catalyzed stereo- and chemoselective carbon−carbon bond formation in the synthesis of bioactive compounds of certain structural complexity.



INTRODUCTION

C-glycosides represent an important class of natural and/or synthetic bioactive compounds of high medicinal significance and therefore have received considerable synthetic attention.[1] Specifically, aryl C-glycosides are of marked pharmaceutical interest because of their biological activities and resistance toward metabolic degradation.[2] As a notable example, aryl C-glycoside-based inhibitors of sodium-glucose cotransporter 2 (SGLT2) have been utilized in the treatment of type 2 diabetes. Although numerous synthetic methods to prepare aryl C-glycosides are available,[3,4] the development of efficient, stereoselective, cost-effective, and nontoxic methods is critical for the advancement of biologically active and pharmaceutically important carbohydrate analogues.

Among the various existing approaches for the synthesis of C-glycosides,[1] C-glycosidation via anomeric glycosyl radical intermediates has been widely used because of its advantages over other methods based on the corresponding glycosyl anions and cations: the reaction conditions are generally mild so that varied functional and protecting groups are tolerated and undesired elimination and/or epimerization reactions are suppressed.[5] However, aryl C-glycoside synthesis using radical C-glycosidation has been a challenge and is virtually undeveloped methodology because of the paucity of suitable arylating agents for the glycosyl radical intermediates. This is primarily due to the inertness of aromatic groups or compounds toward glycosyl radicals.[6]

Recently transition-metal-catalyzed cross-coupling reactions have emerged as a useful method for the synthesis of aryl C-glycosides. In particular, nickel and cobalt catalysts have enabled the cross-coupling reactions between glycosyl bromides and arylzinc or arylmagnesium reagents, providing the saturated aryl C-glycosides, which has not been achieved via conventional palladium catalysis.[7,8] Gagné and co-workers reported a nickel-catalyzed procedure for the synthesis of aryl C-glycosides (eq

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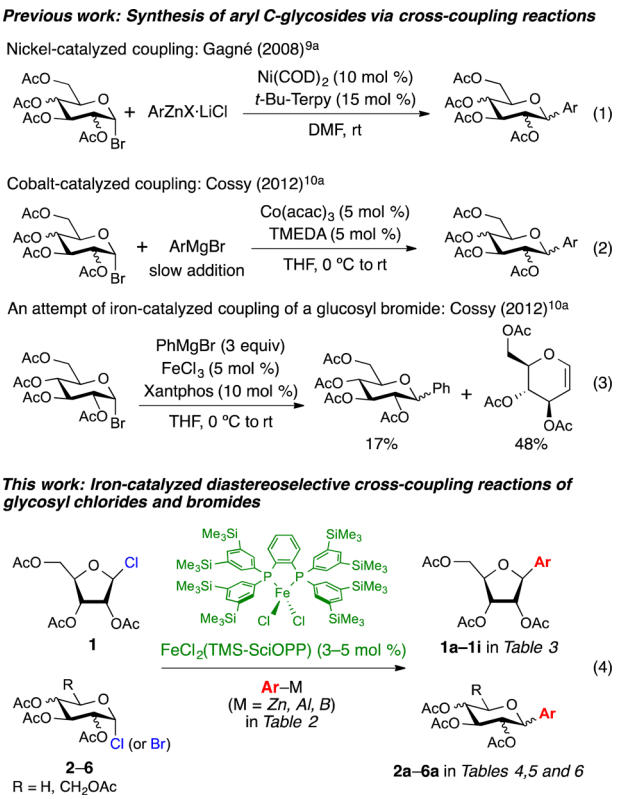
1)[9] and suggested that the reaction might proceed through the generation of glycosyl radical intermediates. Cossy and co-



workers reported the cobalt-catalyzed cross-coupling reaction of glycosyl bromides and aryl Grignard reagents in the synthesis of aryl *C*-glycosides, and illustrated the formation of an anomeric radical intermediate (eq 2).[10] These reports revealed the potential utility of iron-group metals in transition-metal-catalyzed aryl *C*-glycosidation reactions via radical intermediates. There has been, nonetheless, no successful iron catalysis in this synthetically attractive organic transformation.

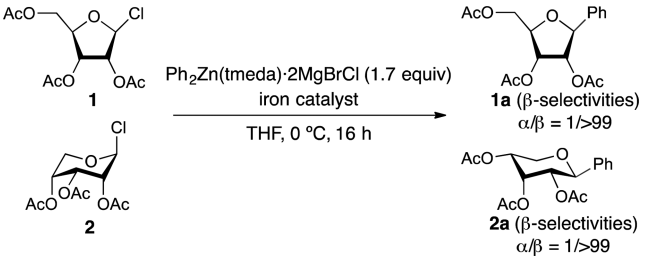
Despite the recent surge in the use of iron catalysts in cross-coupling reaction technologies,[11] the iron-catalyzed cross-coupling has thus remained virtually unexplored in the synthesis of aryl *C*-glycosides: Cossy reported a single example where the cross-coupling of pyranosyl bromides with phenylmagnesium bromide proceeded in the presence of an iron salt and Xantphos to give the desired phenyl *C*-glycoside as a minor product (17–42% yield), due to competing side reactions (e.g., the undesired glucal formation as a major product) (eq 3).[10a,12] Our recent studies regarding the precise control of iron catalysis in the cross-coupling reaction of alkyl halides[13,14] revealed that an iron-chiral bisphosphine ligand (BenzP*) enabled the stereoselective trapping of alkyl radicals;[14a] therefore, we envisaged that the aryliron intermediate derived from well-defined iron phosphine complexes [$FeCl_2$(SciOPP)] would be a suitable arylating agent for glycosyl radical intermediates to achieve a high cross-coupling selectivity in the synthesis of aryl *C*-glycosides.

