JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

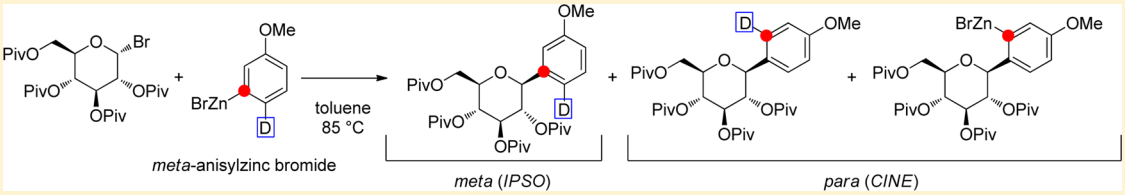
Cine Substitution with Arylzinc Reagents: Scope and Mechanistic Studies

Santiago Barroso,*[,†] Sébastien Lemaire,[†] Vittorio Farina,[†] Andreas K. Steib,[‡] Romain Blanc,[‡] and Paul Knochel[‡]

[†]Pharmaceutical Development and Manufacturing Sciences, Janssen Pharmaceutica, Turnhoutseweg 30, 2340 Beerse, Belgium

[‡]Department of Chemistry and Biochemistry, Ludwig-Maximilians University of München, Butenandtstrasse 5-12, Haus F, 81377 München, Germany

Supporting Information



ABSTRACT: The unexpected ability of arylzinc reagents bearing electron-donating substituents to react in a Friedel−Crafts fashion (*cine*) with electrophiles like perpivaloylated glucoside bromide and benzhydryl bromides in competition with organometallic coupling (*ipso*) is shown. The stereoelectronic factors required to promote the *cine* reactivity versus the classical *ipso*, and the mechanism of this alternative pathway, have been investigated. The Wheland intermediate is deprotonated intramolecularly in a 1,2-shift but also in a longer-range shift, leaving in this case the C−Zn untouched. In the latter case, it is possible to take advantage of this result for further functionalization.

INTRODUCTION

Because of their importance as bioactive compounds, *C*-glycosides are a popular area of research for organic and medicinal chemists.[1] The recent market introduction of new antidiabetic SGLT-2 inhibitors like Canagliflozin (**1**) and Dapagliflozin (**2**) dramatically strengthened the role of *C*-glycosides as synthetic targets (Figure 1).[2]

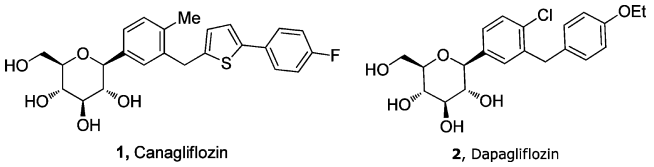


Figure 1. New SGLT-2 inhibitors as breakthrough antidiabetic therapy.

Following up on our recent communication on the direct, noncatalyzed coupling of aryl- and heteroarylzinc compounds with bromosugars in toluene/di-*n*-butyl ether (DBE), we attempted the coupling of *meta*-substituted arylzinc reagents in order to broaden the scope of our new reaction.[3] We were very surprised to observe that coupling reactions of *meta*-anisylzinc species (*meta*-**4**) with bromosugar **5**, in addition to the expected product *meta*-**6**, led to a large amount of *cine*-substitution product *para*-**6** (Scheme 1).

Some examples of *cine* substitution reactions of arylmetallic compounds are reported in the literature.[4] Well-known examples are those involving a benzyne intermediate[5] and the von Richter reaction.[6] Rare examples are found for reactions where the unsaturated derivative acts as a nucleophile. One of the best documented ones is the reaction of vinyl stannanes in Stille coupling, where the substitution can occur not only at the carbon bearing the trialkyltin group but also on the adjacent one.[7] It has also been shown that tributylstannyl-substituted furans and thiophenes react with the benzhydryl cation at a remote position with respect to the one occupied by the tin atom.[8] Another example of *cine* reactivity is found in the reaction of electron-rich arylsilanes with electrophiles, which can lead to *ipso* or *cine* products depending on the conditions employed.[9]

Related to our discovery is the report that bis(*meta*-anisyl)cadmium can undergo acylation either at the *meta* (*ipso* substitution) or at the *para* (*cine* substitution) position.[10] However, to the best of our knowledge, no *cine* reactivity has been described for arylzinc reagents. Our initial results led us to a comprehensive mechanistic study, which led to the first synthetic applications of this unusual reaction mode.

RESULTS

Given the unusual observations described in Scheme 1, we decided to carry out a comprehensive analysis of product distribution and extend the reaction to related *ortho*- and *para*-substituted anisylzinc derivatives.[11] For completeness, we

Received: January 12, 2016

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. *Cine* Substitution with *meta*-Anisylzinc Reagents

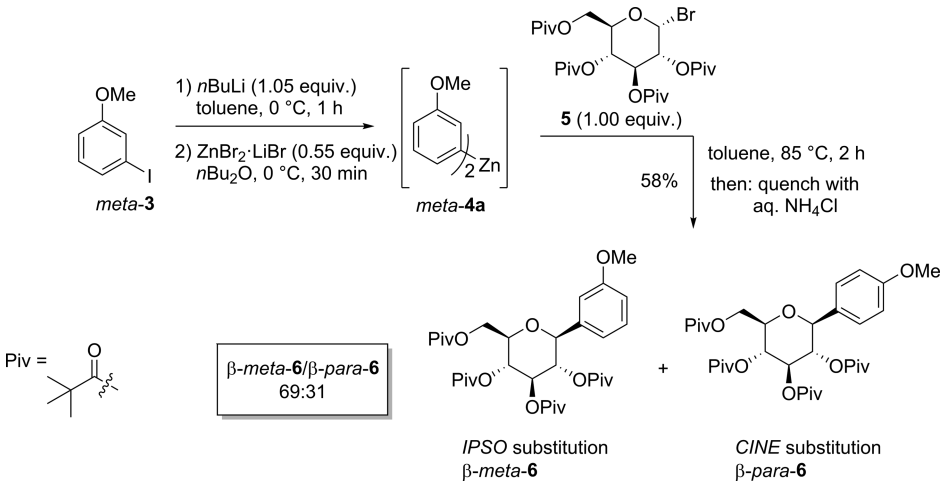
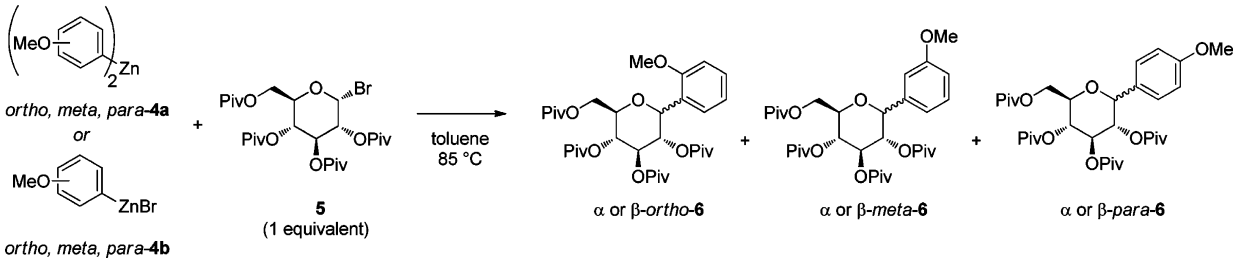
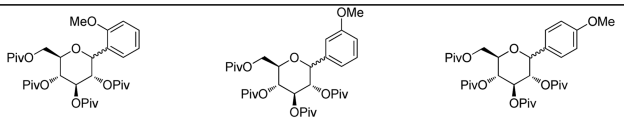


Table 1. Yield and Product Distribution of *ipso*, *cine*, and *tele* Products[a,b]





entry	isomer	reagent	% α	% β	% α	% β	% α	% β	yield[c]
1	*ortho*	R_2Zn (*o*-**4a**)	*i* **0.8**	*i* **98.3**	*c* 0.1	*c* 0	*t* 0.4	*t* 0.4	60 %
2	*ortho*	RZnBr (*o*-**4b**)	*i* **1.7**	*i* **96.0**	*c* <0.1	*c* <0.1	*t* 1.6	*t* 0.6	62 %
3	*meta*	R_2Zn (*m*-**4a**)	*c* 2.1	*c* 5.1	*i* **1.5**	*i* **59.2**	*c* 5.2	*c* 26.9	58 %
4	*meta*	RZnBr (*m*-**4b**)	*c* 5.4	*c* 7.4	*i* **2.2**	*i* **39.7**	*c* 10.9	*c* 34.4	50 %
5	*para*	R_2Zn (*p*-**4a**)	*t* 0.3	*t* 0.2	*c* 1.6	*c* 0	*i* **1.6**	*i* **96.3**	75 %
6	*para*	RZnBr (*p*-**4b**)	*t* 0.3	*t* 0.2	*c* <0.1	*c* <0.1	*i* **0.9**	*i* **98.6**	64 %

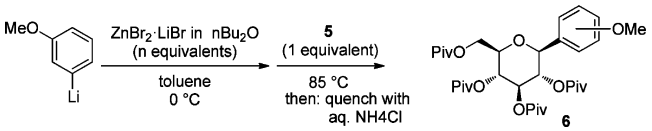
[a]Reaction conditions: dianisylzinc **4a** (3.5 mmol) or anisylzinc bromide **4b** (6.7 mmol), di-*n*-butyl ether (2.6 or 5.2 mL respectively), toluene (25 mL), bromosugar **5** (6.4 mmol), 85 °C. [b]*i* = *ipso* (in bold), *c* = *cine*, *t* = *tele*. [c]Total yields were determined by GC using tetradecane as an internal standard.

decided to compare also the reactivity of diarylzinc species **4a** with their arylzinc bromide counterparts **4b** (Table 1).

As shown in Table 1, we detected in each case a certain amount of *cine* products (new substituent *ortho* to the original C−Zn bond) and even *tele*-products (new substituent *meta* to the original C−Zn bond). We observed very small amounts of these unexpected compounds with the organozinc reagents *ortho*-**4a**/**b** and *para*-**4a**/**b**. Diarylzinc and arylzinc bromide species gave very similar results for these isomers. However, as noted before, large amounts of *cine* products were obtained with the *meta*-organozinc reagent *meta*-**4a** (entry 3) and, especially, with arylzinc bromide reagent *meta*-**4b** (entry 4). In

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Effect of organolithium−zinc ratio



entry	equiv of $ZnBr_2$[a]	formal species	*cine* % *α-ortho*	*cine* % *β-ortho*	*ipso* % *α-meta*	*ipso* % *β-meta*	*cine* % *α-para*	*cine* % *β-para*	% yield[b] (overall)
1	0.25	R_4ZnLi_2	0.9	2.7	1.4	83.7	0.8	10.5	16
2	0.33	R_3ZnLi	1.4	3.9	1.3	67.9	2.9	22.6	40
3	0.55	R_2Zn	2.1	5.1	1.5	59.2	5.2	26.9	58
4	1.05	RZnBr	5.4	7.4	2.2	39.7	10.9	34.4	50
5	1.05[c]	RZnBr	6.4	7.9	2.4	42.5	11.1	29.7	nd
6	2.00[d]	RZn_2Br_3	8.0	9.4	3.4	36.2	14.0	29.0	nd
7	2.00	RZn_2Br_3	12.5	10.8	5.4	25.8	19.7	25.8	nd
8	1.05[e]	RZnBr	6.5	7.4	2.4	38.3	13.1	32.3	60
9	1.05[f]	RZnBr	6.5	9.9	2.7	39.1	11.4	30.4	61

[a]Added from a 25% solution of $ZnBr_2$·LiBr in nBu_2O. [b]Yields were measured by GC using tetradecane as an internal standard. [c]The amount of DBE was doubled after the transmetalation. [d]In this case, 1.0 equiv of solid $ZnBr_2$ and solid LiBr were added after the transmetalation with 1.0 equiv of 25% $ZnBr_2$·LiBr solution in DBE. [e]Reaction ran at 55 °C for 18 h. [f]Reaction ran at 114 °C for 35 min.

addition, α/β ratios were markedly different for the three isomeric products: whereas the *ipso* substitution product was formed with an α/β ratio as high as 1:39 with the *meta*-**4a** reagent, for the *cine* product, the α/β ratios ranged from 1:5 (entry 3, *para*-**6**) to a very low 1:1.4 (entry 4, *ortho*-**6**). In this regard, arylzinc bromide species proved to be less selective than the corresponding diarylzinc species.

