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SHORT COMMUNICATION

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Organocatalysis for the Acid-Free *O*-Arylidenation of Carbohydrates

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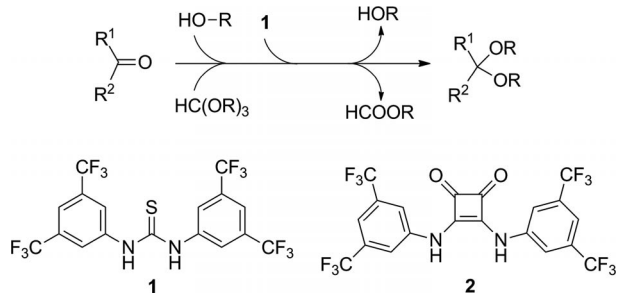
Methyl glycopyranosides of glucose, galactose, and mannose, their 2,3-di-*O*-benzyl-protected derivatives, as well as the unprotected sugars react with *p*-methoxybenzaldehyde dimethyl acetal (**3**) and with benzaldehyde dimethyl acetal (**7**) as reagents in the presence of thiourea **1** or squaramide **2** as the organocatalyst to afford regioselectively 4,6-*O*-arylidenated derivatives **5** and **8**. With an excess amount of **3** or **7**, diarylidenated derivatives are also obtained. In situ formation of acetals of type **3** and **7** from corresponding aldehydes **10** and **13** in the presence of an orthoester and organocatalyst **1** or **2** can be used to generate **5** and **8** directly from the aldehydes. Some substrates also lead to mixed orthoesters with this procedure. The reaction courses are discussed.

Introduction

Arylidene protection plays an important role in carbohydrate chemistry, as it allows the regioselective protection of two hydroxy groups in one reaction; in addition, subsequent regioselective reductive opening of these cyclic acetals permits selective liberation of one of the hydroxy groups.[1,2] For thermodynamic reasons, the formation of 1,3-dioxane rings in the chair conformation with the aryl group in the equatorial position is favored under equilibrating acid-catalysis conditions, and the most important carbohydrates, glucose, mannose, and galactose, react from the pyranose form to generate 4,6-*O*-arylidene-protected derivatives as preferred products.[3–5] This result is independent of the presence or absence of groups at the anomeric oxygen atom or at the oxygen atoms at the C-2 and/or C-3 position(s). Generally, Lewis or Brønsted acids are employed as catalysts for this reaction with arenecarbaldehydes (mainly benzaldehyde and *p*-methoxybenzaldehyde); in addition, the removal of water either by a condensing agent or eventually by azeotropic distillation is required.[6] Alternatively, arenecarbaldehyde acetals in the presence of Lewis or Brønsted acid catalysts can be used,[7] as the formation of cyclic six-membered acetals under release of simple alcohols is thermodynamically also favored.

As these arylidenation reactions are generally catalyzed by quite strong acids [e.g., *p*-toluenesulfonic acid (*p*TsOH), etc.], the search for mild methods is important for compatibility with acid-sensitive substrates. Recently, the organocatalytic, "acid-free" acetalization of aldehydes and ketones was reported by the Schreiner group (Scheme 1).[8] They found that in the presence of an orthoester as a condensing agent in alcohol as solvents thiourea **1**[9] delivered excellent yields of the corresponding acetal. Surprisingly, this method was less efficient or even not successful for electron-rich arenecarbaldehydes.



Scheme 1. Organocatalytic acetalization by the Schreiner group (ref.[8]).

Important steps in these reactions are the activation of the carbonyl group by catalyst **1**, which leads to adduct **A** [Scheme 2, Equation (1)], and the heterolysis of orthoester by **1**, which leads to ion-pair **B** [Scheme 2, Equation (2)].[8] Hence, the question is whether the heterolysis by **1** also takes place in arenecarbaldehyde acetals, which would thus lead to reactive ion-pair intermediates **C** [Scheme 2, Equation (3)] that initiate the formation of cyclic arylidene acetals.