Herein, we present the efficient synthesis of various aryl *C*-glycosides, for the first time, using the iron-catalyzed cross-coupling of glycosyl chlorides and bromides with a variety of aryl-, heteroaryl-, and vinylmetal reagents (eq 4). The reactions are high yielding and diastereoselective and tolerate many functional groups, which allows for the use of synthetically versatile acetate-protected glycosyl donors as well as the inclusion of various functional groups on the aryl moiety. In addition, the practical advantages of iron catalysts derived from the toxicologically benign nature and cost-effectiveness of iron makes the present reaction a synthetically and industrially feasible organic transformation.

RESULTS AND DISCUSSION

1. Arylation of Glycosyl Chlorides and Bromides: Screening of Catalysts, Ligands, and Organometallic Nucleophiles. We began our study by exploring the effects of catalysts and ligands by using a challenging substrate, 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl chloride **1**, which is not viable in nickel- and cobalt-based aryl *C*-glycosidation reactions.[9a,10a] The reactions of **1** with phenylzinc reagent prepared from PhMgBr and $ZnCl_2$(tmeda), Ph_2Zn(tmeda)·2MgBrCl were thus studied (Table 1 and Chart 1).[15,16] The yield of the desired product **1a** depended on the catalysts, and all the reactions proceeded with excellent β-selectivity of product **1a** (entries 1–9, Table 1). The coupling reaction proceeded without addition of a ligand, albeit in a low yield (30%, entry 1, Table 1).[16] In the absence of the catalyst, the coupling reaction did not progress (entry 2). Several bisphosphine ligands such as

Table 1. Screening of Catalyst Precursors and Ligands in the Reaction of 1 and 2 with Phenylzinc Reagent[a]



entry	substrate	iron catalyst (mol %)	% yield of product[b]	RSM (%)[b,c]
1	**1**	$FeCl_3$ (3)	30	0
2	**1**	none	0	0
3	**1**	$FeCl_3$ (3) + DPPE (3)	48	0
4	**1**	$FeCl_3$ (3) + DPPP (3)	50	0
5	**1**	$FeCl_3$ (3) + DPPBz (3)	52	0
6	**1**	$FeCl_3$ (3) + SciOPP (3)	52	0
7	**1**	$FeCl_3$ (3) + TMS-SciOPP (3)	55	0
8	**1**	$FeCl_2$(TMS-SciOPP) (3)	72	0
9	**1**	$FeCl_2$(TMS-SciOPP) (5)	81[d]	0
10	**2**	$FeCl_3$ (3)	11	67
11	**2**	none	0	85
12	**2**	$FeCl_3$(3) + DPPE(3)	7	58
13	**2**	$FeCl_3$(3) + DPPP(3)	21	77
14	**2**	$FeCl_3$(3) + DPPBz(3)	17	56
15	**2**	$FeCl_3$(3) + SciOPP(3)	32	55
16	**2**	$FeCl_3$ (3) + TMS-SciOPP (3)	50	29
17	**2**	$FeCl_2$(TMS-SciOPP) (3)	77	20
18	**2**	$FeCl_2$(TMS-SciOPP) (5)	78	18
19	**2**	$FeCl_2$(TMS-SciOPP) (5)	84[d,e]	12

[a]Reactions were conducted on 0.25 mmol scale. [b]Yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard unless otherwise noted. [c]Recovery of starting material. [d]Isolated yield. [e]Reaction was run at rt.

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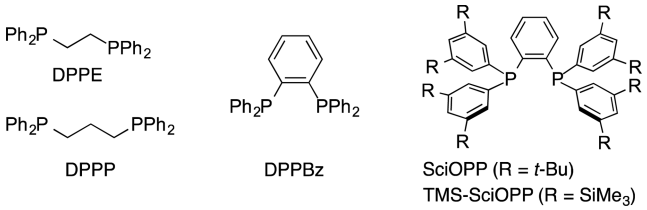
Chart 1. Structures of Ligands



DPPE, DPPP, DPPBz, and SciOPP (Chart 1) showed comparable reactivity and provided the desired cross-coupling products in 48−50% yields (entries 3−6). TMS-SciOPP afforded the corresponding cross-coupling product in 55% yield (entry 7). A well-defined iron complex, $FeCl_2$(TMS-SciOPP), emerged as the most effective catalyst, affording **1a** in 72% yield (entry 8). The highest yield (81%) was obtained with a 5 mol % of the catalyst (entry 9).

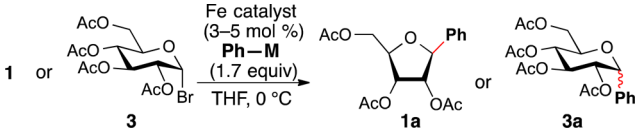
The effects of catalysts and ligands were also investigated using a more challenging substrate, 2,3,4-tri-*O*-acetyl-β-D-ribopyranosyl chloride **2** (entries 10−19, Table 1). All reactions showed excellent β-selectivity of product **2a**. Several bisphosphine ligands showed different reactivities (entries 1−7 vs 10−16). Among the bisphosphine ligands, TMS-SciOPP provided the cross-coupling product in 50% yield (entry 16). $FeCl_2$(TMS-SciOPP) was found to be the most effective catalyst, and it provided **2a** in 77% yield (entry 17). The highest yield (84%) was obtained with 5 mol % of the catalyst, and the reaction was performed at rt (entries 18 and 19).[17]

After screening the catalyst precursors and ligands, we commenced a search for suitable organometallic nucleophiles for the phenylation of 2,3,5-tri-*O*-acetyl-β-ribofuranosyl chloride (**1**) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide (**3**) in the presence of a catalytic amount of $FeCl_2$(TMS-SciOPP) (Table 2). Phenylzinc reagent Ph_2Zn(tmeda)·2MgBrCl proved to be the most effective nucleophile in the model reaction (entries 1 and 5). Phenylaluminum[14k] as well as phenylboron[14m] also showed promising reactivities and provided **3a** in 80% and 70% yield (entries 7 and 8). Notably, this is the first example of the use of organoaluminum and boron reagents in the cross-coupling reaction of glycosyl halides.[9a,10a]