The study on the *meta*-anisyl system was extended to organozinc reagents obtained by using various ratios of $ZnBr_2$ and *meta*-anisyllithium in the transmetalation step, changing the Zn/Ar ratio from 1:4 to 2:1, i.e., ranging from formal tetraarylzincates to arylzinc halides containing extra zinc halide (Table 2).[3a] The formal tetraarylzincate (entry 1) gave the highest selectivity toward the *ipso*-*β* product, although in very low yield. The use of two equivalents of $ZnBr_2$ led to the lowest selectivity (entry 7). Excess of DBE slightly favored the *ipso* product (entry 5). The temperature did not have a significant effect on the product distribution (entries 8 and 9).

After studying the product distribution, we decided to monitor product formation over time. Because the reaction mixtures were heterogeneous,[12] we could not obtain reliable kinetic data. We did notice, however, that arylzinc bromide *meta*-**4b** reacts more readily than diarylzinc *meta*-**4a**. Using a large excess of diarylzinc reagent *meta*-**4a**, we observed a lag phase, resulting in a sigmoidal curve. However, the reaction with an excess of arylzinc bromide *meta*-**4b** did not show a lag phase, evolving similarly to a first order reaction.

The sigmoidal evolution observed with excess *meta*-**4a** may be the consequence of small amounts of the more reactive *meta*-**4b** being formed with the progress of the reaction, i.e., an autocatalytic behavior.[13] Because arylzinc bromide species react at a faster rate than diarylzinc species, the reaction is accelerated up to a steady state phase. In the final stage, when the concentration of bromosugar becomes very low, the reaction rate decreases. This may result in the sigmoidal behavior observed.

When diarylzinc species *meta*-**4a** is used for the coupling, the isomer distribution of the product changes over time. This is a consequence of the formation of monoarylzinc bromide *meta*-**4a**, which has a faster reaction rate although with a lower *ipso*/*cine* selectivity. This change is especially evident when equimolar amounts of bromosugar **5** and diarylzinc *meta*-**4a** are used, as shown in Table 3.

Table 3. Evolution of the Isomer Distribution in the Reaction of 5 Using One Equivalent of *meta*-4a

time (min)	*β-meta*-**6** (*ipso*)	% *β-para*-**6** (*cine*)	% others isomers
1	89%	7%	4%
10	79%	16%	5%
30	73%	20%	7%
60	66%	26%	8%
120	59%	31%	10%

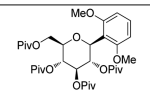
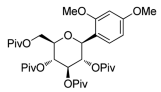
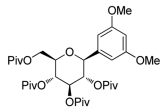
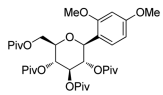
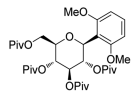
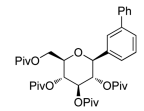
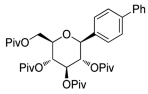
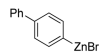
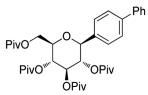
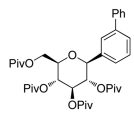
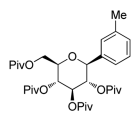
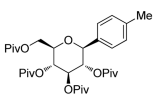
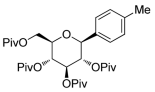
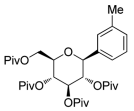
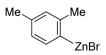
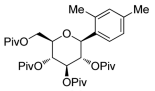
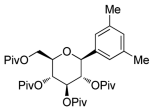
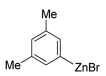
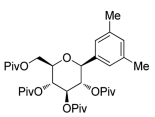
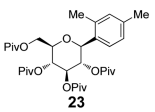
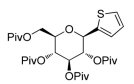
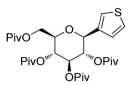
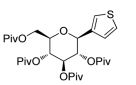
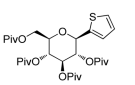
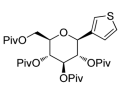
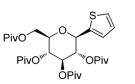
We then extended the reaction scope of this organometallic coupling to other organozinc reagents (Table 4). First, we tested highly electron-rich dimethoxyphenylzinc derivatives prepared by standard methods. When the C−Zn bond is located at a position activated by the two methoxy groups (**7** and **8**), only the expected *ipso* products were obtained. In strong contrast, di(3,5-dimethoxyphenyl)zinc (**9**) did not lead to any significant amount of *ipso* product **20**. In this case, the combined electron-releasing properties of the two methoxy substituents overcame the nucleophilicity of the C−Zn bond, and *cine* product **19** was preferentially obtained with a selectivity of 88%.

We also examined the influence of a phenyl group as a substituent in the *meta*- and *para*- positions. Consistent with the limited electron-releasing ability of this substituent, less than 1% of *cine* product was obtained with organozinc bromides **10** and **11**. Interestingly, whether the phenyl group was *meta* or *para* was irrelevant regarding the amounts of *cine* product (entries 4 and 5). In the presence of other weakly electron-donating groups, namely methyl, *cine* products were detected, although in a low proportion, amounting up to 2.5% (*para*-**22** α+β, entries 6 and 7).

Dimethylphenylzinc derivatives (entry 8 and 9) also gave predominant *ipso* substitution. Interestingly, organozinc reagents derived from an electron-rich heterocycle like thiophene (entries 10−12) were also able to deliver *cine* products in significant proportions, although rigorously speaking, it is impossible to distinguish between *cine* and *tele* substitution. In the case of compounds **17a** and **17b**, where the

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 4. Scope of the Reaction with the Bromosugar 5 as the Electrophile

entry	organozinc[a]	total yield[b]	product		selectivity[b]
1	 **7**	64 %	*ipso*	 **18**	>99 %
2	 **8**	96 %	*ipso*		>97 %
3	 **9**	36 %	*ipso*	 **20**	n.d.[c]
			cine	 **19**	96 %
			cine	 **18**	4 %
4	 **10**	59 %	*ipso*	 *meta*-**21**	α 11 % β 88 %
			cine	 *para*-**21**	β 1 %
5	 **11**	88 %	*ipso*	 *para*-**21**	α 3.9 % β 95.5 %
			cine	 *meta*-**21**	α 0.6 %
6	 **12**	82 %	*ipso*	 *meta*-**22**	α 5.1 % β 92.4 %
			cine	 *para*-**22**	α 1.5 % β 1.0 %
7	 **13**	88 %	*ipso*	 *para*-**22**	α 3.4 % β 95.8 %
			cine	 *meta*-**22**	α 0.6 % β 0.2 %
8	 **14**	96 %	*ipso*	 **23**	α 1.3 % β 98.3 %
			cine	 **24**	α 0.1 % β 0.3 %
9	 **15**	98 %	*ipso*	 **24**	α 2.7 % β 96.0 %
			cine	 **23**	α 0.5 % β 0.8 %
10	 **16**	98 %	*ipso*	 **25**	β 93 %
			cine[d]	 **26**	β 7 %
11	 **17a**	87 %	*ipso*	 **26**	β 77.0 %
			cine[d]	 **25**	β 23.0 %
12	 **17b**	90 %	*ipso*	 **26**	β 75 %
			cine[d]	 **25**	β 25 %

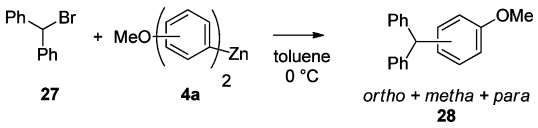
[a]Using 1.5 equiv of the organozinc reagent. [b]Yields were measured by GC using tetradecane as an internal standard. Selectivity was determined by GC A%. [c]The compound could not be identified, but we observed other small isomers appearing in GCMS. [d]Other isomers were present in small amounts, but they could not be identified.

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX

most activated C-2 position is free, the *cine* products amounted to up to 22% of the product mixture.

To understand whether the *cine* mode of reactivity was unique to bromosugars, we also investigated benzhydryl bromide (**27**) as the electrophile and examined its reaction with *ortho*-, *meta*-, and *para*-dianysilzinc. Substrate **27** proved to be a very reactive electrophile and coupling occurred smoothly at room temperature. As shown in Table 5, in all cases, *para*-**28** was the major product. For the zinc reagents *ortho*-**4a** and *para*-**4a**, both *ipso* and *tele* products were obtained, whereas no *cine* reaction took place. With dianysilzinc *meta*-**4a**, *cine* substitution predominated, and only 6% of *ipso* product was obtained.

Table 5. Product Distribution of the Reaction between Diarylzincs 4a and Benzhydryl Bromide 28[a]



diarylzinc reagent	distribution of products		
	% *ortho*	% *meta*	% *para*
ortho-**4a**	(*ipso*) 38%	(*cine*) 0%	(*tele*) 62%
meta-**4a**	(*cine*) 9%	(*ipso*) 6%	(*cine*) 85%
para-**4a**	(*tele*) 8%	(*cine*) 0%	(*ipso*) 92%

[a]Reaction conditions: iodoanisole (3.0 g, 12.8 mmol), toluene (39 mL), *n*BuLi (14.7 mmol), $ZnBr_2$·LiBr in DBE (7.05 mmol, 0.55 equiv), benzhydryl bromide **27** (2.7 g, 10.9 mmol), 0 °C.

We also ran a series of control experiments using anisole (**29**) or 1,3-dimethoxybenzene (**30**) to evaluate the intrinsic nucleophilicity of the aromatic ring in the absence of the C−Zn bond and rule out direct Friedel−Crafts reactions of "quenched" organozinc species.[14] Thus, we stirred a solution of the highly reactive benzhydryl bromide **27** and anisole (**29**) in the presence of $ZnBr_2$·LiBr (Scheme 2, reaction 1). Within 2 h at room temperature, more than 70% of conversion was achieved, obtaining **28** mainly as the *para* isomer.

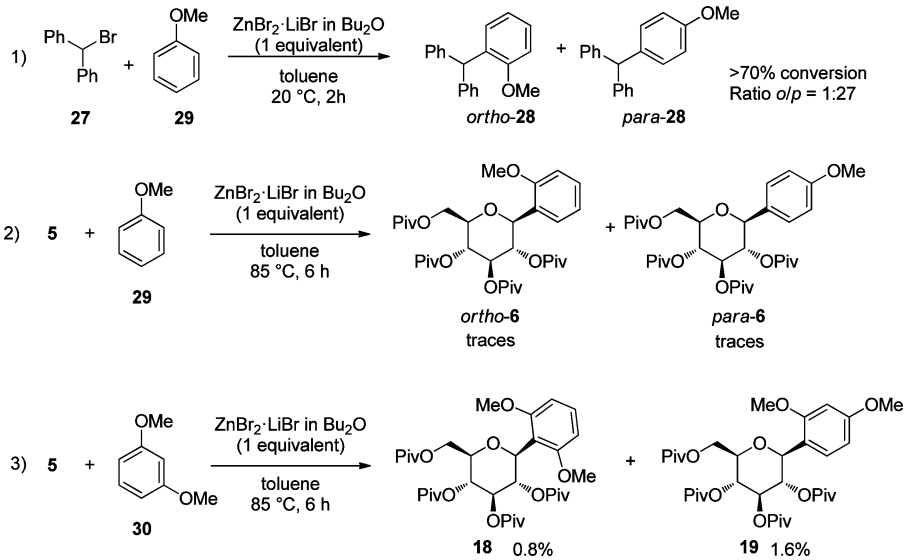
However, a similar reaction using anisole and bromosugar **5** as electrophile gave only traces of product **6** after prolonged heating (Scheme 2, reaction 2). The use of the more nucleophilic 1,3-dimethoxybenzene (**30**) only led to a combined yield of 2.4% for products **18** and **19** (Scheme 2, reaction 3).