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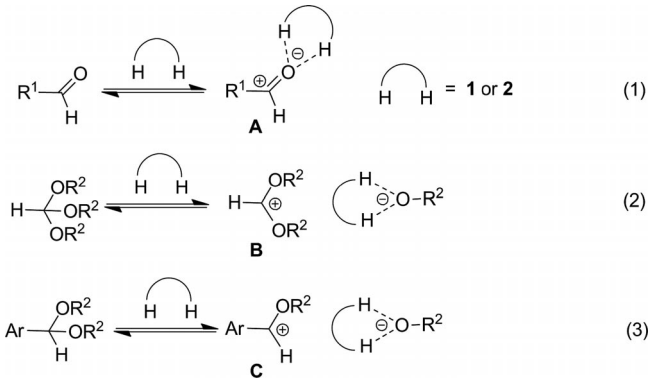
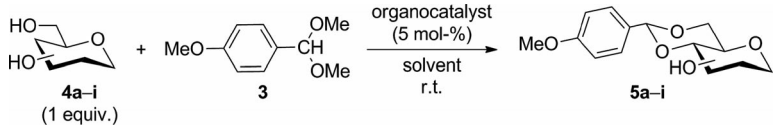


Scheme 2. Activation of carbonyl compounds, orthoesters, or arenecarbaldehyde acetals by organocatalyst **1** or **2**.

Results and Discussion

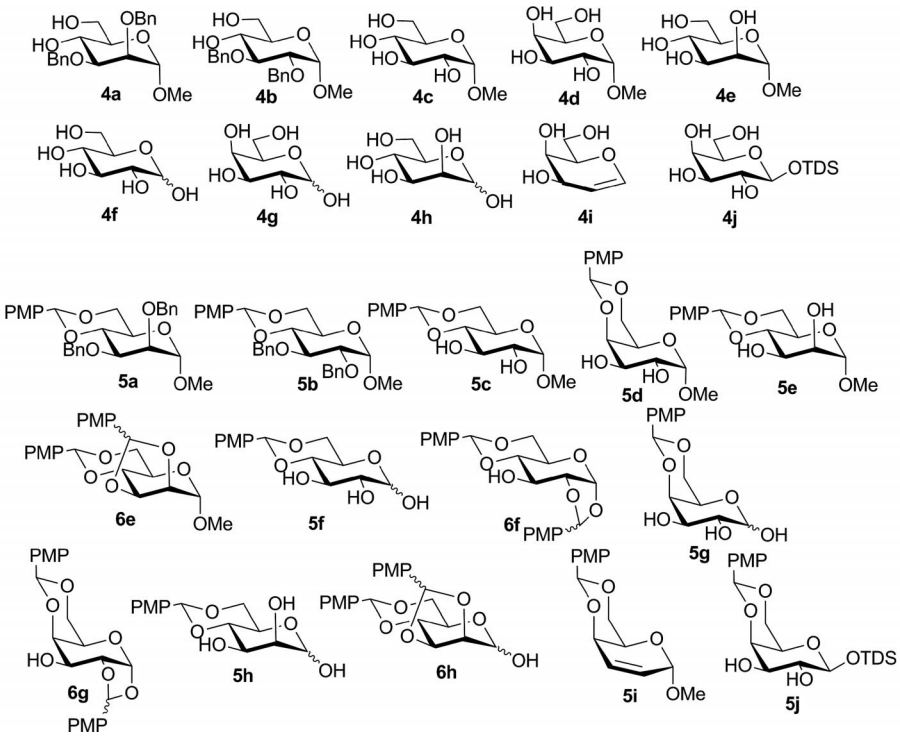
As the cleavage of an alkoxide group from the orthoester is a decisive step in the acetalization reaction [Scheme 2, Equation (2)], we selected *p*-methoxybenzaldehyde dimethyl acetal (**3**) for our studies, though **3** is not accessible by the Schreiner method. However, the electron-donating effect of the *p*-methoxyphenyl group should strongly support the formation of ion-pair intermediate **C**. In addition, owing to acid-catalyzed cleavage, oxidative cleavage, hydrogenolysis, and regioselective reductive ring opening, the *p*-methoxybenzylidene protection has become popular in carbohydrate chemistry.[1,2] Hence, the reaction of **3** (1.5 equiv.) with 4,6-*O*-unprotected mannopyranoside **4a**[10] in the presence of organocatalyst **1** (5 mol-%) in dichloromethane as the solvent was studied (Table 1). After 28 h at room temperature, almost complete formation of desired 4,6-*O*-*p*-methoxybenzylidene-protected mannopyranoside **5a**[11] was observed (Table 1, Entry 1). The same result was obtained with squaramide **2**[12] as the organocatalyst (Table 1, Entry 2), even with a shorter reaction time. Hence, for the following investigations, catalyst **2** was mainly employed. THF as the solvent inhibited the reaction (Table 1, Entry 3), presumably as a result of the interaction of **2** with the ring oxygen atom of THF. Acetonitrile as the solvent led to **5a** (PMP = *p*-methoxyphenyl; Table 1, Entry 4), although a longer reaction time was required. The same result was obtained for corresponding methyl 2,3-*O*-benzylglucopyranoside **4b**[13] (Table 1, Entries 5 and 6): 4,6-*O*-arylidenated product **5b**[14] was formed more quickly in dichloromethane as the solvent than in acetonitrile as the solvent. However, owing to better solubility of most substrates in acetonitrile,[6a] in particular less-protected carbohydrates, this solvent was used for most of the following reactions. Thus, for 2,3,4,6-*O*-unprotected methyl glucopyranoside **4c**[13] and **3** as the reagent under the same reaction conditions with both catalysts (i.e., **1** and **2**), the desired 4,6-*O*-protected product **5c**[15,6a] was selectively obtained in a rather short reaction time (Table 1, Entries 7 and 8). Very good results were also obtained for methyl galactoside **4d**[13] and methyl mannoside **4e**[13] (generating **5d**[14,6a] and **5e**;[11] Table 1, Entries 9 and 10). As expected, treatment of, for example, **4e** with an excess amount of **3** (3 equiv.) led to 2,3:4,6-bis(*O*-*p*-methoxybenzylidene)-protected **6e**[11] as a ca. 1:1 mixture of two diastereomers (Table 1, Entry 11). These results en-