The reaction of **1** gave the desired *C*-glycoside **1a** with nearly perfect β-selectivity (81%, α/β = 1/>99). The phenylation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide (**3**) gave the corresponding *C*-glucopyranoside **3a** as a mixture of anomeric isomers (α/β = 50/50−76/24) (entries 5−8). The reaction with a phenyl aluminum reagent resulted in lower diastereoselectivity (50:50 in entry 7). Although details are unclear, we postulate tentatively the strong Lewis acidity of aluminum species influences the fluctuating conformation of an intermediate glucosyl radical (vide infra): the diastereoselectivity is slightly diverse when using other phenyl nucleophiles. Coexisting TMEDA was critical to prevent the undesired elimination reaction leading to glucal formation; when the phenylzinc reagent was prepared in the absence of TMEDA, the catalytic cross-coupling reaction did not proceed (entry 6).[18] PhMgBr did not give the desired product, and **3** was recovered almost quantitatively (entry 9),[10a] suggesting that the Grignard reagent may allow over-reduction of the catalytic iron(II) species (see the discussion regarding the mechanism of the reaction described below).

2. β-Selective Arylation of Ribofuranosyl and Ribopyranosyl Chlorides with Arylzinc Reagents. The standardized cross-coupling protocol (entry 1, Table 2) was tested with various arylzinc reagents; Table 3 illustrates the scope of the reaction with **1** for the synthesis of diverse aryl *C*-ribofuranosides.[4] All reactions showed excellent β-D-selectivities (α/β = 1/>99). The reaction of **1** with a phenylzinc reagent and other

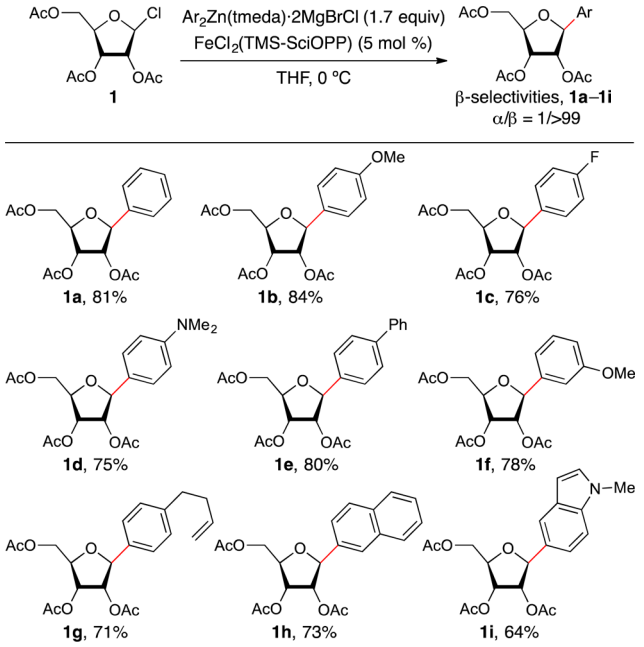
Table 2. Iron-Catalyzed *C*-Glycosidation of Various Phenylmetal Reagents[a]



entry	glycosyl halide	Ph−M	% yield[b] of *C*-glycoside (α/β)	RSM (%)[b,c,d]
1	**1**	Ph_2Zn(tmeda)·2MgBrCl	81 (1/>99)	0
2[e]	**1**	Ph_3Al−3$MgCl_2$	30 (1/>99)	0
3[f]	**1**	PhB(pin) + *t*-BuLi	22 (1/>99)	0
4[g]	**1**	PhMgBr	0	0
5	**3**	Ph_2Zn(tmeda)·2MgBrCl	96 (73/27)	0
6	**3**	Ph_2Zn·2MgBrCl	18 (70/30)	51
7[e]	**3**	Ph_3Al·3$MgCl_2$	80 (50/50)	10
8[f]	**3**	PhB(pin) + *t*-BuLi	70 (76/24)	12
9[g]	**3**	PhMgBr	0	94

[a]Reactions were conducted at 0 °C for 12 h. [b]Yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c]Recovery of the starting material **1** and **3**. [d]Tri-*O*-acetyl-D-glucal was obtained as the byproduct in entries 5−9. [e]1.7 equiv of TMEDA was added in entries 2 and 7. [f]20 mol % of $MgBr_2$ was added as a cocatalyst, and the reaction was run at rt. [g]5 equiv of TMEDA were added in entries 4 and 9, and PhMgBr was added at 0 °C over 3 h using a syringe pump.

Table 3. Iron-Catalyzed Aryl *C*-Glycosidation of Ribofuranosyl Chloride 1[a]



[a]Reactions were performed on a 0.25−0.50 mmol scale. See the Supporting Information for details regarding the reaction conditions for each case.

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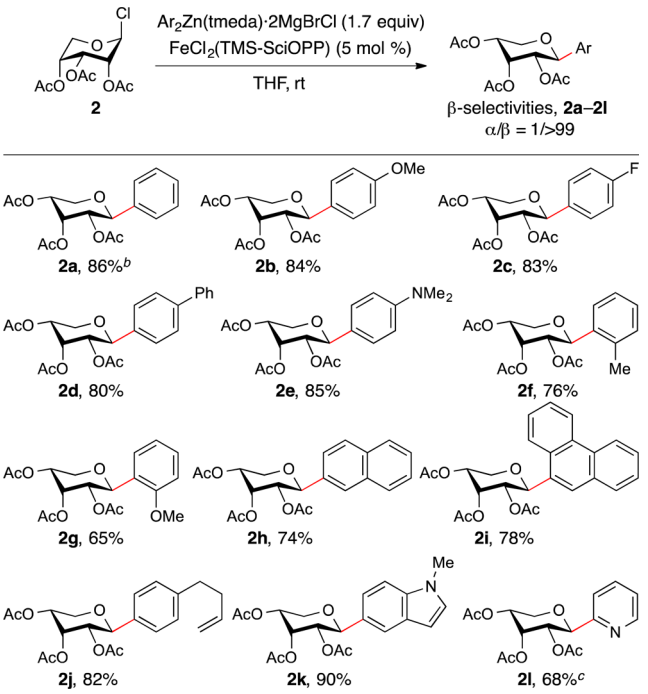
substituted arylzinc reagents containing methoxy, fluoro, phenyl, and *N*,*N*-dimethylamino groups in the *para*-position gave the corresponding products **1a**−**1e** in 75−84% yields.[19] 3-Methoxy phenylzinc also provided a good yield (78%) of **1f**. A terminal olefin moiety, which often undergoes isomerization to an internal olefin under transition metal catalysis,[20] remained intact under the present conditions and provided **1g** in 71% yield. 2-Naphthyl and 5- *N*-methylindolylzinc also reacted smoothly to give **1h** and **1i** in 73% and 64% yields, respectively.

