Synthetic Methods

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Diastereoselective Metal-Catalyzed Synthesis of *C*-Aryl and *C*-Vinyl Glycosides**

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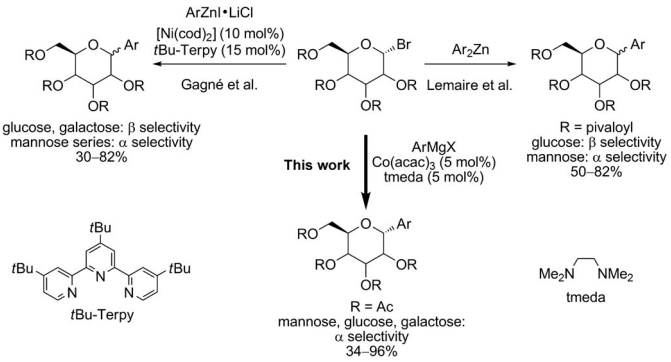
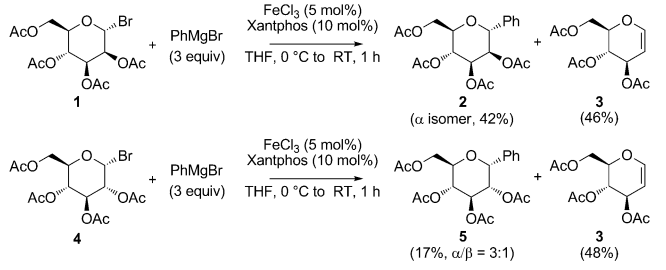
C-glycosides are an important class of carbohydrate analogues with applications as potent pharmaceutical compounds.[1] As they are more resistant to metabolic processes than *O*-glycosides, *C*-glycosides can be good drug candidates for inhibitors of carbohydrate processing enzymes. Moreover, *C*-aryl glycosides have been revealed to be of particular biological importance, with some of them occurring naturally.[1,2] Although numerous methods exist to prepare *C*-glycosides,[1–4] the development of convergent and catalytic methods is of the utmost importance. Metal-catalyzed cross-coupling reactions between 1-halogeno glycosides and organometallics to form an anomeric C–C bond are powerful and versatile reactions to access *C*-glycosides. However, the major drawback of these coupling reactions is a β-H elimination or a β-elimination of the C2-substituent. Gagné et al. have described a diastereoselective Negishi cross-coupling applied to 1-halogeno glycosides, catalyzed by $[Ni(cod)_2]$/*t*Bu-Terpy, (cod = 1,5-cyclooctadiene) leading to fully oxygenated *C*-aryl and *C*-alkyl glycosides, with only traces of the corresponding glucal (Scheme 1).[5,6] Recently, Lemaire et al. have reported a metal-free coupling of Ar_2Zn reagents with 1-bromo glycosides with full β-selectivitiy in the glucose series and full α selectivity in the mannose series, owing to the anchimeric assistance of the *O*-pivaloyl group at C2 (Scheme 1).[7]

Herein, we report the diastereoselective metal-catalyzed cross-coupling between 1-bromo glycosides and easily accessible or commercially available Grignard reagents, which allows for the synthesis of an array of *C*-aryl and *C*-vinyl glycosides with α selectivity when a cobalt- or iron-centered catalytic system is used (Scheme 1).

Motivated by our previous results with iron-catalyzed cross-coupling between vinyl Grignard reagents and alkyl halides,[8,9] and considering the good compatibility of iron catalysts with secondary alkyl halides possessing β-hydrogen atoms,[10] the coupling reaction of *O*-acetyl-α-bromo-D-mannose (**1**) with PhMgBr, which involved a combination of iron salts and ligands, was investigated (see the Supporting Information). The best conditions for the cross-coupling required three equivalents of PhMgBr to reach full conversion of 1-bromo glycoside **1**; however, coupling product **2** was isolated in only 42% and glucal **3** was also produced in 46% yield using $FeCl_3$ (5 mol%)/Xantphos (10 mol%; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; Scheme 2). When the same conditions were applied to *O*-acetyl-α-bromo-D-glucose (**4**), coupling product **5** was isolated in 17% yield with a 3:1 α/β ratio, and the major product obtained was glucal **3** (48%; Scheme 2). Interestingly, 1-bromo glycosides **1** and **4** both diastereoselectively led to cross-products **2** and **5**, respectively, with the α isomer being the major product.