Table 1. Introduction of the *p*-methoxybenzylidene group.



Entry	Substrate	Catalyst	Equiv. of **3**	Solvent	*t* [h]	Product	Yield[a] [%]
1	**4a**	**1**	1.5	CH_2Cl_2	28	**5a**	81
2	**4a**	**2**	1.5	CH_2Cl_2	20	**5a**	83
3	**4a**	**2**	1.5	THF	48	–[b]	–
4	**4a**	**2**	1.5	CH_3CN	36	**5a**	80
5	**4b**	**2**	1.5	CH_2Cl_2	0.42	**5b**	89
6	**4b**	**2**	1.5	CH_3CN	10	**5b**	81
7	**4c**	**1**	1.5	CH_3CN	1	**5c**	67
8	**4c**	**2**	1.5	CH_3CN	0.17	**5c**	90
9	**4d**	**2**	1.5	CH_3CN	14	**5d**	82
10	**4e**	**2**	1.0	CH_3CN	1	**5e**	88
11	**4e**	**2**	3.0	CH_3CN	36	**6e**	85
12	**4f**	**2**	1.0	CH_3CN	16	**5f**	83
13	**4f**	**2**	3.0	CH_3CN	48	**6f**	81
14	**4g**	**2**	1.0	CH_3CN	5	**5g**, **6g**	62, 11[c]
15	**4h**	**2**	1.0	CH_3CN	24	**5h**, **6h**	74, 9
16	**4i**	**2**	1.5	CH_3CN	48	**5i**	76
17	**4j**	**2**	1.5	CH_3CN	168	**5j**	76[d]

[a] Yield of isolated product. [b] No reaction. With less basic Et_2O as the solvent, the reaction was slow: after 7 d, **5a** (61%) was obtained. [c] The reaction was performed at reflux. At r.t., the reaction was very slow. [d] The reaction was performed at 40 °C; after 48 h, **5j** (47%) was formed. At r.t., the reaction was very slow.