Not only ribofuranosyl chloride but also ribopyranosyl chloride **2** participated in the aryl *C*-glycosidation; the cross-coupling reactions of **2** with a variety of aryl and heteroarylzinc reagents furnished the corresponding products in good to excellent yields (65−90%) with excellent β-D-selectivities (α/β = 1/>99) (Table 4).[19] The trimethylsilylmethyl (TMSM) group, which can act as a nontransferable dummy ligand for pyridyl zinc reagents, participated in the reaction[21] and provided the corresponding product **2l** in 68% yield. The isomerization of the terminal olefin was not observed (**2j**). The high reactivity and stereoselectivity of glycosyl chlorides using the iron catalyst demonstrate its advantages over nickel- and cobalt-based glycosidation reactions, which cannot be applied for the diastereoselective arylation of glycosyl chlorides.[9a,10a]

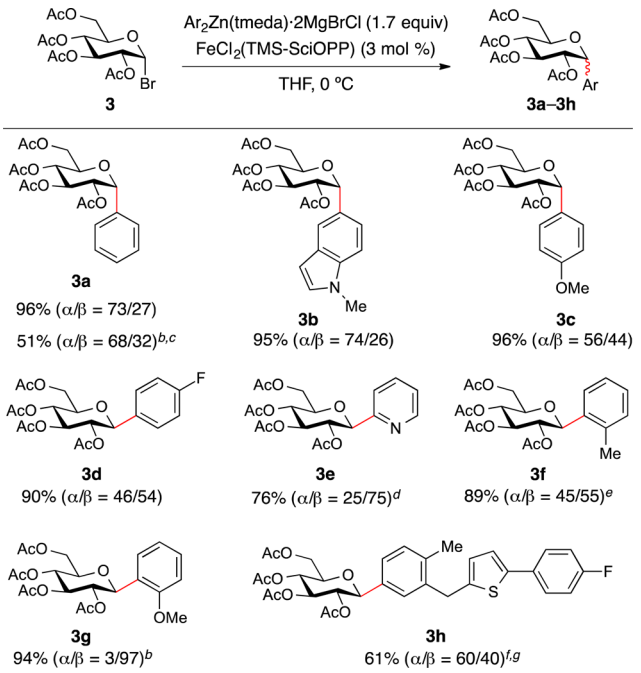
Table 4. Iron-Catalyzed Aryl *C*-Glycosidation of Ribopyranosyl Chloride 2[a]



[a]Reactions were conducted on a 0.25−0.50 mmol scale. [b]Reaction was performed on the gram scale. [c]Arylzinc reagent was prepared from 2-pyridylZnBr, Me_3SiCH_2MgCl, and TMEDA. See the Supporting Information for detailed reaction conditions for each case.

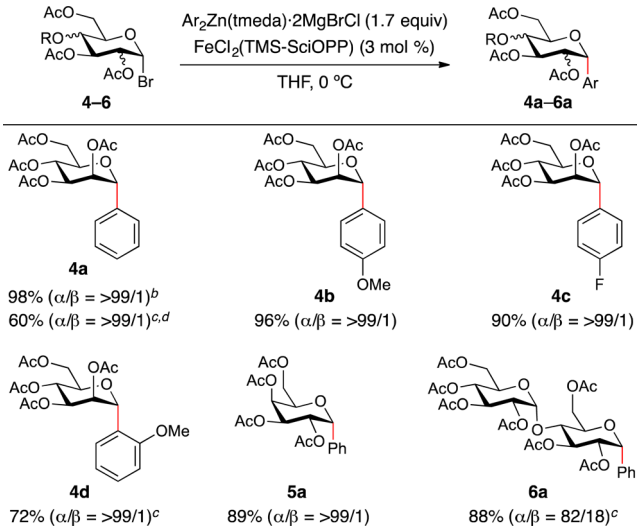
3. Diastereoselective Arylation of Glycosyl Bromides with Arylzinc Reagents. To our delight, the iron catalyst also showed excellent reactivity and selectivity toward various glycosyl bromides (Tables 5 and 6). The cross-coupling reactions of **3** with different aryl and heteroarylzinc reagents afforded the corresponding products (**3a**−**3g**) in 61−96% yields and with varied anomeric selectivities (α/β = 75/25−3/97), favoring the α-D or β-D anomer depending on the aryl nucleophile (Table 5). The reaction of *O*-acetyl-α-D-glucosyl chloride **3′** with phenylzinc gave **3a** in 51% yield with anomeric selectivity of α/β = 68/32.[22] The reactions with *N*-methylindolylzinc proceeded smoothly to afford the corre-

Table 5. Iron-Catalyzed Aryl *C*-Glycosidation of *O*-Acetyl-α-bromo-D-glucose 3[a]



[a]Reactions were performed on a 0.25−1.25 mmol scale. [b]10 mol % of $FeCl_2$(TMS-SciOPP) was used. [c]*O*-Acetyl-α-D-glucosyl chloride (**3′**) was used, and the reaction was run at rt for 36 h. [d]Arylzinc reagent was prepared from 2-pyridylZnBr, Me_3SiCH_2MgCl, and TMEDA. [e]5 mol % of $FeCl_2$(TMS-SciOPP) was used. [f]Arylzinc reagent was prepared from arylmagnesium chloride and $ZnBr_2$ (tmeda). See the Supporting Information for detailed reaction conditions for each case. [g]Minor anomer, β-**3h**, is shown.