We hoped to shed some light on the mechanism of this unusual reaction by preparing deuterium-labeled diarylzinc **31a** and treating it with bromosugar **5** under standard conditions. We obtained the expected mixture of *ipso*- and *cine*-substitution products. GC-MS and ^{1}H NMR analysis of the products after quenching with NH_4Cl (Scheme 3, reaction 1) showed that (*cine*) *ortho*-**32** and (*ipso*) *meta*-**32** retained 100% of their deuterium label. However, the (*cine*) *para* product was a mixture of nondeuterated *para*-**6** and deuterated *para*-**32**, the latter being a result of an apparent 1,2-deuterium shift. As shown in Table 6, we observed larger amounts of 1,2-deuterium shift (*ortho*-**32** and *para*-**6**) with arylzinc bromide species relative to those of the corresponding diarylzinc reagents. Another noteworthy finding was that α anomers have a higher proportion of 1,2-D shift products than those of β anomers.

We repeated the experiments, quenching this time with iodine, to determine any arylzinc species present in the reaction product. GC/MS analysis of samples quenched with iodine (Scheme 3, reaction 2) showed that the *cine-para* product was composed solely of deuterated *para*-**32**. Although the nondeuterated *para*-**6** was missing, we found that this compound was quantitatively replaced by the same proportion of a new peak corresponding to iodinated compound *para*-**33**, whose structure was confirmed by NMR. This confirms that, at the end of the reaction, before the quench, there is a substantial presence of *cine* product still containing the original C−Zn bond.

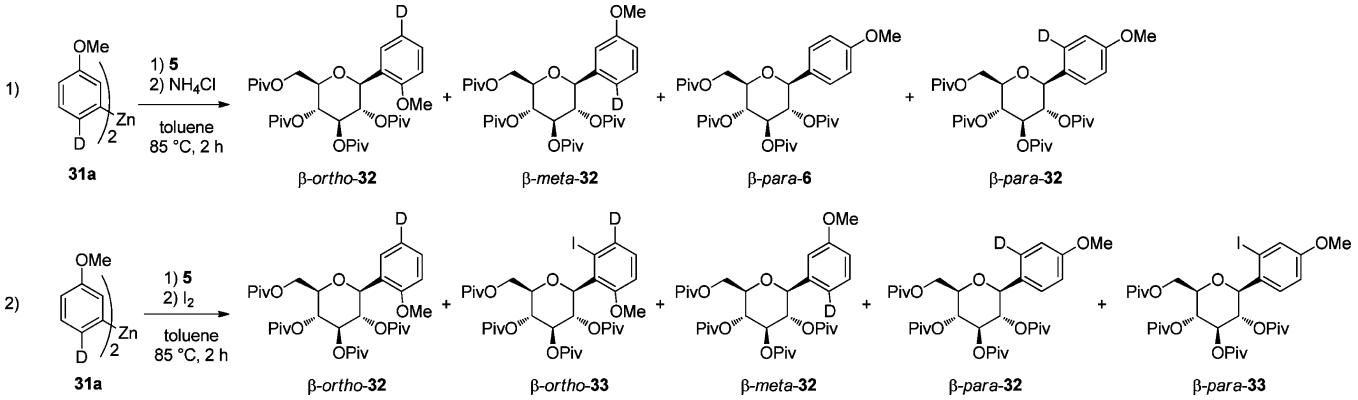
To investigate the nature (intra- vs intermolecular) of the 1,2-hydrogen(deuterium) shift, we carried out a crossover study (Scheme 4). First, a slight excess of bromosugar **5** was added to a 1:1 solution of labeled compounds **31b** and **34**. Analysis of the products showed no crossover. From a parallel experiment using a limiting amount of bromosugar **5**, we

Scheme 2. Control Experiments with Aromatic Reagents Lacking a C−Zn Bond



DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 3. Deuterium-Labeling Experiment[a]



[a]For clarity, the α anomers are not depicted. For indicative ratios of all products (with nondeuterated reagents), see Table 1.

Table 6. Proportion of Apparent 1,2-Deuterium Shift in the Reaction between 5 and Deuterated *meta*-Anysilzinc Species 31a As Determined by D Retention[a]

reagent	*β-ortho*	*α-ortho*	*β-para*	*α-para*
R_2Zn **31a**	nd	nd	35%	60%
RZnBr **31b**	61%	79%	47%	63%

[a]Analyzed using GCMS.

calculated a small D kinetic isotope effect of around 1.07 for the *cine* substitution pathway.

We also analyzed the anisole formed in these reactions and found anisole-*d2* (**29**-*d2*) in equal amounts to product *para*-**6**. To establish whether the D retention pathway and the reaction leading to D loss had the same or different molecularity, we carried out a series of dilution experiments. To perform such experiments, we prepared soluble organozinc reagent **37**. We carried out two series of experiments, one with a constant DBE/substrate ratio, and a second with a constant DBE/toluene ratio, thus accounting for any cosolvent effect. As shown in Table 7, the influence of dilution on the proportion of 1,2-deuterium shift is essentially nil, showing that the processes studied have the same molecularity.

We considered the possibility that the unusual reactivity displayed by these arylzinc species could be of synthetic utility. We postulated that, if the 1,2-proton shift could be avoided, perhaps using a strong base to scavenge the resulting proton, two different electrophiles could be introduced in a sequential, one-pot procedure via organozinc intermediate **41**, which normally would lead to product **42** after acidic quenching (Scheme 5a).

Indeed, intermediate **41** could be generated in the presence of TMPZnCl·LiCl (Scheme 5a), which presumably forms heteroleptic organozinc species with *meta*-**4a**; upon quenching with iodine, it afforded aryl iodide **43** in 49% yield. The latter underwent a Negishi coupling in 81% yield (Scheme 5b)[15] as well as a sequence of lithiation and addition to benzaldehyde (Scheme 5c).

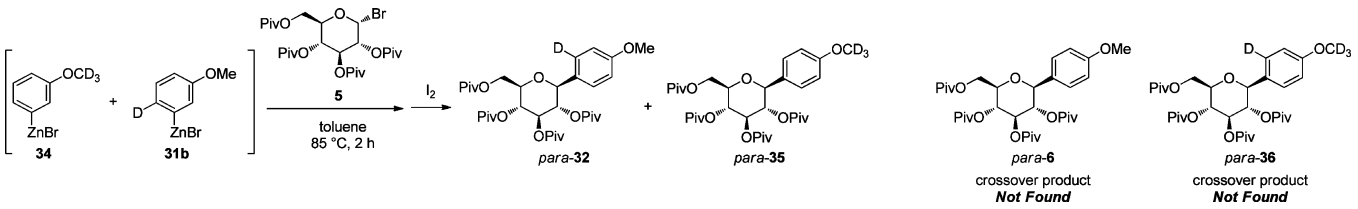
Furthermore, intermediate **41** could also be transmetalated to the corresponding organocopper reagent to furnish a direct, one-pot acylation (Scheme 5d), albeit in low yield. Particularly remarkable was the Friedel–Crafts/allylation sequence that yielded **48** from **41** in 58% yield (Scheme 5e). Although the yields of these transformations are still modest in terms of synthetic value, further optimization may be possible, and we are now focusing on better defining these tandem functionalization processes. Results will be communicated in due course.

DISCUSSION

As a result of our findings, we propose the mechanism depicted in Scheme 6. The nucleophilic addition of the arylzinc reagent to the oxocarbenium intermediate generated from the glycosyl halide leads either to the expected *ipso* coupling or to the competing *cine* substitution, which can be considered a Friedel–Crafts reaction, generating Wheland intermediate **49**. Then, this highly reactive intermediate faces two competing pathways: the first one (A) is a proton quench by the vicinal C–Zn bond (i.e., 1,2-D(H) shift), giving product *para*-**32**. In the alternative pathway B, the proton (deuteron) is quenched by another species containing a C–Zn bond, leading to intermediate *para*-**50** and labeled anisole **29**-*d2*, both of which are duly detected in a 1:1 ratio

The control experiments show that these products are not due to quenched anisole reacting in a Friedel–Crafts mode but derive directly from the anisylzinc reagent. The small secondary KIE in the *cine*-substitution process suggests that

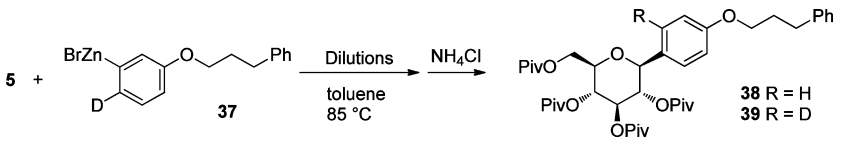
Scheme 4. Crossover Experiment[a]



[a]For clarity, only *para* (*cine*) products are depicted.

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX–XXX

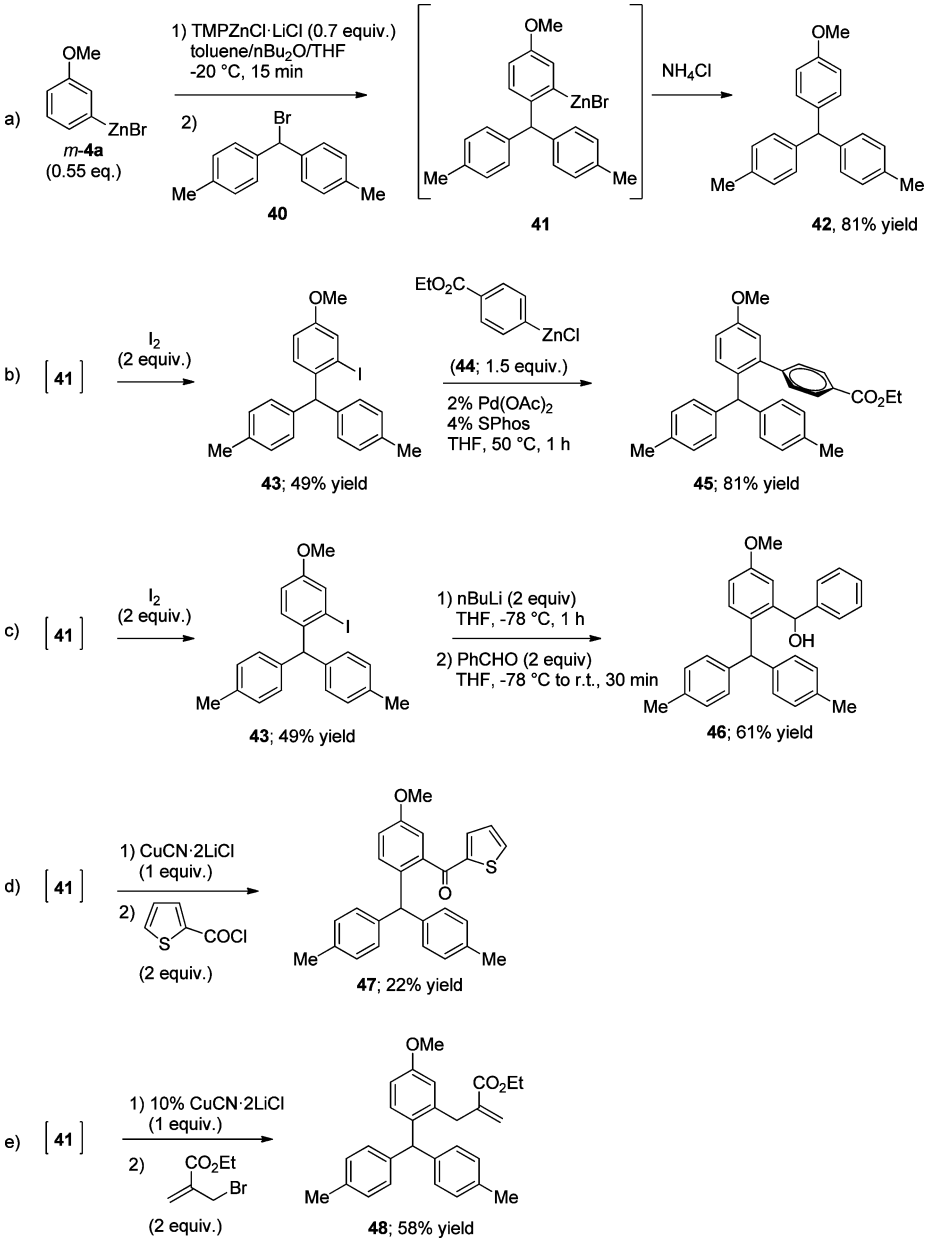
Table 7. Dilution Experiments



	constant equiv of DBE			constant concentration of DBE		
dilution[a]	1	3	9	1	3	9
38/**39** ratio	54:46	54:46	49:51	49:51	51:49	43:57

[a]Dilution measured as the total volume divided by the volume of stock solution of **37** added to the reaction. Ratios determined by GCMS.