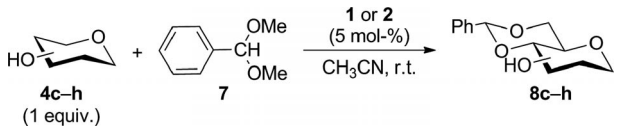


couraged us to study the important regioselective monoarylidenation of totally unprotected carbohydrates. Thus, under the same reaction conditions, D-glucose (**4f**)[13] delivered 4,6-*O*-*p*-methoxybenzylidene-protected **5f**[16] in very good yield (Table 1, Entry 12), and excess **3** (3 equiv.) furnished 1,2:4,6-bis(*O*-*p*-methoxybenzylidene)-protected **6f** again as a 2:1 mixture of diastereomers (Table 1, Entry 13). Reaction of galactose (**4g**)[13] with **3** in the presence of **2** required heating to reflux and led, in addition to expected product **5g** (62%), to a minor amount of diarylidenated product **6g** (11%; Table 1, Entry 14). Reaction of mannose (**4h**)[13] at room temperature led to expected product **5h** (74%) and a minor amount of diarylidenated product **6h** (9%; Table 1, Entry 15). Owing to the very mild reaction conditions, it was expected that acid-sensitive glycals, for instance galactal (**4i**),[13] would not be degraded but rather arylidenated under these conditions, and indeed, after a rather long reaction time under concomitant Ferrier rearrangement at room temperature desired 4,6-*O*-arylidenated product **5i**[17] was obtained in good yield (Table 1, Entry 16). According to the recent work of Galan et al.,[18] formation of methyl 2-deoxy-4,6-*O*-(4-methoxybenzylidene)-α-D-galactopyranoside was expected; however, this compound was not found. The reaction with acetal **3** and catalyst **2** was also extended to substrates having acid-sensitive silyl protecting groups, as shown for thexyldimethylsilyl (TDS) galactopyranoside (**4j**), which underwent a slow reaction at 40 °C to afford 4,6-*O*-protected **5j** (Table 1, Entry 17). The large difference in the reaction rates found for differently protected substrates is presumably the result of different solubilities and/or eventually aggregation phenomena.

As *O*-benzylidene-protected carbohydrates are commonly employed as building blocks for various purposes, benzaldehyde dimethyl acetal (**7**) was also studied in our reaction protocol. As the support for the generation of ion-pair intermediate **C** [Scheme 2, Equation (3)] was diminished, it was no surprise that the room-temperature reaction of glucopyranoside **4c** with thiourea **1** as the organocatalyst in acetonitrile gave almost no reaction (Table 2, Entry 1). However, organocatalyst **2** led cleanly to desired 4,6-*O*-benzylidenated product **8c**[19] (Table 2, Entry 2). The same results were obtained for galactoside **4d** and mannoside **4e**, which upon reaction with **7** furnished 4,6-*O*-benzylidenated product **8d**[20] and **8e**,[21] respectively, in very good yield (Table 2, Entries 3 and 4). Upon the addition of **7** (3 equiv.) to the reaction mixture containing **4e** at 40 °C, dibenzylidenated mannoside **9e**[22] was furnished in very good yield (Table 2, Entry 5). At a slightly elevated temperature, even the reaction of unprotected glucose (**4f**) with reagent **7** led to 4,6-*O*-benzylidenated derivative **8f**[23] in acceptable yield (Table 2, Entry 6). However, under reflux conditions, unprotected galactose (**4g**) did not afford the desired product (Table 2, Entry 7). Mannose (**4h**) gave 4,6-*O*-benzylidenated derivative **8h**[22] only in modest yield (Table 2, Entry 8).

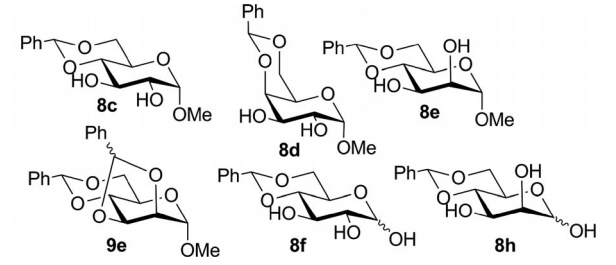
The Schreiner group found that under their experimental conditions (Scheme 1) arenecarbaldehyde acetals with electron-donating substituents were less readily accessible.[8] This result was also confirmed in our studies; as shown in Scheme 3, from *p*-methoxybenzaldehyde (**10**) only a trace amount of diethyl acetal **11** was formed with **2** as the catalyst. This is presumably the result of the high preference of **2** or **1** to form a complex with the basic carbonyl oxygen

Table 2. Introduction of the benzylidene group.

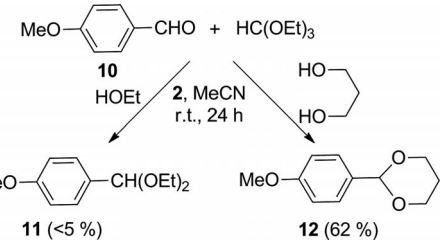


Entry	Substrate	Catalyst	Equiv. of 7	*t* [h]	Product	Yield[a] [%]
1	**4c**	**1**	1.5	48	–[b]	–
2	**4c**	**2**	1.5	1	**8c**	91
3	**4d**	**2**	1.5	48	**8d**	78[c]
4	**4e**	**2**	1.0	2.5	**8e**	86
5	**4e**	**2**	3.0	24	**9e**	81[c]
6	**4f**	**2**	1.0	48	**8f**	67[c]
7	**4g**	**2**	1.0	48	–[b,d]	–
8	**4h**	**2**	1.0	48	**8h**	39[c]

[a] Yield of isolated product. [b] No reaction. [c] The reaction was performed at 40 °C. At r.t., the reaction was very slow. [d] The reaction was performed at reflux.