Scheme 1. Recent developments in the coupling of 1-halogeno glycosides and aryl organometallic reagents. Ac = acetate, acac = acetylacetonate, cod = 1,5-cyclooctadiene, dppe = 1,2-bis(diphenylphosphino)ethane, tmeda = *N*,*N*′-tetramethylethylenediamine.



Scheme 2. Iron-catalyzed cross-coupling of PhMgBr and 1-bromo glycosides **1** and **4**.

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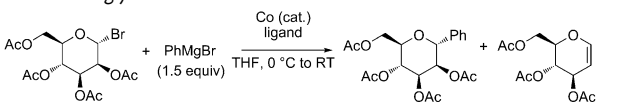
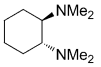
Iron-catalyzed cross-coupling reactions have been suggested to proceed by an oxidative addition of a low-valent iron intermediate into the C1–Br bond, a process which involves the formation of a carbon-centered radical.[8,11] As a carbon-centered anomeric radical intermediate can be hypothesized to account for the observed α selectivity (Scheme 2),[4b,6,12] and as carbon-centered radical intermediates were also suggested to occur in cobalt-catalyzed cross-coupling reactions between alkyl halides and Grignard reagents,[13,14] we turned our attention to the cobalt-catalyzed coupling of *O*-acetyl-α-bromo-D-mannose (**1**) with PhMgBr (Table 1). Moreover, as cobalt-catalyzed cross-coupling reactions between aryl Grignard reagents and alkyl halides do not suffer from β-H elimination,[13] and tolerate α-oxygenated substituents on alkyl halides,[14a,c–g,i–l] the formation of glucal **3** should be decreased.

Table 1: Optimization of the cobalt-catalyzed cross-coupling of PhMgBr and 1-bromo glycoside **1**.[a]



1 **2** **3**

Entry	Cobalt source (mol%)	Ligand (mol%)	Yield of **2** [%][b]	**3**[c]
1	$[Co(acac)_3]$ (5)	–	10%	trace
2	$CoCl_2$ (5)	–	13%	–
3	$CoCl_2$ (5)		74%	–
4	$CoCl_2$ (5)	dppe (5)	73%	–
5	**$[Co(acac)_3]$ (5)**	**tmeda (5)**	**76%**	**–**
6	$[Co(acac)_3]$ (1)	tmeda (1)	75%	–
7[d]	$[Co(acac)_2]$ (5)	tmeda (5)	54%	–

[a] Conditions: **1** (0.1 M in THF), PhMgBr (1 M in THF; 1.5 equiv) was added at a rate of 2 mL min^{-1}; once the addition was complete, the reaction medium was warmed to RT. [b] Yield of isolated product. [c] Detected by GC-MS. [d] 2.2 equiv of PhMgBr were used. acac = acetylacetonate, dppe = 1,2-bis(diphenylphosphino)ethane, tmeda = *N*,*N*′-tetramethylethylenediamine.

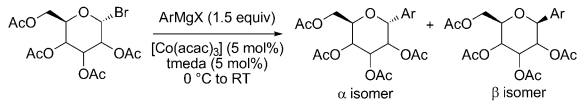
The cobalt-centered catalytic system in the cross-coupling of *O*-acetyl-α-bromo-D-mannose (**1**) and PhMgBr (1.5 equiv) in THF was examined, and the results are reported in Table 1. The use of $[Co(acac)_3]$ (5 mol%) in the absence of any ligand led to product **2** in only 10% yield with traces of glucal **3** (Table 1, entry 1), and the use of $CoCl_2$ (5 mol%) led to **2** in only 13% yield (Table 1, entry 2). With the combination of $CoCl_2$ and *N*,*N*′-tetramethyl-*trans*-cyclohexanediamine as a ligand, (5 and 6 mol%, respectively),[14f] the expected product **2** was obtained in 74% yield as a single α isomer (Table 1, entry 3). Replacing *N*,*N*′-tetramethyl-*trans*-cyclohexanediamine with 1,2-bis(diphenylphosphino)ethane (dppe; 5 mol%)[14l] led to a similar result (73% yield of **2**; Table 1, entry 4), and the use of $[Co(acac)_3]$ (5 mol%) and tmeda (*N*,*N*′-tetramethylethylenediamine)[14a] (5 mol%) afforded **2** in 75% yield as a single α isomer (Table 1, entry 5).[15] The catalytic loading could be decreased to 1 mol% of $[Co(acac)_3]$ and tmeda without significantly affecting the yield of **2** (Table 1, entry 6). However, the replacement of $[Co(acac)_3]$ by $[Co(acac)_2]$ decreased the yield of **2** (54%) (Table 1, entry 7). On the basis of these results, we selected $[Co(acac)_3]$ as the cobalt source, as it is less hygroscopic than $CoCl_2$, and tmeda, which is cheaper than *N*,*N*′-tetramethyl-*trans*-cyclohexanediamine or dppe, as the additive.