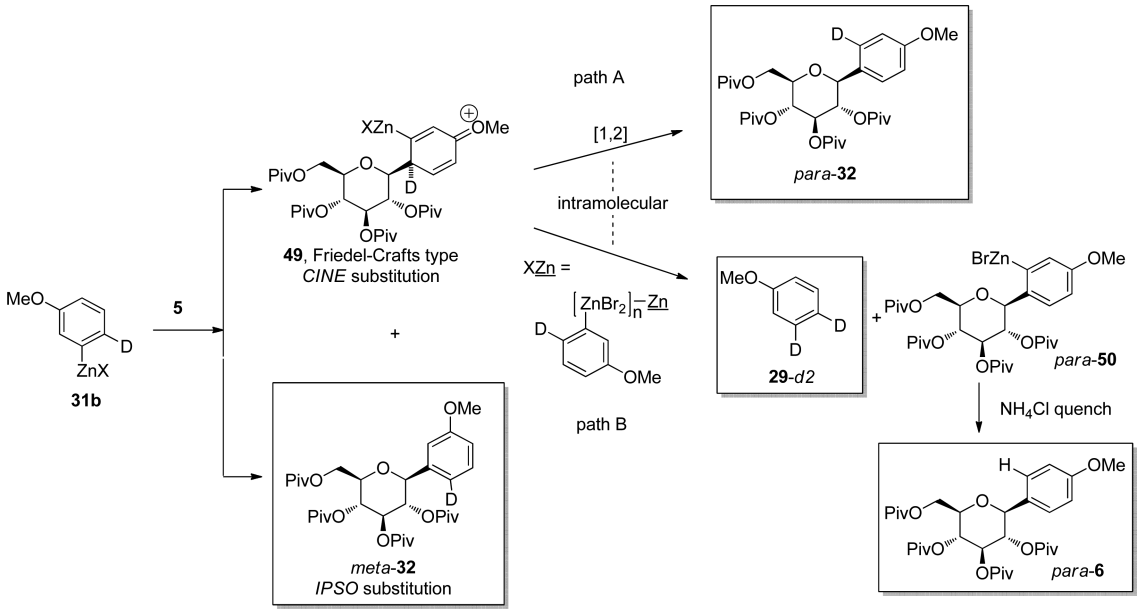
Scheme 5. Synthetic Applications of *cine* Substitution



the formation of the Wheland intermediate is rate determining, i.e., in the key step, the C−H bond is not yet cleaved, only rehybridized. The crossover study and the dilution experiments clearly prove that both path A and B in Scheme 5 are intramolecular. This is a very surprising result: it is not difficult to believe that the 1,2-proton shift that leads to D retention (path A) occurs intramolecularly, but we are forced to acknowledge that transfer of a proton to another molecule or arylzinc reagent is also intramolecular. Because the diarylzinc reagent leads mostly to the *ipso* product, and we have shown that the *cine* substitution originates mostly after the induction period forming arylzinc halides (Table 3), it

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 6. Proposed Mechanism of the Anomalous Coupling with *meta*-Anisylzinc Reagents



follows that the *cine*-substitution process takes place from dimeric or oligomeric arylzinc halide species and that proton transfer within these aggregates is kinetically competitive with the 1,2-H shift.[16]

More difficult to interpret are the observations that the *cine* process is less β-selective than the *ipso* substitution process, as it is not clear how the α-glycosides form. We have provided evidence that β-selectivity originates, in the desired *ipso* mode, from anchimeric participation of the pivaloyl group at C-2.[3a] Conversely, α-selectivity could originate from an unlikely participation of the C-6 pivaloyl group, from the reaction of a simple oxocarbenium intermediate or through S_N2 of an intermediate β-bromosugar anomer.

Any one of these pathways may be responsible for the production of the α-anomer, and somehow the *cine*-substitution transition state may be better disposed energetically to accommodate these pathways. Likewise, the specific geometry of this novel transition state is more compatible with substantial 1,2-H migration than longer-range shifts within arylzinc aggregates. More specific explanations at this point would be sheer conjecture.

CONCLUSIONS

In conclusion, we have demonstrated that arylzinc reagents bearing electron-donating substituents may react with activated electrophiles, such α-bromosugars or benzhydryl bromides, via a Friedel–Crafts mechanism in close competition with direct organometallic coupling. The Friedel–Crafts mechanism consists of two competing intramolecular pathways, one of which leaves the C–Zn bond untouched. The selectivity between the different pathways is determined by the nature of the organozinc reagent but is insensitive to concentration. In comparison with diarylzinc species, arylzinc bromides are poorly selective toward the *ipso* coupling but more selective toward 1,2-H shift in the case of *cine* products. We have shown that this unexpected reactivity could be synthetically useful and allows us to add two electrophiles in a 1,2-fashion onto an electron-rich arylzinc reagent. This may open up new avenues in the chemistry of C–Zn bond-containing species, which is currently dominated by their Ni- and Pd-catalyzed reactions. We have also shed preliminary light onto the mechanistic details of this novel process but much is left to be done in terms of understanding the structure and reactivity of these complex organozinc reagents in toluene/DBE solution, both with α-bromosugars but especially with other activated electrophiles. In this area, ab initio calculations may be very useful, especially if solution structures of these organozinc reagents in our reaction media can be pinpointed. We believe that our newly reported solvent system offers a great advantage over traditional THF in which the organozinc reagents may be too unstable to undergo many useful synthetic transformations that are now, for the first time, possible in a toluene-rich medium at high temperatures.[20] Further work in this area will be reported soon.

EXPERIMENTAL SECTION

General Methods. Unless otherwise indicated, all reactions were carried out with magnetic stirring and in flame-dried glassware under an inert atmosphere. Syringes used to transfer reagents and solvents were dried and purged with argon or nitrogen prior to use.

Solvents used for the reactions were purchased anhydrous in sealed bottles containing molecular sieves and used as received under an inert atmosphere. *n*BuLi was used as a 25% solution in heptane. All other reagents were used as received. Zinc bromide was used as a solution of $ZnBr_2$·LiBr in nBu_2O with a $ZnBr_2$ content of 25% w/w.

Reactions were monitored by gas chromatography (GC and GC-MS) or thin layer chromatography (TLC). TLC was performed on silica gel (Merck 60, F-254) and visualized by UV detection. Purification via column chromatography was performed using silica gel 60 (40–63 mm 230–400 mesh ASTM from Merck) or using preparative high-performance liquid chromatography (Kromasil C18) in 0.25% ammonium carbonate in water and acetonitrile (20:80 to 0:100).

NMR spectra were recorded in $CDCl_3$, and chemical shifts (δ) are reported in parts per million (ppm). Mass spectra and high resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) and a TOF analyzer. GCs analysis was performed using a Hewlett-Packard column with 5% phenylmethylpolysiloxane (length = 15 m, diameter = 0.25 mm, film thickness = 0.25 mm) or an Rxi-1HT (df = 0.1 μm, diameter = 0.32 mm, length = 30 m).

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX–XXX

*General Procedure for the Coupling of Organozinc Reagents with Bromosugar **5** (Procedure A).* A dry, argon-flushed 50 mL flask was charged with the corresponding iodoarene (6.4 mmol), tetradecane (2.5 mmol) as internal standard, and anhydrous toluene (25 mL). *n*-BuLi (6.7 mmol, 1.05 equiv) was slowly added dropwise at −10 °C, and then the reaction was allowed to warm to 0 °C.[17] The reaction was monitored at this temperature until samples quenched with MeOH showed full iodine−lithium exchange by HPLC analysis. Subsequently, a solution of $ZnBr_2$·LiBr in $(nBu)_2O$ (0.55 or 1.05 equiv) was added dropwise, and the reaction mixture was heated slowly to 60 °C.[18] Bromosugar **5** (1.0 equiv)[19] was added in one portion, and the reaction mixture was heated to 85 °C and stirred until full conversion was achieved. Reactions were monitored by GC (quantitative) and HPLC (qualitative) analysis. Two solutions were prepared each time: the first one by quenching a sample of the reaction with an aqueous solution of NH_4Cl solution. A second sample was quenched with a solution of I_2 in MTBE followed by aq sodium sulfite treatment. In both cases, only the organic layer was analyzed. Upon full conversion of one of the reactants, the reaction was quenched with a sat. aqueous NH_4Cl, and the organic layer was quantitatively analyzed by GC.

Yields and ratios obtained with the different substrates are reported in Tables 1−3.

*2,3,4,6-Tetra-O-pivaloyl 1-(2-Anisyl)-1-deoxy-β-D-glucopyranose (β-ortho-**6**).* The NMR spectral data match published data.[3a]

*2,3,4,6-Tetra-O-pivaloyl 1-(4-Anisyl)-1-deoxy-β-D-glucopyranose (β-meta-**6**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 2.2 Hz, 1H), 6.83 (dd, *J* = 8.2, 2.6 Hz, 1H), 5.42 (t, *J* = 9.3 Hz, 1H), 5.32 (t, *J* = 9.6 Hz, 1H), 5.25 (t, *J* = 9.5 Hz, 1H), 4.39 (d, *J* = 9.8 Hz, 1H), 4.21 (dd, *J* = 12.4, 1.9 Hz, 1H), 4.11 (dd, *J* = 12.5, 4.0 Hz, 1H), 3.85 (ddd, *J* = 9.7, 3.9, 1.9 Hz, 1H), 3.78 (s, 3H), 1.22 (s, 9H), 1.16 (s, 9H), 1.10 (s, 9H), 0.89 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.0, 177.3, 176.4, 176.0, 159.5, 137.6, 129.3, 120.2, 114.8, 112.9, 80.8, 76.5, 73.7, 72.1, 67.9, 61.8, 55.2, 38.9, 38.8, 38.7, 38.5, 27.2, 27.09, 27.07, 27.0. IR ATR ν (cm^{-1}): 2975, 2873, 1734, 1615, 1588, 1482, 1461, 1398, 1367, 1269, 1174, 1154, 1134, 1095, 1077, 1040, 983, 939, 916, 890, 876, 786, 772, 761, 702. HRMS (EI) calcd for $[C_{33}H_{50}O_{10} + H]$ 607.3477, found 607.3473.

