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Introduction of 4-Chlorophenyl: A Protecting Group for the Hydroxy Function

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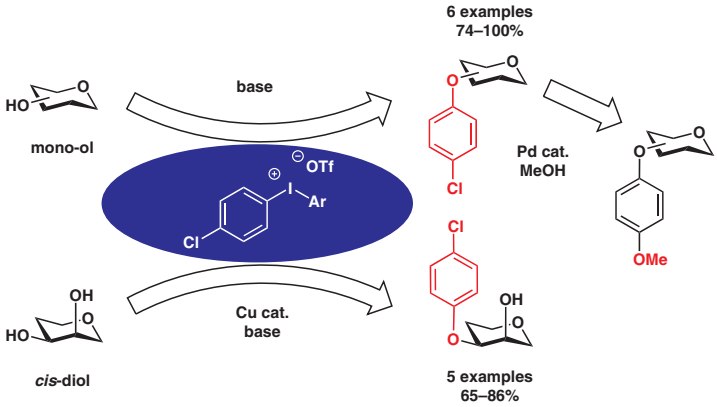

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Abstract 4-Chlorophenyl ether was utilized as a new protecting group for the hydroxy function. This group was readily introduced to a sugar hydroxy group by using diaryliodonium triflate. Regioselective introduction of this protecting group at the vicinal *cis*-diol was achieved by using a copper catalyst and diaryliodonium triflate. This protecting group is stable under the Lewis acidic conditions of glycosylation, but it can be readily removed by the initial conversion into the corresponding 4-methoxyphenyl ether with use of a Pd catalyst, followed by oxidation with ammonium cerium (IV) nitrate [$(NH_4)_2Ce(NO_3)_6$] (CAN).

Key words 4-chlorophenyl ether, 4-methoxyphenyl ether, carbohydrate, protecting group, hydroxy function, regioselective arylation

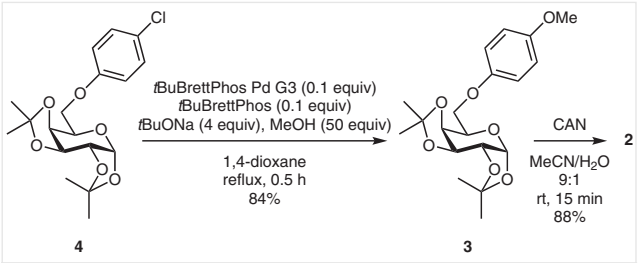
The selective protection and removal of particular hydroxy groups play a crucial role in the multistep syntheses of complex carbohydrates and other polyhydroxylated compounds.[1] 4-Methoxyphenyl (MP) ether has been used for protecting the anomeric hydroxy function of carbohydrates, but it has not yet been applied to protect other hydroxy groups because efficient introduction methods are lacking.[2] The MP ether is stable under various reaction conditions, including Lewis acid-catalyzed glycosylation, and it can be readily cleaved through oxidation by ammonium cerium (IV) nitrate [$(NH_4)_2Ce(NO_3)_6$]. Conversely, the MP ether is inert to oxidation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), whereas a 4-methoxyphenylmethyl (MPM) ether is readily cleaved by both DDQ and CAN oxidation.[3] Recently, Olofsson et al. reported *O*-arylation of hydroxy functions using electrophilic diaryliodonium salts in the presence of a base.[4] Various phenyl groups, such as 4-nitrophenyl, 3-trifluoromethylphenyl, 3-azidopheyl, 4-azidophenyl, phenyl, and 4-*t*Bu-phenyl groups, were introduced to hydroxy groups on sugars. However, the direct introduction of an MP group to a hydroxy group by this method was not successful. Therefore, in this paper, we describe the use of 4-chlorophenyl ether (4-ClPhe) as a protecting group for hydroxy functions. The 4-ClPhe can be readily introduced to hydroxy functions by using diaryliodonium salts, and this protecting group can then be removed by CAN through conversion of 4-ClPhe into MP by using a Pd catalyst. The regioselective introduction of 4-ClPhe ether into sugar vicinal *cis*-diols was also possible by utilizing diaryliodonium salts and a copper catalyst developed by Onomura et al.[5]