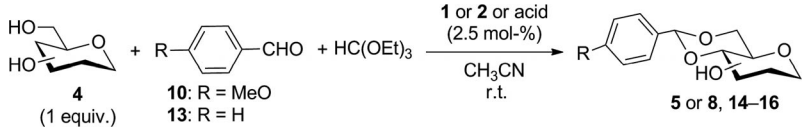


atom of **10** [→ **A**, Scheme 2, Equation (1)] over an ion pair with the orthoester [→ **B**, Scheme 2, Equation (2)], and this pushes the reaction to acetal formation. This assumption was confirmed by the reaction with 1,3-propanediol, which led to thermodynamically favored six-membered cyclic acetal **12** in good yield. Hence, it seemed to be possible to combine arenecarbaldehyde acetal formation – even for arenecarbaldehydes having electron-donating substituents – with the thermodynamically favored arylidenation of carbohydrates. Thus, from arenecarbaldehydes, orthoesters, and carbohydrates as substrates in the presence of **1** or **2** as the organocatalyst, arylidenated products should become directly accessible. The results in Table 3 confirm this hypothesis. From aldehyde **10**, glucoside **4c**, ethyl orthoester, and **1** or **2** as the catalyst, desired product **5c** was readily obtained in very good yields (Table 3, Entries 1 and 2). Clearly, the presence of the catalyst and the orthoester as the condensing agent were required for product formation (Table 3, Entries 3 and 4). Catalysis of this reaction with a strong acid such as *p*TsOH was also possible; however, an increase only in the rate but not in the yield was observed (Table 3, Entry 5). Reaction of glycosides with axial hydroxy groups, as in galactoside **4d** and mannoside **4e**, led not only to 4,6-*O*-arylidenated products **5d** and **5e**, respectively, but also to orthoester derivatives **14d** and **14e**. Their structures were confirmed by NMR spectroscopy and MS data. Clearly, with **4d** as the substrate, ion-pair intermediate **B** [Scheme 2, Equation (2)] did not only support the formation of 4,6-*O*-*p*-methoxybenzaldehyde dimethyl acetal, but



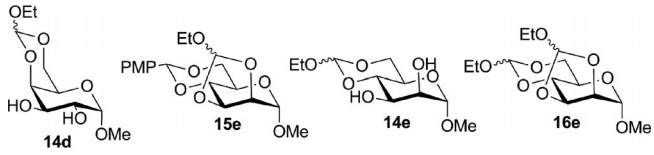
Scheme 3. Acetal formation with *p*-methoxybenzaldehyde and **2** as the catalyst.

Table 3. Combination of arenecarbaldehyde acetal formation with the arylidenation of carbohydrates.



Entry	Substrate	Catalyst	Aldehyde	Equiv. of aldehyde	Equiv. of orthoester	*t* [h]	Product	Yield[a] [%]
1	**4c**	**1**	**10**	2.0	2.0	0.5	**5c**	83
2	**4c**	**2**	**10**	2.0	2.0	0.17	**5c**	87
3	**4c**	–	**10**	2.0	2.0	48	–[b]	–
4	**4c**	**2**	**10**	2.0	–	48	–[b]	–
5	**4c**	*p*TsOH	**10**	2.0	2.0	0.083	**5c**	88
6	**4d**	**2**	**10**	2.0	2.0	24	**5d**, **14d**	30, 18
7	**4e**	**2**	**10**	1.0	1.0	2	**5e**, **15e**	65, 12
8	**4e**	**2**	**10**	2.0	2.0	12	**15e**	71
9	**4f**	**2**	**10**	1.1	1.1	18	**5f**	67
10	**4c**	**1**	**13**	2.0	2.0	6	**8c**	80
11	**4c**	**2**	**13**	2.0	2.0	5	**8c**	81
12	**4d**	**2**	**13**	2.0	2.0	48	**14d**	59
13	**4e**	**2**	**13**	1.0	1.0	48	**14e**, **16e**	38,15