*2,3,4,6-Tetra-O-pivaloyl 1-(2-Anisyl)-1-deoxy-β-D-glucopyranose (β-para-**6**).* The NMR spectral data match published data.[3a]

*2,3,4,6-Tetra-O-pivaloyl 1-(2,6-Dimethoxyphenyl)-1-deoxy-β-D-glucopyranose (β-**18**).* The NMR spectral data match published data.[3a]

*2,3,4,6-Tetra-O-pivaloyl 1-(2,4-Dimethoxyphenyl)-1-deoxy-β-D-glucopyranose (β-**19**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.5 Hz, 1H), 6.41 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 5.43−5.27 (m, 2H), 5.24 (t, *J* = 9.6 Hz, 1H), 4.85 (d, *J* = 9.0 Hz, 1H), 4.12 (dd, *J* = 12.4, 1.6 Hz, 1H), 4.02 (dd, *J* = 12.4, 3.8 Hz, 1H), 3.79 (ddd, *J* = 10.3, 3.7, 1.8 Hz, 1H), 3.71 (6H), 1.15 (s, 9H), 1.09 (s, 9H), 1.05 (s, 9H), 0.79 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.1, 177.3, 176.4, 176.3, 161.1, 158.5, 129.4, 116.8, 104.4, 98.2, 76.5, 74.0, 71.4, 68.0, 61.9, 55.3, 38.83, 38.71, 38.69, 38.5, 27.2, 27.1, 26.7. HRMS (EI) calcd for $[C_{34}H_{52}O_{11} + H]$ 637.3582, found 637.3576.

*2,3,4,6-Tetra-O-pivaloyl 1-(Biphenyl-3-yl)-1-deoxy-β-D-glucopyranose (α-meta-**21**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78−7.45 (m, 5H), 7.45−7.24 (m, 34), 5.70 (t, *J* = 8.7 Hz, 1H), 5.44−5.27 (m, 2H), 5.13 (t, *J* = 9.1 Hz, 1H), 4.09−3.92 (m, 2H), 3.71−3.59 (m, 1H), 1.11 (s, 9H), 1.06 (s, 9H), 1.04 (s, 9H), 0.97 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.0, 177.2, 177.0, 176.6, 141.6, 140.5, 136.0, 128.8, 127.5, 127.3, 127.02, 126.96, 73.6, 71.1, 70.4, 68.4, 62.3, 38.73, 38.67, 27.2, 27.1, 27.0, 26.9. HRMS (EI) calcd for $[C_{38}H_{52}O_9 + H]$ 653.3684, found 653.3681.

*2,3,4,6-Tetra-O-pivaloyl 1-(Biphenyl-3-yl)-1-deoxy-β-D-glucopyranose (β-meta-**21**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67−7.47 (m, 4H), 7.38 (dt, *J* = 19.6, 6.1 Hz, 5H), 5.55−5.29 (m, 3H), 4.50 (d, *J* = 9.5 Hz, 1H), 4.25 (d, *J* = 11.8 Hz, 1H), 4.15 (dd, *J* = 12.4, 3.7 Hz, 1H), 3.89 (d, *J* = 8.4 Hz, 1H), 1.23 (s, 9H), 1.18 (s, 9H), 1.13 (s, 9H), 0.86 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 177.7, 177.0, 176.0, 175.8, 141.1, 140.5, 136.4, 128.61, 128.58, 127.6, 127.2, 126.9, 126.7, 126.5, 80.8, 76.4, 73.5, 71.8, 67.7, 61.6, 38.6, 38.52, 38.5, 38.3, 27.0, 26.91, 26.88, 26.7. HRMS (EI) calcd for $[C_{38}H_{52}O_9 + H]$ 653.3684, found 653.3679.

*2,3,4,6-Tetra-O-pivaloyl 1-(Biphenyl-4-yl)-1-deoxy-β-D-glucopyranose (α-para-**21**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 5.8 Hz, 2H), 7.48 (d, *J* = 5.1 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 5.77−5.59 (m, 1H), 5.34−5.31 (m, 2H), 5.08 (t, *J* = 9.3 Hz, 1H), 4.02−3.89 (m, 2H), 3.55 (ddd, *J* = 9.6, 5.2, 2.4 Hz, 1H), 1.09 (s, 9H), 1.07 (s, 9H), 1.02 (s, 9H), 0.95 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.0, 177.3, 177.0, 176.6, 141.0, 140.2, 134.3, 129.1, 128.8, 127.6, 127.1, 127.0, 73.5, 71.1, 70.4, 70.1, 68.6, 62.3, 38.8, 38.74, 38.68, 27.2, 27.1, 27.0. HRMS (EI) calcd for $[C_{38}H_{52}O_9 + H]$ 653.3684, found 653.3683.

*2,3,4,6-Tetra-O-pivaloyl 1-(Biphenyl-4-yl)-1-deoxy-β-D-glucopyranose (β-para-**21**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52−7.44 (m, 4H), 7.39−7.31 (m, 4H), 7.26 (t, *J* = 7.2 Hz, 1H), 5.39 (t, *J* = 9.3 Hz, 1H), 5.29 (t, *J* = 9.5 Hz, 1H), 5.24 (t, *J* = 9.5 Hz, 1H), 4.39 (d, *J* = 9.7 Hz, 1H), 4.16 (dd, *J* = 12.4, 1.6 Hz, 1H), 4.07 (dd, *J* = 12.5, 3.9 Hz, 1H), 3.81 (ddd, *J* = 9.7, 3.5, 1.6 Hz, 1H), 1.16 (s, 9H), 1.10 (s, 9H), 1.05 (s, 10H), 0.82 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.0, 177.3, 176.3, 176.0, 141.8, 140.5, 135.1, 128.7, 128.2, 127.4, 127.0, 80.7, 76.6, 73.7, 72.0, 67.9, 61.8, 38.8, 38.71, 38.67, 38.5, 27.14, 27.07, 27.0, 26.9. HRMS (EI) calcd for $[C_{38}H_{52}O_9 + H]$ 653.3684, found 653.3681.

*2,3,4,6-Tetra-O-pivaloyl 1-(3-Toluyl)-1-deoxy-β-D-glucopyranose (β-meta-**22**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24−7.15 (m, 1H), 7.12 (d, *J* = 6.5 Hz, 3H), 5.41 (t, *J* = 9.3 Hz, 1H), 5.32 (t, *J* = 9.5 Hz, 1H), 5.23 (t, *J* = 9.5 Hz, 1H), 4.37 (d, *J* = 9.8 Hz, 1H), 4.21 (dd, *J* = 12.4, 1.7 Hz, 1H), 4.11 (dd, *J* = 12.4, 3.9 Hz, 1H), 3.84 (ddd, *J* = 9.7, 3.8, 1.8 Hz, 1H), 2.30 (s, 3H), 1.22 (s, 9H), 1.16 (s, 9H), 1.10 (s, 9H), 0.88 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.1, 177.3, 176.3, 176.0, 137.8, 136.0, 129.7, 128.3, 128.2, 124.9, 80.9, 76.5, 73.7, 72.2, 67.9, 61.8, 38.9, 38.72, 38.68, 38.5, 27.2, 27.08, 27.05, 26.9, 21.3. HRMS (EI) calcd for $[C_{33}H_{50}O_9 + H]$ 591.3528, found 591.3524.

*2,3,4,6-Tetra-O-pivaloyl 1-(4-Tolyl)-1-deoxy-β-D-glucopyranose (β-para-**22**).* The NMR spectral data match published data.[3a]

*2,3,4,6-Tetra-O-pivaloyl 1-(2,4-Dimethylphenyl)-1-deoxy-β-D-glucopyranose (β-**23**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.93 (s, 1H), 5.52−5.37 (m, 2H), 5.31 (t, *J* = 9.5 Hz, 1H), 4.64 (d, *J* = 9.3 Hz, 1H), 4.19 (d, *J* = 12.3 Hz, 1H), 4.07 (dd, *J* = 12.4, 4.1 Hz, 1H), 3.85 (ddd, *J* = 10.0, 3.9, 1.5 Hz, 2H), 2.40 (s, 3H), 2.25 (s, 3H), 1.20 (s, 9H), 1.16 (s, 9H), 1.11 (s, 9H), 0.85 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.0, 177.4, 176.4, 176.2, 138.4, 136.6, 131.4, 130.8, 127.7, 126.8, 77.7, 76.7, 74.0, 71.1, 67.9, 61.9, 38.8, 38.7, 38.4, 27.2, 27.07, 27.06, 26.8, 21.0, 19.4. HRMS (EI) calcd for $[C_{34}H_{52}O_9 + H]$ 605.3684, found 605.3682

*2,3,4,6-Tetra-O-pivaloyl 1-(3,5-Dimethylphenyl)-1-deoxy-β-D-glucopyranose (β-**24**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02−6.71 (m, 3H), 5.40 (t, *J* = 9.2 Hz, 1H), 5.32 (t, *J* = 9.5 Hz, 1H), 5.21 (t, *J* = 9.5 Hz, 1H), 4.34 (d, *J* = 9.8 Hz, 1H), 4.22 (dd, *J* = 12.4, 1.7 Hz, 1H), 4.10 (dd, *J* = 12.4, 3.9 Hz, 1H), 3.83 (ddd, *J* = 9.6, 3.6, 1.7 Hz, 1H), 2.26 (s, 6H), 1.23 (s, 9H), 1.16 (s, 9H), 1.10 (s, 9H), 0.89 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.1, 177.3, 176.3, 176.0, 137.7, 136.0, 130.5, 125.4, 80.9, 76.4, 73.8, 72.3, 67.9, 61.8, 38.9, 38.73, 38.69, 38.5, 27.2, 27.09, 27.06, 26.9, 21.2. HRMS (EI) calcd for $[C_{34}H_{52}O_9 + H]$ 605.3684, found 605.3680.

*2,3,4,6-Tetra-O-pivaloyl 1-(2-Thienyl)-1-deoxy-β-D-glucopyranose (β-**25**).* The NMR spectral data match published data.[3a]

*2,3,4,6-Tetra-O-pivaloyl 1-(2-Thienyl)-1-deoxy-β-D-glucopyranose (β-**26**).* The compound could only be purified as a mixture with its isomer β-**25**. Selected peaks for the product are described. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19−7.13 (m, 2H), 6.98 (dd, *J* = 4.4, 1.9 Hz, 1H), 5.27 (d, *J* = 9.2 Hz, 1H), 5.19 (t, *J* = 9.5 Hz, 1H), 5.17 (t, *J* = 9.5 Hz, 1H), 4.44 (d, *J* = 9.8 Hz, 1H), 4.09 (dd, *J* = 12.4, 1.8 Hz, 1H), 3.99 (dd, *J* = 12.4, 4.2 Hz, 1H), 3.73 (ddd, *J* = 10.0, 4.1, 1.9 Hz, 1H), 1.10 (s, 9H), 1.05 (s, 9H), 1.00 (s, 9H), 0.80 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.1, 177.3, 176.3, 176.2, 137.2, 126.4, 126.3, 124.6, 76.5, 76.4, 73.6, 71.7, 67.9, 61.8, 38.9, 38.8, 38.7,

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX

38.6, 27.2, 27.10, 27.07, 26.9. HRMS (EI) calcd for [$C_{30}H_{46}O_9S$ + H] 583.2935, found 583.2934.