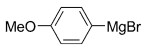
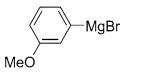
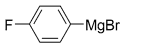
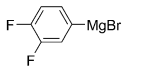
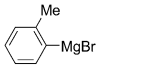
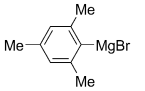
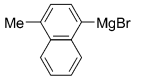
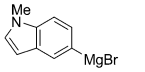
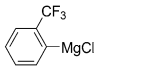
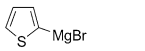
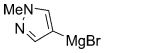
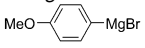
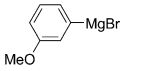
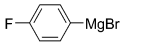
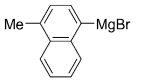
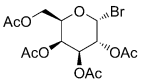
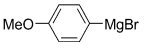
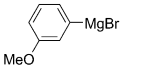
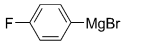
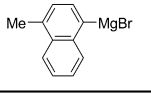
The optimized conditions were applied to evaluate the scope and limitations of the cobalt-catalyzed cross-coupling of aryl Grignard reagents with 1-bromo glycosides **1**, **4**, and **6**; the results are reported in Table 2. With 1-bromo mannose derivative **1** (Table 2, entries 1–8), the cross-coupling was diastereoselective, as only the α isomer was detected. Electron-rich or electron-poor Grignard reagents led to similar results (70–83% yield of isolated product; Table 2, entries 1–5); however, bulkier Grignard reagents induced lower yields (Table 2, entries 6 and 7). The cross-coupling was also possible with an *N*-methylindole Grignard reagent, which afforded the corresponding coupling product in 53% yield (Table 2, entry 8). On the other hand, with *o*-CF_3-PhMgCl, 2-thienylmagnesium bromide, and an *N*-methylpyrazole derived Grignard reagent, no cross-coupling products were observed, and **1** was recovered (Table 2, entries 9–11). With 1-bromo glycoside **4**, which is derived from glucose, the coupling with aryl Grignard reagents was still diastereoselective in favor of the α isomers, which were obtained in good yields, but with a lower α/β ratio (1.3:1–3:1; Table 2, entries 12–16). When *O*-acetyl-α-bromo-D-galactose (**6**) was used as the electrophile, the cross-coupling was diastereoselective (only the α isomer was detected) and the *C*-aryl glycosides were obtained in moderate to good yields (Table 2, entries 17–21).

As an extension of this study, and owing to the synthetic value of *C*-vinyl glycosides, the reactivity of bromides **1**, **4**, and **6** with alkenyl Grignard reagents was evaluated (Table 3). We were delighted to isolate the expected *C*-vinyl glycosides with full α selectivity for bromides **1** and **6** (Table 3, entries 1, 2, 5, and 6). In the case of 1-bromo glycoside **4**, a moderate α/β selectivity (1.5:1) was observed (Table 3, entry 4). Unexpectedly, vinylMgBr failed to react, and the starting bromide was recovered (Table 3, entry 3).