Table 6. Iron-Catalyzed Aryl *C*-Glycosidation of Various Bromosugars 4−6[a]



[a]Reactions were conducted on a 0.25−0.50 mmol scale. [b]Reaction was performed on the gram scale. [c]10 mol % $FeCl_2$(TMS-SciOPP) was used. [d]*O*-Acetyl-α-D-mannosyl chloride (**4′**) was used and the reaction was run at rt for 36 h. See the Supporting Information for details.

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sponding coupling product **3b** in 95% yield. Electron-deficient aromatic groups were introduced using an appropriate arylzinc reagent to give the corresponding aryl *C*-glycosides (**3d** and **3e**) in 90% and 76% yield, respectively. The reactions with *O*-tolylzinc proceeded smoothly and provided **3f** in 89% yield. A notable stereochemical switch was observed when the 2-tolyl group was replaced with a 2-anisyl group to produce the β-D-anomer **3g** with high selectivity (α/β = 3/97). This selectivity may result from electronic (or coordinating) effects of the methoxy group, as judged by the 45/55 selectivity of the 2-tolylzinc reagent. These results contrast with the corresponding nickel-[9a] and cobalt-catalyzed[10a] arylation reactions, which are not suitable for introducing 2-substituted aromatic and pyridyl rings. The cross-coupling reaction of **3** with an arylzinc reagent bearing a heteroaromatic ring was also applicable for the synthesis of pharmaceutically important molecule **3h** in 61% yield.

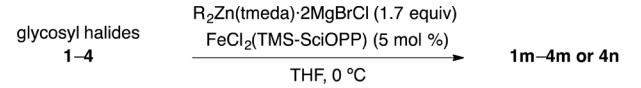
Next, our cross-coupling protocol was applied to other glycosyl halides (Table 6). The cross-coupling reactions of *O*-acetyl-α-D-mannosyl bromide and chloride (**4** and **4′**) were highly diastereoselective and produced only the α-D-anomers (α/β = > 99/1). Electron-neutral, electron-rich, and electron-deficient arylzinc reagents participated in the high-yielding arylation (90−98%, **4a**−**4d**). The phenylation of *O*-acetyl-α-bromo-D-galactose **5** proceeded diastereoselectively to give only the α-D-anomer **5a** in 89% yield. A disaccharide, hepta-*O*-acetyl-α-D-maltosyl bromide **6**, also participated and afforded the desired aryl *C*-glycoside, **6a** in 88% yield.

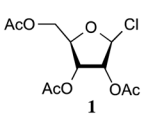
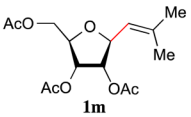
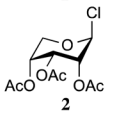
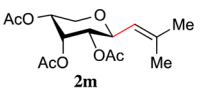
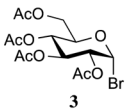
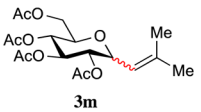
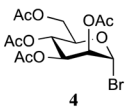
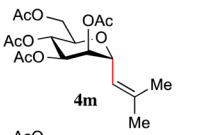
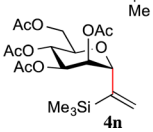
4. Vinyl *C*-Glycoside Synthesis. Having established the optimal procedure for aryl-*C*-glycoside synthesis, we examined the cross-couplings between glycosyl halides and alkenylzinc reagents because vinyl *C*-glycosides are also potentially useful intermediates leading to a variety of carbasugars and *C*-glycosyl compounds.[23] Among them, intra- and intermolecular glycosyl radical additions to alkynes[24] are useful, because of their mild reaction conditions, which allow for the presence of various polar functional groups on the sugar derivatives. The synthesis of vinyl *C*-glycosides was performed using glycosyl halides **1**−**4**, and the desired cross-coupling products were obtained in good to excellent yields (70−96%) with high diastereoselectivities (Table 7).

5. Deprotection of Acetyl Group. An advantage of the present reaction is the use of acetyl protection, which is easily removed under mild conditions. Tetraacetylmannose α-**4a** was synthesized on a gram scale (eq 5) and deprotected by transesterification using Bu_2SnO/MeOH[25] to afford the desired 1-α-phenyl D-mannose (**7a**) in a 90% yield (eq 6). Because of the small molecular weight of acetyl protecting groups, the loss of the molecular weight during the deprotection is far less than those of benzyl-, benzoyl-, and pivaloyl-protection, which are commonly used in organometallic reactions of glycosyl donors.[26] The acetyl groups of isolated β-**3h** were also cleanly removed using the tin oxide catalyst in refluxing methanol (eq 7), which stereoselectively provided a representative type 2 antidiabetic drug, Canagliflozin (**7b**, 95% yield).

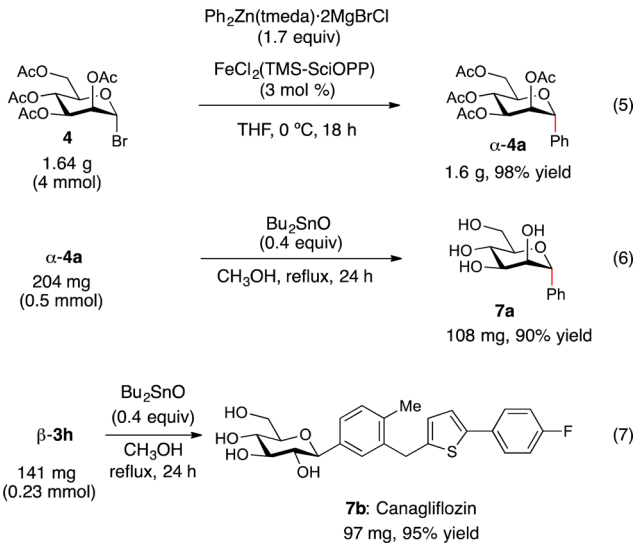
6. Mechanistic Considerations: Radical Probe Experiments and Plausible Catalytic Cycle. In order to gain mechanistic insight into the cross-coupling reaction, we performed the cross-coupling reaction with a radical probe **8** and phenylzinc under the reaction conditions described above (Scheme 1). The radical probe experiment produced a diastereomeric mixture of bicyclic compound **9** (d.r. = 60:40), supporting the intermediacy of the corresponding glycosyl radical intermediate.[5b,e,10a] We observed the exclusive formation of the ring-closing product, **9**, and no anomeric arylation product **9′**. This selectivity can be attributed to the fast 5-*exo*-*trig* cyclization of the allyl ether moiety and subsequent cross-coupling reaction with a phenylzinc reagent.[27]

