

Synthetic Methods

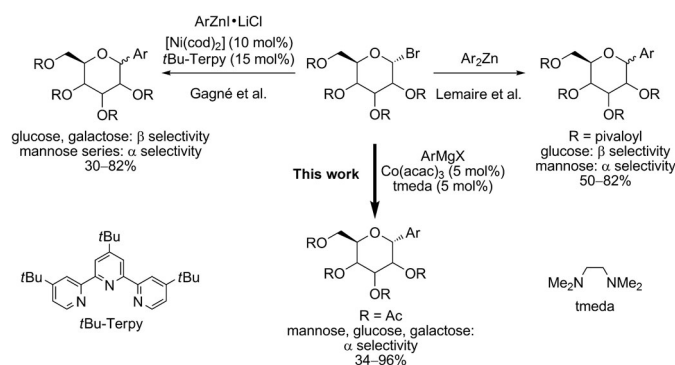
Diastereoselective Metal-Catalyzed Synthesis of C-Aryl and C-Vinyl Glycosides**

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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 $[\text{Ni}(\text{cod})_2]/t\text{Bu-Terpy}$, (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 -selectivity 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]

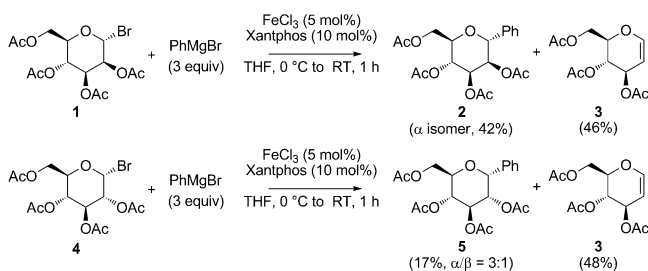
Herein, we report the diastereoselective metal-catalyzed cross-coupling between 1-bromo glycosides and easily accessible or commercially available Grignard reagents, which allows for the synthesis of an array of C-aryl and C-vinyl glycosides with α selectivity when a cobalt- or iron-centered catalytic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

Motivated by our previous results with iron-catalyzed cross-coupling between vinyl Grignard reagents and alkyl



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.

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

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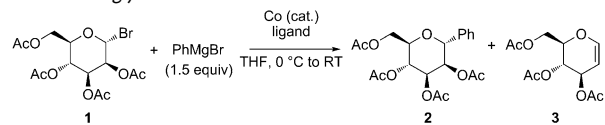
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[**] Janssen Research & Development (grant to L.N.) is gratefully acknowledged.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201204786>.

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]



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 CoCl₂ (5 mol %) led to **2** in only 13% yield (Table 1, entry 2). With the combination of CoCl₂ 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 %)^[14h] 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

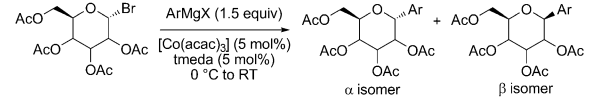
affecting the yield of **2** (Table 1, entry 6). However, the replacement of [Co(acac)₃] by [Co(acac)₂] decreased the yield of **2** (54%) (Table 1, entry 7). On the basis of these results, we selected [Co(acac)₃] as the cobalt source, as it is less hygroscopic than CoCl₂, and tmeda, which is cheaper 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*-CF₃-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]

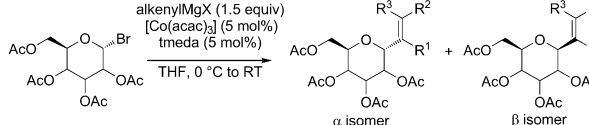
Table 2: Scope of the cobalt-catalyzed cross-coupling of ArMgX and 1-bromo glycosides **1**, **4**, and **6**.^[a]

				
Entry	Substrate	ArMgX	Yield [%] ^[b]	α/β ^[c]
1	1	MeO-C ₆ H ₄ -MgBr	70	> 9:1
2	1	MeO-C ₆ H ₄ -MgBr	82	> 9:1
3	1	F-C ₆ H ₄ -MgBr	83	> 9:1
4	1	F-C ₆ H ₄ -MgBr	72	> 9:1
5	1	Me-C ₆ H ₄ -MgBr	77	> 9:1
6	1	Me-C ₆ H ₄ -MgBr	37	> 9:1
7	1	Me-C ₆ H ₄ -MgBr	39	> 9:1
8	1	Me-C ₆ H ₄ -MgBr	53	> 9:1
9	1	CF ₃ -C ₆ H ₄ -MgCl	— ^[d]	—
10	1	Thiophene-MgBr	— ^[d]	—
11	1	MeN-C ₆ H ₄ -MgBr	— ^[d]	—
12	4	PhMgBr	96	3:1
13	4	MeO-C ₆ H ₄ -MgBr	83	2.4:1
14	4	MeO-C ₆ H ₄ -MgBr	85	2.3:1
15	4	F-C ₆ H ₄ -MgBr	81	2:1
16	4	Me-C ₆ H ₄ -MgBr	34	1.3:1
17	4	PhMgBr	61	> 9:1
18	6	MeO-C ₆ H ₄ -MgBr	82	> 9:1
19	6	MeO-C ₆ H ₄ -MgBr	73	> 9:1
20	6	F-C ₆ H ₄ -MgBr	75	> 9:1
21	6	Me-C ₆ H ₄ -MgBr	53	> 9:1

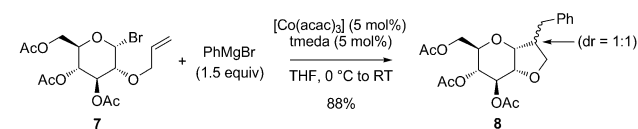
[a] ArMgBr (1.5 equiv) was added at a rate of 2 mL min⁻¹; once the addition was complete, the reaction medium was warmed to RT. [b] Yield of isolated product. [c] Determined by ¹H NMR spectroscopy. [d] **1** was recovered.

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

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	BrMg-CH=CH-CH ₃	66	> 9:1
2	1	BrMg-CH=CH-CH ₃	62 ^[d]	> 9:1
3	1	BrMg-CH=CH-CH ₃	—	—
4	4	BrMg-CH=CH-CH ₃	79	1.5:1
5	6	BrMg-CH=CH-CH ₃	77	> 9:1
6	6	BrMg-CH=CH-CH ₃	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 ¹H NMR spectroscopy. [d] AlkenylMgBr (2 equiv).



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

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.

Received: June 16, 2012

Published online: September 28, 2012

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

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- [15] The cross-coupling of **1** and PhMgBr is not possible in Et₂O. However, when the cross-coupling was performed in THF using a solution of PhMgBr in Et₂O (3M), the yield of **2** remained 76%.
- [16] The use of TEMPO (20 mol %) partially inhibits the coupling of **1** and PhMgBr (**2** was isolated in 14%); whereas, with one equivalent of TEMPO, the cross-coupling is fully inhibited.