We first attempted the direct introduction of the MP ether into 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**) by using bis(4-methoxyphenyl)iodonium triflate (**1**), which had been prepared from 4-methoxyiodobenzene and anisole,[6] in the presence of *t*BuOK as a base (Table 1).[4] However, the yield of the desired product **3** was unsatisfactory and byproducts were formed by aromatic ring modifications owing to the electron-rich aromatic system possessing a methoxy group (Table 1, entry 1). To avoid these side reactions, we attempted to introduce a 4-ClPhe group instead of an MP ether. In fact, in 2013, Buchwald et al. proposed a useful method for performing the methoxylation of aryl chlorides by using a Pd precatalyst system (*t*BuBrettPhos Pd G3).[7] Jensen et al. also reported the methoxylation of 4-chlorobenzyl ether using the same precatalyst system.[8] We expected that the 4-ClPhe ether can be readily removed through a two-step procedure consisting of the conversion of the 4-ClPhe ether to an MP ether, followed by CAN oxidation. So far, the 4-ClPhe group has been rarely used as a protecting group for hydroxy functions because of the rather harsh conditions required for the removal of 4-ClPhe: Birch reduction followed by acid hydrolysis.[9] We then elucidated 4-chlorophenylation by using the

symmetric diaryliodonium triflates **6** and the asymmetric diaryliodonium triflates **5** and **7**. As expected, 4-chlorophenylation proceeded smoothly with bis(4-chlorophenyl)-iodonium triflate (**6**) to give the desired **4** in good yield (81%) (Table 1, entry 3). The reaction with 4-chlorophenyl(4-methoxyphenyl)iodonium triflate (**7**) afforded **4** in the 83% yield, which is the highest among the reactions evaluated (Table 1, entry 4).

Methoxylation of the 4-ClPhe ether was then carried out by employing the conditions developed by Buchwald et al.[7] Upon treatment of **4** with *t*BuBrettPhos Pd G3 (0.1 equiv), *t*BuBrettPhos (0.1 equiv), *t*BuONa (4 equiv), and MeOH (50 equiv) in 1,4-dioxane under reflux, the methoxylated product **3** was obtained in good yield (Scheme 1). The MP ether of the galactopyranose **3** was easily removed by using CAN in MeCN/H_2O to give **2** in 88% yield. Notably, the 4-ClPhe ether was stable under various conditions (see Supporting Information).

The introduction and removal of a 4-ClPhe ether were then investigated with the secondary alcohols of glucopyranoside **8**, fucopyranoside **9**, and mannopyranoside **10** (Table 2). 4-Chlorophenylation using **7** proceeded smoothly to give the corresponding 4-ClPhe ethers in good yields. Methoxylation of the 4-ClPhe ethers thus obtained also afforded good results. In the presence of the TIPS group and the Piv group, methoxylation was carried out under milder conditions by using Cs_2CO_3 as a base (entries 4 and 5). Cleavage of the resulting MP ethers also proceeded smoothly by using CAN. Although, during MP removal, the benzylidene group of mannopyranoside **20** and the TIPS group of glucopyranoside **21** were partially cleaved at room temperature as a result of the acidic nature of CAN, the yields of these removal reactions were improved when they were conducted at 0 °C for five minutes.

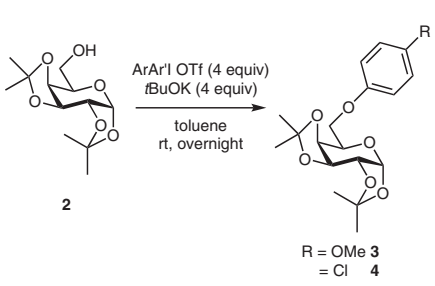


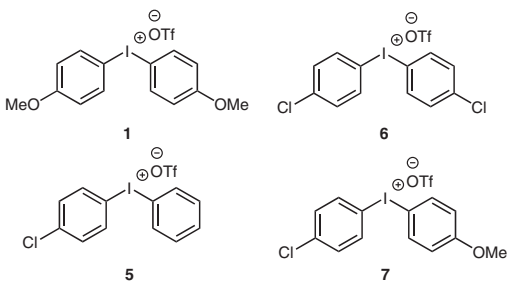
Scheme 1 Methoxylation and removal of MP ether

As described above, the 4-ClPhe group was proven to be a useful protecting group for the hydroxy function. Next, we attempted the regioselective introduction of the 4-ClPhe ether into vicinal *cis*-diols. Recently, Taylor et al. achieved the regioselective *O*-arylation of the sugar triols using $Cu(OAc)_2$ and an arylboronic acid.[10] Niu et al. also reported the regioselective *O*-arylation using $Cu(OTf)_2$, diaryliodonium triflate, and a chiral ligand.[11] However, the regioselective introduction of an aryl ether into vicinal diols, in the absence of chiral ligands, has not been reported yet. Benzyl α-D-mannopyranoside **23** was chosen as a diol substrate for the investigation of a selective *O*-arylation performed by using Onomura's method.[5] First, the role of copper reagents in phenylation conducted with use of diphenyliodonium triflate in the presence of Na_3PO_4 in toluene under reflux was investigated (Table 3).