Table 7. Iron-Catalyzed Cross Coupling of Glycosyl Halides with Alkenylzinc Reagents[a]

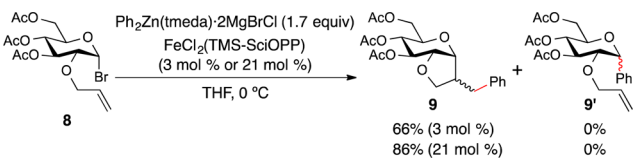


entry	glycosyl halide	alkenyl *C*-glycoside	yield (%)	α/β[b]
1	 **1**	 **1m**	70	1/>99
2[c]	 **2**	 **2m**	83	1/>99
3	 **3**	 **3m**	96	49/51
4	 **4**	 **4m**	91	>99/1
5	**4**	 **4n**	90	>99/1

[a]Reactions were performed on a 0.25 mmol scale. [b]The anomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Reaction was run at rt.



Scheme 1. Cross-Coupling Reaction Using Radical Probe 8



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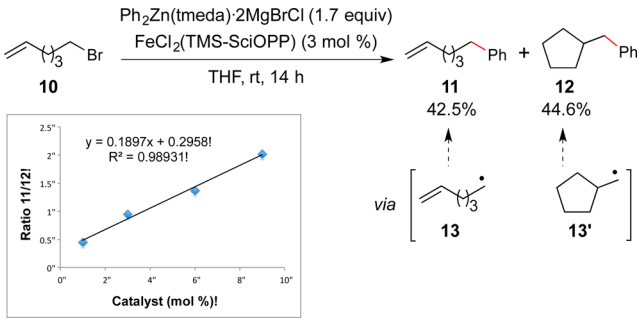
6-Bromo-1-hexene **10** was next adopted as a model radical probe to investigate the dependence of the ratio of the direct arylation and cyclization/arylation on catalyst loading.[28] The reaction with phenylzinc gave a mixture of direct arylation (uncyclized) product **11** and cyclized **12** at different catalyst loadings, which was consistent with the formation of an alkyl radical intermediate as described above. This radical probe reaction with various catalyst loadings of $FeCl_2$(TMS-SciOPP) resulted in the observation of an almost linear relationship between the ratio of **11**/**12** and the catalyst loading (inset in Scheme 2). This supports the possibility that once formed, the

Scheme 2. Cross-Coupling Reaction Using Model Radical Probe 10



alkyl radical intermediate escapes from the solvent cage and undergoes cyclization/arylation or direct arylation with an aryl iron species, which is different from the one that reacts with the alkyl halide to generate the corresponding alkyl radical intermediate.[29,30]

Figure 1 shows a plausible mechanism for the present cross-coupling reaction based on a bimetallic (*out-of-cage*) mecha-

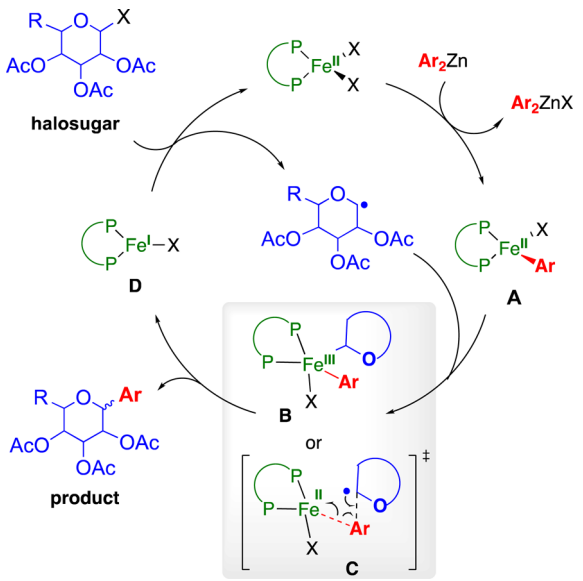


Figure 1. Plausible reaction mechanism (P ∩ P, X, and R denote TMS-SciOPP, halogen, and H or CH_2OH, respectively.).

nism, which we recently proposed in the iron-catalyzed enantioselective cross-coupling reaction.[29,30] The catalytic cycle starts from the formation of reactive divalent organoiron species **A**, which is generated from $FeCl_2$(TMS-SciOPP) and an aryl zinc reagent. The organoiron **A** reacts with a glycosyl radical intermediate to give the corresponding aryl *C*-glycoside and iron(I) species **D** possessing one bulky TMS-SciOPP ligand.[14l] Iron(I) species is reported to show high reactivity toward haloalkanes in Negishi and other types of coupling reactions.[31] We therefore consider that **D** is the most likely species responsible for the homolytic cleavage of the C−X bond of halosugars,[32] and once it forms under the reaction conditions the radical chain reaction may proceed smoothly.[30a]

The mechanism of C−C bond formation of the glycosyl radical with the intermediate **A** in Figure 1 has been unclear and under intensive theoretical investigation. We are tentatively postulating two possible pathways, e.g., a reversible formation of aryl(glycosyl)iron(III) species **B** and subsequent reductive elimination, or an ipso-substitution of the aryl group of the intermediate **A** by the attack of the glycosyl radical via TS **C** to furnish the cross-coupling product and the iron(I) species **D**. The correlation between the conformational stability of glycosyl radical interemediates and the observed anomeric stereoselectivity (*vide infra*) implies the second mechanism via the direct ipso-substitution may operate but does not exclude the possibility of the first trap/reductive elimination mechanism (Figure 1).[33]