[a] Yield of isolated product. [b] No reaction.



it also attacked the substrate directly to give orthoester **14d**, which was not cleaved under the reaction conditions (Table 3, Entry 6). In the case of mannoside **4e**, if 1.0 equiv. of each reagent was used, 4,6-*O*-arylidenated **5e** was partly transformed into 2,3-*O*-orthoester **15e**, which reduced the yield of the expected product (Table 3, Entry 7); an increase in the amounts of both reagents led exclusively to **15e** (Table 3, Entry 8). The same result was obtained for unprotected sugars. With glucose (**4f**), 4,6-*O*-arylidenated **5f** was obtained (Table 3, Entry 9). This arylidenation methodology was also extended to benzaldehyde (**13**) and ethyl orthoformate as reagents, as shown for glucoside **4c**; both catalysts (i.e., **1** and **2**) furnished 4,6-*O*-benzylideneglucopyranoside **8c** in very good yields (Table 3, Entries 10 and 11). However, galactoside **4d** afforded only orthoester **14d**, and mannoside **4e** led to a mixture of orthoesters **14e** and **16e** (Table 3, Entries 12 and 13). Hence, glucose and glucosides have a much higher tendency to undergo 4,6-*O*-arylidenation than mannose and galactose and their glycosides. In particular, galactose and galactosides compete successfully for intermediate **B**. Owing to the accumulation of orbitals for the lone pairs of electrons of the oxygen atom on the β-side (at C-3, C-4, and C-6), galactopyranose is more nucleophilic than mannopyranose and particularly more nucleophilic than glucopyranose.

Conclusions

Arenecarbaldehyde acetals **3** and **7** can be activated by thiourea **1** or squaramide **2** as the organocatalyst to afford cyclic acetals from carbohydrates. 4,6-*O*-Arylidenated compounds can be readily obtained under mild conditions from glucose, galactose, mannose, and their glycopyranosides. Acid-sensitive galactals can also be arylidenated at the 4,6-*O*-positions. The combination of this method with in situ acetal formation from arenecarbaldehydes and orthoesters was possible; however, competing side reactions resulting in the generation of orthoesters were observed.

Experimental Section

General Procedure for the Arylidenation Reaction

Procedure A: *p*-Methoxybenzaldehyde dimethyl acetal (**3**) or benzaldehyde dimethyl acetal (**7**; 0.6 mmol, 1.5 equiv.) was added to a solution of monosaccharide **4** (0.4 mmol, 1.0 equiv.) in anhydrous CH_3CN or CH_2Cl_2 (4.0 mL) under nitrogen. Organocatalyst **1** or **2** (0.02 mmol, 0.05 equiv.) was then added, and the reaction mixture was stirred at the same temperature until TLC indicated the complete consumption of the starting material. The reaction mixture was then quenched with a drop of Et_3N and concentrated in vacuo. The crude product was purified by flash column chromatography [petroleum ether/ethyl acetate, petroleum ether/acetone, or ethyl acetate/methanol containing 1% (v/v) Et_3N] to afford desired 4,6-*O*-arylidene-protected **5** or **8**. Diarylidene-protected **6** or **9** could be obtained in some cases.

Procedure B: Monosaccharide substrate **4** (0.4 mmol, 1.0 equiv.) was dissolved in anhydrous CH_3CN (4.0 mL) at room temperature. *p*-Methoxybenzaldehyde (**10**) or benzaldehyde (**13**; 0.8 mmol, 2.0 equiv.) and triethyl orthoformate (0.8 mmol, 2.0 equiv.) were added under nitrogen, followed by the addition of organocatalyst **1** or **2** (0.01 mmol, 0.025 equiv.). The reaction mixture was stirred at the same temperature until TLC indicated the complete consumption of the starting material. The reaction mixture was then concentrated in vacuo. The crude product was purified by flash column chromatography [petroleum ether/ethyl acetate, petroleum ether/acetone, or ethyl acetate/methanol containing 1% (v/v) Et_3N] to afford desired 4,6-*O*-arylidene-protected **5** or **8**. Orthoesters **14**–**16** were formed in some cases.

Supporting Information (see footnote on the first page of this article): Experimental details, ^1H and ^{13}C NMR spectra of new compounds, and ^1H NMR spectra of known compounds.

Acknowledgments

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