From a mechanistic point of view, the stereochemical outcome of this cobalt-catalyzed cross-coupling seems to support a radical pathway, as suggested in the literature.[13,14] In our case, the formation of an anomeric radical intermediate at C1 during the oxidative addition of low-valent cobalt species would induce an α-selective cross-coupling.[4b,6,12] To verify if a radical pathway is operational in the cobalt-catalyzed cross-coupling of 1-bromo glycosides with aryl Grignard reagents, the reactivity of δ-olefinic 1-bromo glycoside **7** was examined (Scheme 3). Treatment of **7** with PhMgBr under our reaction conditions [PhMgBr (1.5 equiv), $[Co(acac)_3]$ (5 mol%), tmeda (5 mol%)] produced an epimeric mixture of bicyclic compound **8** (d.r. = 1:1), which was isolated in 88% yield. This product results from the formation of an anomeric radical that leads to a 5-*exo*-*trig* cyclization followed by cross-coupling with PhMgBr, which suggests that the cyclization is faster than the direct cross-coupling.[16]

Table 2: Scope of the cobalt-catalyzed cross-coupling of ArMgX and 1-bromo glycosides **1**, **4**, and **6**.[a]

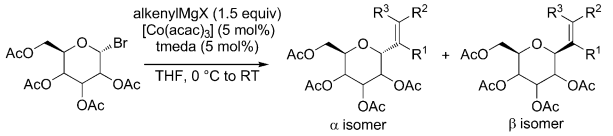


Entry	Substrate	ArMgX	Yield [%][b]	α/β[c]
1	**1**		70	>9:1
2	**1**		82	>9:1
3	**1**		83	>9:1
4	**1**		72	>9:1
5	**1**		77	>9:1
6	**1**		37	>9:1
7	**1**		39	>9:1
8	**1**		53	>9:1
9	**1**		–[d]	–
10	**1**		–[d]	–
11	**1**		–[d]	–
12	**4**	PhMgBr	96	3:1
13	**4**		83	2.4:1
14	**4**		85	2.3:1
15	**4**		81	2:1
16	**4**		34	1.3:1
17		PhMgBr	61	>9:1
18	**6**		82	>9:1
19	**6**		73	>9:1
20	**6**		75	>9:1
21	**6**		53	>9:1

[a] ArMgBr (1.5 equiv) was added at a rate of 2 mL min^{-1}; once the addition was complete, the reaction medium was warmed to RT. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] **1** was recovered.

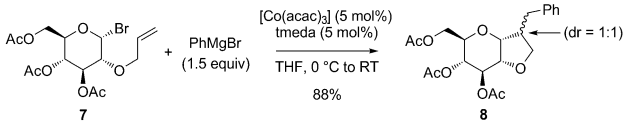
In conclusion, we have described the diastereoselective cobalt-catalyzed cross-coupling of 1-bromo glycosides with aryl and vinyl Grignard reagents. The [Co(acac)$_3$]/tmeda catalytic system is convenient (both the catalyst and the ligand are commercially available), inexpensive, and air-stable. When *O*-acetyl-α-bromo-D-glucose (**4**) was used, good diastereoselectivities were obtained with moderate α/β ratios of 1.5:1–3:1. The cross-coupling is fully α-selective in the case of *O*-acetyl-α-bromo-D-mannose (**1**), and *O*-acetyl-α-bromo-D-galactose (**6**). The observed diastereoselectivities with 1-bromo glycosides **1**, **4**, and **6**, as well as the cyclization of olefinic 1-bromo glycoside **7** strongly support a radical pathway for the oxidative addition step of the cross-coupling, which involves the formation of an anomeric radical.

Table 3: Scope of the cobalt-catalyzed cross-coupling of alkenyl Grignard reagents and 1-bromo glycosides **1**, **4**, and **6**.[a]



Entry	Substrate	AlkenylMgBr	Yield [%][b]	α/β[c]
1	**1**		66	>9:1
2	**1**		62[d]	>9:1
3	**1**		–	–
4	**4**		79	1.5:1
5	**6**		77	>9:1
6	**6**		70[d]	>9:1

[a] AlkenylMgBr (1.5 equiv) was added at a rate of 2 mL min^{-1}; once the addition was complete, the reaction medium was warmed to RT. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] AlkenylMgBr (2 equiv).



Scheme 3. Cross-coupling of 1-bromo glycoside **7** with PhMgBr.

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Keywords: *C*-glycosides · cobalt · cross-coupling · diastereoselectivity · Grignard reagent

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