7. Correlation of Stereoselectivity of Anomeric Arylation to Conformational Stability of Glycosyl Radicals. In the preceding sections, we show that the arylation of glycosyl halides proceeds through the formation of glycosyl radicals. Giese and Togo reported that the stability of glycosyl radical conformations could influence the stereoselectivity of intermolecular reaction of glycosyl radicals with olefins to produce the corresponding alkyl *C*-glycosides.[34,35] In our case, the observed anomeric diastereoselectivity of the aryl *C*-glycosides can also be correlated to the conformation of the glycosyl radical intermediates. The results obtained by density functional theory (DFT) calculations are summarized in Figure 2.[17]

Aryl *C*-glycosidation of mannopyranosyl bromide **4** showed excellent α-D-selectivity (α/β = >99/1) of **4a**−**4d**, (Table 6). As shown in Figure 2a, the $^4C_1$ conformer of the mannopyranosyl radical is more favorable than the $^1C_4$ conformer (ΔG = 3.2 kcal/mol) where the α-face exhibits less steric hindrance than the β-face. The recombination (C−C bond forming step) between the mannopyranosyl radical and aryliron species **A** may take place from the selective α-face and bring about the α-selectivity of the products.

Aryl *C*-glycosidation of ribopyranosyl chloride **2** demonstrated excellent β-D-selectivity (α/β = 1/>99) of **2a**−**2l** (Table 4). In the case of ribopyranosyl radicals, the $^1C_4$ conformer is more stable and exhibits strong steric hindrance at the α-face with the aryliron species and would result in β-D-selectivity (Figure 2b).

Aryl *C*-glycosidation of glucopyranosyl bromide **3** showed varied α/β selectivities, ranging from 75/25 to 3/97 (**3a**−**3g** as in Table 5). This was probably due to the fluctuating conformational changes of the glucosyl radical intermediates (Figure 2c), which makes the diastereoselectivity sensitive to the structure of the aryl nucleophiles.[34]

From our DFT calculations, we found that the $B^{2,5}$ boat conformer (average structure of $^4C_1$ and $^1C_4$ conformers) is slightly more stable than the other conformers (ΔG_1 = 0.25 kcal/mol and ΔG_2 = 0.57 kcal/mol). The radical at C-1 of the boat conformation has *p*-character, providing a planar carbon center (i.e., it is a π radical) with potential to form both anomers through α- and β-attacks.[34] As shown in Table 5, the α/β

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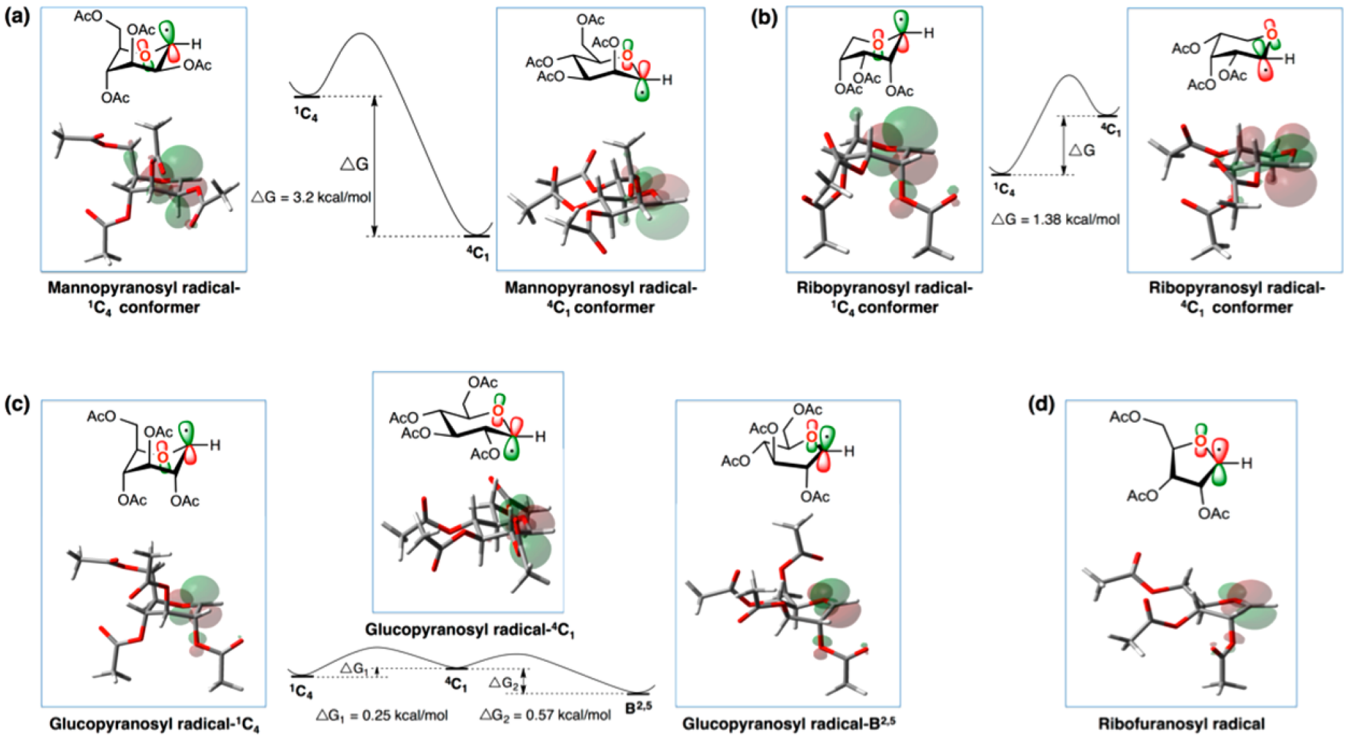

Figure 2. Relative DFT stabilities of conformers of glycosyl radical intermediates.

selectivity depended on the aryl nucleophiles. Although the reason for the unique high selectivity in the case of 2-anisyl is unclear, the interaction or coordination of the methoxy group to the iron center or to the accompanying Lewis acidic metal salts may alter the coordination environment of the iron center.