*Coupling of Bromobenzhydryl Bromide (**30**) with Dianisylzinc Reagents (Procedure B).* A dry and argon-flushed 50 mL flask was charged with the corresponding iodoanisole (3.00 g, 12.8 mmol), tetradecane (0.5 g, 2.5 mmol) as internal standard, and anhydrous toluene (39 mL). *n*BuLi (13.4 mmol, 1.05 equiv) was slowly added dropwise at −10 °C, and then the reaction was allowed to warm to 0 °C. The reaction was monitored at that temperature until samples quenched with MeOH showed full iodine−lithium exchange by HPLC analysis. Subsequently, a solution of $ZnBr_2$·LiBr in nBu_2O (7.05 mmol, 0.55 equiv) was added dropwise. Benzhydryl bromide **27** (2.68 g, 10.9 mmol, 0.85 equiv) was added in one portion, and the reaction mixture was stirred at 0 °C until full conversion. Upon full conversion of one of the reactants, the reaction was quenched with sat. aqueous NH_4Cl, and the organic layer was analyzed by GC.

*1-Benzhydryl-2-methoxybenzene (ortho-**28**).* The NMR spectral data match published data.[21]

*1-Benzhydryl-3-methoxybenzene (meta-**28**).* The NMR spectral data match published data.[22]

*1-Benzhydryl-4-methoxybenzene (para-**28**).* The NMR spectral data match published data.[21]

*Synthesis of 4-Deutero-3-iodoanisole (**51**) (Procedure C).* A dry and nitrogen-flushed 250 mL Schlenk-tube was charged with 3-bromoanisole (30.0 g, 160 mmol), and anhydrous THF (110 mL) was added. *n*BuLi (168 mmol, 1.05 equiv; 2.5 M solution in heptane) was added dropwise at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min (HPLC analysis showed full conversion). Then, chlorotrimethylsilane (19.2 g, 1.10 equiv) was slowly added, and the mixture was allowed to slowly reach room temperature. Upon full conversion (∼15 min), water was added, and the volatiles were partially removed under reduced pressure. The mixture was diluted with MTBE and washed with water. The organic layer was treated with activated charcoal, filtered, and concentrated.

Without further purification, the crude product was diluted with AcOH (480 mL), and water (7 mL) was added. The mixture was cooled to 10 °C, and bromine (1.0 equiv) was added dropwise (reaction is almost immediate) until full conversion. An aqueous solution of $NaHSO_3$ was added to quench residual bromine, and then the volatiles were removed under reduced pressure. The crude product was diluted in MTBE and washed twice with NaOH (2 M) and brine. The organic layer was treated with Na_2SO_4 and activated charcoal and then filtered. The solvent was removed under reduced pressure, and the crude product was dried twice by azeotropic distillation of toluene, also under reduced pressure.

Without further purification, the crude product was dissolved in anhydrous THF (110 mL). *n*BuLi (168 mmol, 1.05 equiv; 2.5 M solution in heptane) was added dropwise at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min (HPLC analysis showed full conversion). The aryllithium intermediate was then quenched by addition of CH_3OD (3.0 equiv). Volatiles were partially removed under reduced pressure, and the mixture was diluted with MTBE and washed with water and brine. The organic layer was treated with activated charcoal, filtered, and concentrated. The crude product was dissolved in anhydrous CH_2Cl_2 (400 mL), and a solution of ICl (1.0 equiv) in CH_2Cl_2 (30 mL) was slowly added over 5 h at −40 °C. After warming to room temperature, the reaction was quenched with aqueous $NaHSO_3$, and CH_2Cl_2 was partially removed under reduced pressure. The crude was diluted with MTBE and washed with water and brine. The organic layer was dried with Na_2SO_4, treated with activated charcoal, and concentrated. Column chromatography (SiO_2; hexane) furnished 27.0 g of product **51** (72% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, J = 2.5 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 8.4, 2.5 Hz, 1H), 3.68 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 160.0, 130.6, 129.7 (C−D), 129.41, 129.07, 122.88, 113.68, 94.20, 55.31. IR ATR ν (cm^{-1}): 3002, 2935, 2834, 1580, 1560, 1460, 1434, 1403, 1336, 1293, 1271, 1230, 1222, 1181, 1150, 1126, 1054, 1030, 979, 873, 861, 842, 817, 714, 682, 667. HRMS (EI) calcd for [C_7H_6DIO] 234.9604, found 234.9599.

*Synthesis of 2-Deutero-1-iodo-3-(3-phenylpropoxy)benzene (**52**).* In a flask, 3-bromopropylbenzene (23.0 g, 116 mmol), 3-bromophenol (21.0 g, 1.05 equiv), potassium carbonate (20.8 g, 1.3 equiv), and DMF (70 mL) were mixed and stirred at 80 °C until full conversion. Then, the reaction was diluted with water and extracted thrice with heptane. The combined organics were washed twice with NaOH (2 M) and brine, dried over Na_2SO_4, and filtered, and finally, the volatiles were removed under reduced pressure. The crude showed a high purity and was brought directly into the next step. At this point, procedure C described above was followed to yield the final product as a colorless oil in 50% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26−7.00 (m, 6H), 6.84 (d, J = 8.3 Hz, 1H), 6.72 (dd, J = 8.3, 2.2 Hz, 1H), 3.77 (t, J = 6.2 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 1.95 (p, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 159.6, 141.4, 130.7, 129.5 (C−D), 128.6, 128.5, 126.1, 123. 7, 114.3, 94.4, 67.1, 32.1, 30.8. HRMS (EI) calcd for [$C_{15}H_{14}DIO$] 339.0230, found 339.0191.

*Synthesis of 1-(Trideuteromethoxy)-3-iodoanisole (**53**).* Iodomethane-*d3* (5.0 g, 34.5 mmol) was added to a mixture of 3-iodophenol (8.35 g, 1.1 equiv) and potassium carbonate (5.24 g, 1.1 equiv) in DMF (35 mL). The mixture was stirred at room temperature until full conversion. Then, the reaction was diluted with water and extracted thrice with heptane. The organic layer was washed twice with NaOH (2 M) and brine and dried over Na_2SO_4, and finally, the volatiles were removed under reduced pressure. The resulting oil (8.0 g, 98% yield) showed sufficient purity and was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, J = 7.7 Hz, 1H), 7.26 (t, J = 2.2 Hz, 1H), 7.00 (t, J = 8.0 Hz, 1H), 6.87 (dd, J = 9.5, 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 160.1, 130.7, 129.7, 122.9, 113.7, 94.3. HRMS (EI) calcd for [$C_7H_4D_3IO$] 236.9730, found [M]$^+$ 236.9658.

Experiments with Labeled Materials (Scheme 3). 4-Deutero-3-iodoanisole was employed as a starting material using procedure A. Quantitative results are shown in Table 6. Analyses were performed by GCMS. The mass spectra of each chromatographic peak corresponding to the products were analyzed. The ratios of 1,2-deuteron or 1,2-proton shifts were calculated from the relative isotopic abundance of selected fragmentations in the mass spectra. The peaks at m/z = 203, 287, and 300 (M, not deuterated) are representative of a molecular fragment containing the aryl moiety and can be used for that purpose. The abundance of molecules with M + 1 mass due to natural ^{13}C content was taken into account, and the pertinent subtraction was performed in our calculations.

For the *para* isomer, the proportion of 1,2-shift was calculated from samples quenched with NH_4Cl. In that case, the M +1 peaks represent the abundance of product with the 1,2-deuterium shift.

For the *ortho* isomer, the 1,2-shift was calculated from samples quenched with MeOD. In that case, the M + 1 peak represents the abundance of product with the 1,2-proton shift. The M + 2 peak represents the uptake of a second deuterium from MeOD, which corresponds to the pathway with C−Zn bond conservation. Illustrative MS spectra from GCMS separation for both types of quenching, in addition to those with I_2 quenching, are shown in the Supporting Information.

*2,3,4,6-Tetra-O-pivaloyl 1-(2-Deutero-5-methoxyphenyl)-1-deoxy-β-D-glucopyranose (β-meta-**32**).* Although NH_4Cl quenching was used for the mechanistic investigations, for product characterization purposes, the reaction was quenched with MeOD to exclusively afford *β-meta*-**32** (vs *β-meta*-**6**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, J = 8.2 Hz, 1H), 6.81 (d, J = 2.4 Hz, 1H), 6.77 (dd, J = 8.2, 2.5 Hz, 1H), 5.36 (t, J = 9.3 Hz, 1H), 5.26 (t, J = 9.6 Hz, 1H), 5.18 (t, J = 9.5 Hz, 1H), 4.33 (d, J = 9.8 Hz, 1H), 4.15 (dd, J = 12.4, 1.7 Hz, 1H), 4.05 (dd, J = 12.4, 4.0 Hz, 1H), 3.79 (ddd, J = 9.7, 3.8, 1.7 Hz, 1H), 3.72 (s, 3H), 1.15 (s, 9H), 1.10 (s, 9H), 1.04 (s, 9H), 0.83 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 178.0, 177.3, 176.3, 176.0, 159.4, 137.4, 129.2, 119.9, 114.7, 112.8, 80.7, 76.5, 73.7, 72.0, 67.9, 61.8, 55.1, 38.8, 38.7, 38.67, 38.5, 27.14, 27.06, 27.0, 26.9. IR ATR ν (cm^{-1}): 2976, 2874, 1734, 1610, 1582, 1480, 1462, 1438, 1397, 1367, 1275, 1259, 1174, 1153, 1134, 1094, 1077, 1050, 1038,

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX

998, 983, 939, 918, 906, 890, 876, 837, 774, 761. HRMS (EI) calcd for [$C_{33}H_{50}DO_{10}$] 608.3540, found 608.3536.

*2,3,4,6-Tetra-O-pivaloyl 1-(2-Deutero-4-methoxyphenyl)-1-deoxy-β-D-glucopyranose (β-para-**32**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, J = 9.2 Hz, 1H), 6.78 (dt, J = 4.1, 2.1 Hz, 3H), 5.35 (t, J = 9.3 Hz, 1H), 5.25 (t, J = 9.3 Hz, 1H), 5.19 (t, J = 9.3 Hz, 1H), 4.30 (d, J = 9.8 Hz, 1H), 4.13 (dd, J = 12.4, 1.7 Hz, 1H), 4.04 (dd, J = 12.4, 4.0 Hz, 1H), 3.78 (ddd, J = 9.7, 3.7, 1.8 Hz, 1H), 3.71 (s, 3H), 1.15 (s, 10H), 1.10 (s, 9H), 1.04 (s, 9H), 0.82 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.1, 177.3, 176.3, 176.1, 160.0, 129.1, 128.2, 113.7, 113.6, 80.5, 76.4, 73.7, 72.0, 67.9, 61.9, 55.2, 38.8, 38.73, 38.69, 38.5, 27.2, 27.08, 27.05, 26.9. IR ATR ν (cm^{-1}): 2973, 2873, 1735, 1610, 1582, 1480, 1462, 1439, 1398, 1367, 1318, 1275, 1259, 1250, 1172, 1155, 1133, 1095, 1078, 1066, 1038, 999, 983, 939, 918, 892, 876, 836, 830, 823, 804, 773, 761, 656. HRMS (EI) calcd for [$C_{33}H_{50}DO_{10}$] 608.3540, found 608.3539.

*2,3,4,6-Tetra-O-pivaloyl 1-(2-Iodo-4-methoxyphenyl)-1-deoxy-β-D-glucopyranose (β-para-**33**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, J = 2.6 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 6.90 (dd, J = 8.8, 2.6 Hz, 1H), 5.47 (t, J = 9.2 Hz, 1H), 5.39 (t, J = 9.4 Hz, 1H), 5.28 (t, J = 9.6 Hz, 1H), 4.81 (d, J = 9.6 Hz, 1H), 4.20 (dd, J = 12.4, 1.8 Hz, 1H), 4.08 (dd, J = 12.4, 4.6 Hz, 1H), 3.92 (ddd, J = 9.3, 4.1, 1.3 Hz, 1H), 3.76 (s, 3H), 1.21 (s, 9H), 1.17 (s, 9H), 1.12 (s, 9H), 0.90 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.1, 177.3, 176.5, 176.4, 160.1, 130.3, 128.9, 124.6, 114.5, 83.2, 76.8, 73.8, 71.6, 68.1, 62.0, 55.5, 38.9, 38.78, 38.75, 38.6, 27.21, 27.15, 27.1, 26.9. HRMS (EI) calcd for [$C_{33}H_{50}IO_{10}$] 733.2443, found 733.2438.