Our DFT study on the ribofuranosyl radical also revealed that it displays only one stable conformer, possessing an envelope structure with a trigonal planar carbon radical (Figure 2d). The two-acetoxy groups sterically crowded the α-face of the furanosyl radical, leaving the β-face open for further reactions.[34a,36] Based on this structure, anomeric C−C bond formation with an aryliron species can be expected to proceed selectively from the β-face and provided the corresponding aryl *C*-ribofuranosides (**1a**−**1i**) with exclusive β-D-selectivity (α/β = 1/>99). Although there remains room for discussion on the detailed mechanism of the C−C bond forming step, the qualitative understanding and prediction of the anomeric selectivity is shown to be possible by using DFT analysis of conformational stability of glycosyl radical intermediates.

CONCLUSION

In summary, we have developed the efficient synthesis of aryl *C*-glycosides and vinyl *C*-glycosides through the iron-catalyzed stereoselective cross-coupling reaction of a variety of glycosyl chlorides and bromides with diverse aryl, heteroaryl, and vinyl metal reagents. This is the first example of the highly selective cross-coupling of rather unreactive glycosyl chlorides. The reaction proceeded via a glycosyl radical intermediate, and the anomeric diastereoselectivity of the products was explained by the relative stability of glycosyl radical intermediate and thus was predictable to some extent. We hope that this simple, efficient, and practical synthesis of *C*-glycosides will provide a new entry to development of a wide array of functional sugar derivatives of medicinal and clinical interest. We believe that the present study demonstrates the potential of iron-catalyzed stereo- and chemoselective C−C bond formation and spurs their application to the synthesis of complex molecules of biological importance.

EXPERIMENTAL SECTION

Representative Procedure for the Cross Coupling of *O*-Acetyl-α-D-mannosyl Bromide 4 with Phenylzinc Reagent (Gram Scale Reaction). A THF solution of phenylmagnesium bromide (12.2 mL, 1.11 M in THF, 13.6 mmol) was added to a suspension of $ZnCl_2$ (tmeda) (1.72 g, 6.8 mmol) in 6 mL of THF at ambient temperature; the reaction mixture was stirred at 0 °C for 45−60 min. 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl bromide (1.64 g, 4.0 mmol) was added to the reaction mixture at 0 °C followed by a THF solution of $FeCl_2$ (TMS-SciOPP) (1.6 mL, 0.1 M in THF solution, 0.16 mmol). The coupling reaction was carried out for 18 h at 0 °C. After dilution with 50 mL of CH_2Cl_2 at 0 °C, the solution was filtered using a pad of Florisil and concentrated in vacuo. The cross-coupling product **4a** (1.6 g, 98% yield) was obtained as a white solid after silica-gel column chromatography (hexane/EtOAc = 80/20).

Representative Procedure for Deprotection of Acetyl Group from Sugar Derivative. The β-D-anomeric product **3h** (141 mg, 0.23 mmol), dibutyltin oxide (25 mg, 0.092 mmol), and MeOH (1.7 mL) were placed in a Schlenk tube, and the mixture was stirred at the reflux for 24 h. After cooling to ambient temperature, 5.0 mL of water were added and the mixture was stirred for 10 min at rt. The entire reaction mixture was transferred into a 100 mL round-bottom flask, and water was evaporated by azeotropic distillation with additional MeOH. The residue was dried in vacuo and purified by short silica-gel column chromatography (MeOH/EtOAc = 10/90) to give the desired product Canagliflozin **7b** as an off-white solid (97 mg, 95% yield).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b03867.

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Experimental details, procedures, compound characterization data, NMR spectra, and X-ray crystallographic data (PDF)
Crystallographic data (CIF, CIF)
(CIF)

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Notes

The authors declare no competing financial interest.

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(17) Details are provided in the Supporting Information.

(18) Qing reported that the combination of TMEDA and DPPP as a ligand improved the Fe-catalyzed Negishi-type cross-coupling reaction of alkyl halides bearing β-fluorine. See ref 14h.

(19) The stereochemistry of the anomers was determined by ^{1}H NMR analysis and confirmed by single crystal X-ray analysis. X-ray structures are shown in the Supporting Information.

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(26) Molecular weight loss of the corresponding acetyl-, benzyl- and benzoyl-protected 1-phenyl mannose were theoretically calculated as 41% (MW change: 408.40 to 240.26), 60% (MW change: 600.76 to 240.26), and 63% (MW change: 656.69 to 240.26), respectively.

(27) A similar observation was noted in the nickel-catalyzed cross-coupling of δ-olefinic 1-bromo alkane with PhMgCl; see: Breitenfeld, J.; Wodrich, M. D.; Hu, X. *Organometallics* **2014**, *33*, 5708.

(28) For formation of an alkyl radical intermediate from alkyl halides in iron-catalyzed cross-coupling reactions, see ref 14c, i, and 14m.

(29) Recently, we reported a bimetallic (*out-of-cage*) mechanism for iron-catalyzed enantioselective cross-coupling reactions of α-chloroesters with aryl Grignard reagents (see ref 14a and references cited therein). This does not exclude the possibility of competition of an *in-cage* mechanism (see ref 14d and 14m).

(30) Bimetallic mechanisms are reported for nickel catalysts; see: (a) Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588. (b) Choi, J.; Martín-Gago, P.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 12161. (c) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192. For a discussion of related nickel-catalyzed bimetallic mechanisms, see ref 27.

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(33) We do not exclude the possibility of the mechanism via the formation of iron (III) intermediate and following reductive elimination of the carbon–carbon bond formation. We consider that the reductive elimination from iron(III)-glycosyl-aryl complex B should be rapid due to instability of the iron(III) intermediate and can be stereospecific to reflect the stereochemistry of the stable radical conformer. Our ongoing extensive DFT study on the mechanism of iron-catalyzed enantioselective coupling suggests potential competition of both mechanisms via B or TS C in Figure 1. The results will be reported in due course. Insightful comments on this point by a reviewer are gratefully acknowledged.

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