Crossover Experiments (Scheme 4). A 1:1 mixture of 1-(trideuteromethoxy)-3-iodoanisole and 4-deutero-3-iodoanisole was employed as starting material. Procedure A was used with the following modifications: (a) First, only 0.07 equiv of bromosugar **5** was added. After a while, a sample was taken and quenched with I_2, and the ratio of *para*-**32** to *para*-**35** was measured. This ratio corresponds, approximately, to the deuterium kinetic isotope effect in the 1,2-shift mechanism. (b) Then, an additional 0.93 equiv of bromosugar **5** was added, and the reaction was quenched upon full conversion.

Mass spectra (GCMS) corresponding to the mixture of the different *meta* (*ipso*) and *para* (*cine*) products are shown in the Supporting Information. Upon quenching with I_2, no crossover products were found.

Dilution Experiments (Table 6). 2-Deutero-1-iodo-3-(3-phenylpropoxy)benzene (**52**) was employed as a starting material using Procedure A just for the preparation of the organozinc reagent. Then, three different vials were charged, each with approximately 6 mL of the organozinc solution, 1 equiv of bromosugar **5**, and a certain amount of toluene (a = 0 mL, b = 12 mL, c = 48 mL). The reactions were then stirred at 80 °C until completion and quenched with NH_4Cl, and the isotopic abundance of the *meta*-products was analyzed by GCMS.

A second round of reactions was set in the same way but adding nBu_2O to the vials in such a way that the concentration would be the same in the three vials. An MS spectrum showing a mixture of **38** and **39** is included in the Supporting Information.

*2,3,4,6-Tetra-O-pivaloyl 1-(4-(3-Phenylpropoxy)phenyl)-1-deoxy-β-D-glucopyranose (β-para-**38**).* The NMR corresponds to a sample synthesized from nondeuterated organozinc reagent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27−7.07 (m, 7H), 6.76 (d, J = 8.7 Hz, 2H), 5.35 (t, J = 9.3 Hz, 1H), 5.25 (t, J = 9.4 Hz, 1H), 5.17 (t, J = 9.4 Hz, 1H), 4.29 (d, J = 9.8 Hz, 1H), 4.13 (dd, J = 12.4, 1.8 Hz, 1H), 4.04 (dd, J = 12.4, 3.9 Hz, 1H), 3.87 (dd, J = 6.1, 3.2 Hz, 1H), 3.83 (dd, J = 6.0, 3.3 Hz, 1H), 3.78 (ddd, J = 9.7, 3.8, 1.9 Hz, 1H), 2.72 (t, J = 7.5 Hz, 2H), 2.07−1.94 (m, 2H), 1.15 (s, 9H), 1.10 (s, 9H), 1.04 (s, 9H), 0.82 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 178.1, 177.3, 176.4, 176.1, 159.5, 141.4, 129.1, 128.5, 128.4, 128.2, 125.9, 114.3, 80.6, 76.4, 73.7, 72.0, 67.9, 66.8, 61.9, 38.9, 38.74, 38.7, 38.5, 32.0, 30.7, 27.2, 27.1, 27.06, 26.9. HRMS (EI) calcd for [$C_{41}H_{59}O_{10}$] 711.4103, found 711.4097.

*2,3,4,6-Tetra-O-pivaloyl 1-(2-Deutero-4-(3-phenylpropoxy)-phenyl)-1-deoxy-β-D-glucopyranose (β-para-**39**).* HRMS (EI) calcd for [$C_{41}H_{57}DO_{10}$ + NH_4] 729.4436, found 729.4639.

*4,4′-((4-Methoxyphenyl)methylene)bis(methylbenzene) (**42**).* A dry and argon-flushed 10 mL Schlenk tube was charged with 3-iodoanisole (1 mmol) and anhydrous toluene (3.5 mL). *n*BuLi (1.05 mmol; 2.4 M solution in heptane) was added dropwise at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. Subsequently, $ZnBr_2$·LiBr (0.55 mmol, 25% weight in nBu_2O) was added dropwise, and the reaction mixture was allowed to warm to room temperature. Bis(*p*-tolyl)bromomethane (**40**) (1 mmol, 1 M in toluene) was added, and the reaction mixture was stirred at room temperature for 15 min. The mixture was quenched with brine and extracted with EtOAc. Removal of the solvent and purification via flash chromatography (SiO_2; hexane/EtOAc 10:1) furnished 244 mg of product **42** (0.81 mmol, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96−7.15 (m, 10 H), 6.79−6.87 (m, 2 H), 5.44 (s, 1 H), 3.79 (s, 3 H), 2.33 (s, 6 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 157.9, 141.5, 136.5, 135.6, 130.3, 129.2, 128.9, 113.3, 55.3, 55.2, 21.0. IR ATR ν (cm^{-1}): 3019, 3000, 2921, 2861, 2834, 1607, 1578, 1510, 1496, 1463, 1454, 1442, 1413, 1327, 1309, 1284, 1247, 1214, 1179, 1160, 1110, 1089, 1039, 1021, 995, 953, 944, 911, 869, 848, 807, 792, 767, 716, 701, 660. HRMS (EI) calcd for [$C_{22}H_{22}O$] 302.1671, found 302.1659.

*Ethyl 2′-(Di-p-tolylmethyl)-5′-methoxy-[1,1′-biphenyl]-4-carboxylate (**45**).* A dry and argon-flushed 10 mL Schlenk tube was charged with 3-iodoanisole (1 mmol) and anhydrous toluene (3.5 mL). *n*BuLi (1.05 mmol; 2.4 M solution in heptane) was added dropwise at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. Subsequently, $ZnBr_2$·LiBr (0.55 mmol, 25% weight in nBu_2O) was added dropwise, and the reaction mixture was allowed to warm to room temperature. At −20 °C, TMPZnCl·LiCl (1.4 equiv; 1.2 M in THF) was added, and then bis(*p*-tolyl)bromomethane (**40**) (1 mmol, 1 M in toluene) was added. The reaction mixture was allowed to warm to room temperature and then stirred for 2 h. The mixture was cooled to 0 °C, and I_2 (2 mmol; 2 M in THF) was added dropwise. The mixture was quenched with a sat. aqueous $Na_2S_2O_3$ solution and extracted with EtOAc. Removal of the solvent and purification via flash chromatography (SiO_2; hexane/Et_2O 30:1) furnished 209.9 mg of intermediate **43** (0.49 mmol, 49% yield), which was dissolved in THF (0.2 mL). $Pd(OAc)_2$ (2 mol %) and SPhos (4 mol %) were added to the mixture, and 4-(ethoxycarbonyl)phenylzinc chloride (**44**, 0.75 mmol, 0.48 M in THF) was added dropwise.[23] The reaction mixture was stirred at 50 °C for 1 h. The reaction mixture was quenched with a sat. aqueous NH_4Cl solution and extracted with EtOAc. Removal of the solvent and purification via flash chromatography (SiO_2; hexane/Et_2O 10:1) furnished 180 mg of product **45** (40% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J = 7.05 Hz, 3 H), 2.31 (s, 6 H), 3.80 (s, 3 H), 4.40 (q, J = 7.00 Hz, 2 H), 5.35 (s, 1 H), 6.77 (d, J = 2.76 Hz, 1 H), 6.80−6.91 (m, 5 H), 6.98−7.09 (m, 5 H), 7.21 (m, J = 8.02 Hz, 2 H), 8.00 (m, J = 8.29 Hz, 2 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 14.4, 21.0, 51.6, 55.3, 61.0, 113.5, 114.9, 128.9, 129.15, 129.23, 131.4, 133.9, 135.5, 141.6, 142.3, 146.3, 157.5, 166.5. IR ATR ν (cm^{-1}): 2979, 2922, 1714, 1604, 1574, 1566, 1510, 1487, 1464, 1444, 1399, 1367, 1308, 1270, 1220, 1210, 1176, 1108, 1098, 1039, 1016, 909, 889, 873, 853, 838, 808, 790, 772, 767, 732, 716, 707, 668, 656. HRMS (EI) calcd for [$C_{31}H_{30}O_3$] 450.2195, found 450.2161.

*(2-(Di-p-tolylmethyl)-5-methoxyphenyl) (Phenyl)methanol (**46**).* A dry and argon-flushed 10 mL Schlenk tube was charged with 3-iodoanisole (1 mmol) and anhydrous toluene (3.5 mL). *n*BuLi (1.05 mmol; 2.4 M solution in heptane) was added dropwise at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. Subsequently, $ZnBr_2$·LiBr (0.55 mmol, 25% weight in nBu_2O) was added dropwise, and the reaction mixture was allowed to warm to room temperature. At −20 °C, TMPZnCl·LiCl (1.4 equiv; 1.2 M in THF) was added, and then bis(*p*-tolyl)bromomethane (**40**) (1 mmol, 1 M in toluene) was added. The reaction mixture was allowed to warm to room temperature and was then stirred for 2 h. The mixture was cooled to 0 °C, and I_2 (2 mmol; 2 M in THF) was added dropwise. The mixture was quenched with a sat. aqueous $Na_2S_2O_3$ solution and extracted with EtOAc. Removal of the solvent and purification via

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX

flash chromatography (SiO_2; *i*-hexane/Et_2O 30:1) furnished 209.9 mg of intermediate **43** (0.49 mmol, 49% yield), which was dissolved in THF (1 mL). *n*BuLi (1 mmol, 2.4 M solution in heptane) was added dropwise at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h. Subsequently, benzaldehyde (1 mmol) was added dropwise, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was quenched with a sat. aqueous NH_4Cl solution and extracted with EtOAc. Removal of the solvent and purification via flash chromatography (SiO_2; hexane/EtOAc 4:1) furnished 122.6 mg of product **46** (0.3 mmol, 30% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30−7.33 (m, 2 H), 7.25−7.29 (m, 3 H), 7.12 (d, J = 2.74 Hz, 1 H), 7.08 (d, J = 7.80 Hz, 2 H), 6.98 (m, J = 8.01 Hz, 2 H), 6.91 (m, J = 8.01 Hz, 2 H), 6.78 (d, J = 8.64 Hz, 1 H), 6.72 (dd, J = 8.64, 2.74 Hz, 1 H), 6.68 (d, J = 8.01 Hz, 2 H), 5.92 (s, 1 H), 5.55 (s, 1 H), 3.77 (s, 3 H), 2.32 (s, 3 H), 2.27 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.2, 143.0, 142.7, 141.1, 140.5, 135.9, 135.6, 133.7, 131.3, 129.22, 129.18, 129.1, 128.9, 128.5, 127.7, 127.1, 112.8, 112.5, 72.6, 55.2, 50.7, 21.0, 20.9. IR ATR ν (cm^{-1}): 3436, 3021, 2922, 2857, 2835, 1736, 1606, 1577, 1510, 1491, 1463, 1453, 1425, 1377, 1308, 1285, 1236, 1185, 1156, 1110, 1088, 1077, 1040, 1032, 1020, 936, 911, 878, 867, 847, 809, 799, 764, 726, 716, 699, 665. HRMS (EI) calcd for [$C_{29}H_{28}O_2$] 408.2089, found 408.2066.

(2-(Di-p-tolylmethyl)-5-methoxyphenyl) (Thiophen-2-yl)-methanone (47). A dry and argon-flushed 10 mL Schlenk tube was charged with 3-iodoanisole (1 mmol) and anhydrous toluene (3.5 mL). *n*BuLi (1.05 mmol; 2.4 M solution in heptane) was added dropwise at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. Subsequently, $ZnBr_2$·LiBr (0.55 mmol, 25% weight in nBu_2O) was added dropwise, and the reaction mixture was allowed to warm to room temperature. At −20 °C, TMPZnCl·LiCl (1.4 equiv; 1.2 M in THF) was added, and then bis(*p*-tolyl)bromomethane (**40**) (1 mmol, 1 M in toluene) was added. The reaction mixture was allowed to warm to room temperature and was then stirred for 2 h. The mixture was cooled to −20 °C, and CuCN·2LiCl (1 mmol; 1 M in THF) was added dropwise. Thiophene-2-carbonyl chloride (2 mmol) was added, and the reaction mixture was stirred for 1 h at room temperature. The mixture was quenched with brine and extracted with EtOAc. Removal of the solvent and purification via flash chromatography (SiO_2; hexane/Et_2O 10:1) furnished 90.7 mg of product **47** (0.22 mmol, 22% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64−7.74 (m, 1 H), 7.60 (dd, J = 4.98, 1.11 Hz, 1 H), 7.36−7.47 (m, 1 H), 7.09−7.21 (m, 2 H), 6.88−7.02 (m, 9 H), 5.74 (s, 1 H), 3.78 (s, 3 H), 2.25 (s, 6 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 190.1, 159.6, 157.1, 144.4, 140.5, 140.1, 139.4, 135.7, 135.5, 134.9, 134.8, 134.6, 134.2, 131.4, 129.4, 128.8, 127.9, 127.7, 121.7, 118.6, 115.3, 113.8, 113.2, 55.5, 55.4, 51.0, 20.9. IR ATR ν (cm^{-1}): 3090, 3001, 2920, 2835, 1728, 1638, 1604, 1573, 1511, 1493, 1462, 1451, 1426, 1410, 1354, 1288, 1227, 1183, 1147, 1111, 1086, 1077, 1036, 1022, 994, 949, 928, 914, 860, 805, 790, 777, 740, 723, 684, 656. HRMS (EI) calcd for [$C_{27}H_{24}O_2S$] 412.1497, found 412.1472.

Ethyl 2-(2-(Di-p-tolylmethyl)-5-methoxybenzyl)acrylate (48). A dry and argon-flushed 10 mL Schlenk tube was charged with 3-iodoanisole (1 mmol) and anhydrous toluene (3.5 mL). *n*BuLi (1.05 mmol; 2.4 M solution in heptane) was added dropwise at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. Subsequently, $ZnBr_2$·LiBr (0.55 mmol, 25% weight in nBu_2O) was added dropwise, and the reaction mixture was allowed to warm to room temperature. At −20 °C, TMPZnCl·LiCl (1.4 equiv; 1.2 M in THF) was added, and then bis(*p*-tolyl)bromomethane (**40**) (1 mmol, 1 M in toluene) was added. The reaction mixture was allowed to warm to room temperature and was then stirred for 2 h. The mixture was cooled to −20 °C, and CuCN·2LiCl (0.1 mmol; 1 M in THF) was added dropwise. Allyl bromide (2 mmol) was added, and the reaction mixture was stirred for 15 min at room temperature. The mixture was quenched with brine and extracted with EtOAc. Removal of the solvent and purification via flash chromatography (SiO_2; hexane/Et_2O 20:1) furnished 240.4 mg of product **48** (0.58 mmol, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06 (d, J = 8.02 Hz, 4 H), 6.91 (d, J = 8.02 Hz, 4 H), 6.78−6.84 (m, 1 H), 6.60−6.74 (m, 2 H), 6.24 (d, J = 1.11 Hz, 1 H), 5.51 (s, 1 H), 5.21−5.36 (m, 1 H), 4.21 (q, J = 7.10 Hz, 2 H), 3.76 (s, 3 H), 3.51 (s, 2 H), 2.31 (s, 6 H), 1.22−1.35 (m, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.0, 158.0, 141.0, 140.1, 138.1, 135.6, 135.2, 131.0, 129.2, 128.9, 125.8, 116.1, 111.4, 60.8, 55.1, 51.3, 35.0, 21.0, 14.2. IR ATR ν (cm^{-1}): 3018, 2981, 2922, 2835, 1714, 1630, 1607, 1578, 1511, 1498, 1464, 1454, 1444, 1428, 1408, 1390, 1368, 1324, 1310, 1285, 1250, 1184, 1159, 1131, 1112, 1093, 1041, 1022, 949, 926, 860, 848, 808, 794, 768, 727, 716, 701, 684. HRMS (EI) calcd for [$C_{28}H_{30}O_3$] 414.2195, found 414.2171.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00074.

Mass spectra from the labeling studies and NMR spectra for all new compounds and intermediates (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sbarroso@its.jnj.com.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Štambaský, J.; Hocek, M.; Kočovský, P. *Chem. Rev.* **2009**, *109*, 6729−6764. (b) Lee, D.Y. W.; He, M. *Curr. Top. Med. Chem.* **2005**, *5*, 1333−1350. (c) Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913−9959. (d) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599. (e) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55−83. (f) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Elsevier, 1995. (g) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press, 1995.

(2) (a) Dapagliflozin: Meng, W.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P. M.; Morrison, E. P.; Biller, S. A.; Zahler, R.; Deshpande, P. P.; Pullockaran, A.; Hagan, D. L.; Morgan, N.; Taylor, J. R.; Obermeier, M. T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. G.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.; Washburn, W. N. *J. Med. Chem.* **2008**, *51*, 1145−1149. (b) Canagliflozin: Nomura, S.; Sakamaki, S.; Hongu, M.; Kawanishi, E.; Koga, Y.; Sakamoto, T.; Yamamoto, Y.; Ueta, K.; Kimata, H.; Nakayama, K.; Tsuda-Tsukimoto, M. *J. Med. Chem.* **2010**, *53*, 6355−6360.

(3) (a) Lemaire, S.; Houpis, I. N.; Xiao, T.; Li, J.; Digard, E.; Gozlan, C.; Liu, R.; Gavryushin, A.; Diène, C.; Wang, Y.; Farina, V.; Knochel, P. *Org. Lett.* **2012**, *14*, 1480−1483. (b) The Ingleson group has independently reported on the scope of direct C(sp2)-C(sp3) coupling of diarylzinc reagents under conditions that are very similar to ours. See: Dunsford, J. J.; Clark, E. R.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 5688−5692.

(4) Suwiński, J.; Świerczek, K. *Tetrahedron* **2001**, *57*, 1639−1662.

(5) (a) Heaney, H. *Chem. Rev.* **1962**, *62*, 81−97. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701−730. (c) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550−3577.

(6) (a) von Richter, V. *Ber. Dtsch. Chem. Ges.* **1871**, *4*, 459−468. (b) Bunnett, J. F. *Q. Rev., Chem. Soc.* **1958**, *12*, 1−16. (c) Epishina, M. A.; Kulikov, A. S.; Ignat'ev, N. V.; Schulteb, M.; Makhova, N. N. *Mendeleev Commun.* **2015**, *25*, 41−43.

(7) (a) Stork, G.; Isaacs, R. C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7399−7400. (b) Busacca, C. A.; Swestock, J.; Johnson, R. E.; Bailey, T. R.; Musza, L.; Rodger, C. A. *J. Org. Chem.* **1994**, *59*, 7553−7556. (c) Farina, V.; Hossain, M. A. *Tetrahedron Lett.* **1996**, *37*, 6997−7000.

(8) Herrlich, M.; Mayr, H. *Org. Lett.* **2001**, *3*, 1633−1635.

(9) (a) Calas, R.; Gerval, J. C. *R. Acad. Sci., Ser. II* **1985**, *301*, 1289−1292. (b) Bennetau, B.; Krempp, M.; Dunoguès, J. *J. Organomet. Chem.* **1987**, *334*, 263−267. (c) Ishibashi, H.; Sakashita, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1953−1957. (d) Herrlich, M.; Hampel, N.; Mayr, H. *Org. Lett.* **2001**, *3*, 1629−1632.

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX

(10) (a) Klemm, L. H.; Mann, R.; Lind, C. D. *J. Org. Chem.* **1958**, *23*, 349−353. (b) Dauben; Collette, J. W. *J. Am. Chem. Soc.* **1959**, *81*, 967−972. (c) Walravens, J.; Martin, R. H. *Bull. Soc. Chim. Belg.* **1960**, *69*, 165−166. (d) Jones, P. R.; Shelnut, J. G. *J. Org. Chem.* **1979**, *44*, 696−699.

(11) In all cases, the quenching of the organometallic species with iodine exclusively gave the starting aryl iodide; we never observed any isomerization of the organometallic compounds.

(12) Diarylzinc *meta*-**4** gives a colloidal solution, whereas *meta*-**4b** gives a very fine precipitate. On the other hand, bromosugar **5** is freely soluble in pure toluene, but its complexation to zinc species causes precipitation. Analysis of the supernatant of the resulting mixtures indeed showed a much lower concentration of organozinc species **4a**/**b**, bromosugar **5,** and products **6** in comparison to the solid phase.

(13) Reaction of **4a** with 1 equiv of **5** generates 1 equiv of **4b** as a byproduct. Furthermore, the reaction of **4b** generates $ZnBr_2$, which together with one equiv of **4a** forms two equiv of **4b** via Schlenk-like equilibrium.

(14) A hypothetical Friedel−Crafts reaction of anisole coming from the quenching of organozinc **4** would generate HBr, which would quench more **4**, generating anisole again.

(15) (a) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497−2500. (b) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794−9824.

(16) We are currently studying the structure of these species in solution by DOSY NMR spectroscopy. Results will be reported separately.

(17) In all cases, we made the organozinc reagents starting with iodoarenes except for the following cases: 1,3-dimethoxybenzene was directly deprotonated with *n*BuLi (Table 3, entry 1); 1-bromo-3,5-dimethoxybenzene was converted overnight with Mg and Et_2O to its Grignard reagent, titrated, and then transmetallated to the organozinc (entry 4); and 3-bromobiphenyl was used for the transmetalation, which was carried out at 60 °C (entry 4).

(18) See scheme above, e.g, for diarylzinc species, n = 0.55 equiv was used, whereas for arylzinc bromides, n = 1.05 equiv was used. More information regarding the different organozinc species generated is found in Table 2.

(19) In the reactions starting with (*meta*-, *ortho*-, or *para*)-iodoanisole, 1.0 equiv of bromosugar **5** was added, whereas for reactions with other substrates, 0.67 equiv of **5** was added (limiting reagent for yield calculations).

(20) Ref 3a discloses the opening of the THF ring to form 4-chlorobutanol by arylzinc chloride upon warming along with decomposition of bromosugar **5**. In addition, ref 3b points to THF as a strong ligand for diarylzinc species, which prevents the formation of $Ar_2Zn(X\text{-alkyl})_n$ species, a presumably key step in the coupling.

(21) Aoyama, T.; Hayakawa, M.; Ogawa, S.; Nakajima, E.; Mitsuyama, E.; Iwabuchi, T.; Takido, T.; Kodomari, M. *Synlett* **2014**, *25*, 2493−2497.

(22) Sun, Y.-Y.; Yi, J.; Lu, X.; Zhang, Z.-Q.; Xiao, B.; Fu, Y. *Chem. Commun.* **2014**, *50*, 11060−11062.

(23) (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340−348. (b) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802−6806. (c) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085.

DOI: 10.1021/acs.joc.6b00074
J. Org. Chem. XXXX, XXX, XXX−XXX