Although the reaction progressed even in the absence of copper, the yield of the phenylated product was 24% in this case, and the selectivity was low (2-OH/3-OH 1:1.5) (entry 1). Conversely, although the use of $Cu(OTf)_2$ previously gave a simple diol in high yield, the yield and selectivity of our reaction (entry 2) were low. Subsequently, other copper reagents, i.e., CuI, $CuCl_2$, CuCl, and CuBr, were tested, but the

Table 1 Introduction of MP Ether and 4-Chlorophenyl Ether





Entry	Diaryliodonium triflate	Product	Isolated Yield (%)
1	**1**	**3**	68[a]
2	**5**	**4**	64
3	**6**	**4**	81
4	**7**	**4**	83

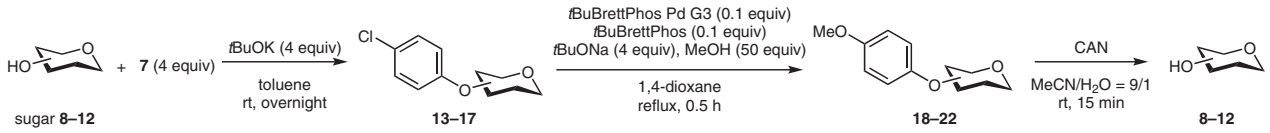
[a] Yield includes byproducts modified on the aromatic ring.

yield and the selectivity of the reaction did not improve (entries 3–6). On the other hand, when $CuBr_2$ was used, the desired product was obtained in 68% yield with good regioselectivity (2-OH/3-OH 1:7.9) (entry 7). Among the bases tested, Na_3PO_4 was the best, both in terms of yield and regioselectivity, as shown in Table 3. The use of diaryliodonium triflate **6** and *t*BuOK at room temperature resulted in low yield and selectivity (entry 13). Diphenylated compound **25** was obtained by using Cs_2CO_3 as a base in 32% yield.

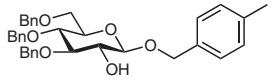
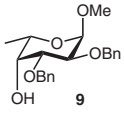
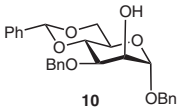
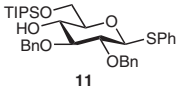
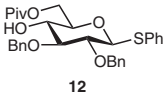
As discussed above, the combination of $CuBr_2$ and Na_3PO_4 was found to be superior for the regioselective phenylation of *cis*-diols. We then examined the 4-methoxyphenylation and 4-chlorophenylation of mannopyranoside **23** by using the iodonium triflates **1**, **5**, **6**, and **7** under similar conditions. The reaction of **23** with bis(4-methoxyphenyl)iodonium triflate (**1**) afforded the MP mannose derivatives **26a** and **26b** in 10% total yield. Furthermore, large amounts of the by-products were obtained (Table 4, entry 1). The reaction of **23** with the asymmetric 4-chlorophenyl(phenyl)iodonium triflate (**5**) resulted in the formation of a mixture of the desired 4-ClPhe ethers **27a** and **27b** along with the undesired phenylated products **24a** and **24b** (entry 2). A mixture of the desired 4-ClPhe ethers **27a** and **27b** alongside the MP derivatives **26a** and **26b** was obtained by using the asymmetric 4-chlorophenyl(4-methoxyphenyl)iodonium triflate (**7**) (entry 3). Notably, use of symmetric and highly reactive bis(4-chlorophenyl)iodonium triflate (**6**) resulted in the formation of the desired products **27a** and **27b** in good yield (75%) with moderate regioselectivity (**27a**/**27b** 1:5) (entry 4).

The regioselective 4-chlorophenylation using bis(4-chlorophenyl)iodonium triflate (**6**) was then attempted on other vicinal *cis*-diols (Table 5). The regioselectivity of the reaction using ribofuranoside **28** was poor (entry 1). Conversely, the 4-chlorophenylation of other 6-membered sugars, in particular rhamnopyranoside **29**, galactopyranoside **30**, and fucopyranoside **31**, proceeded with a reasonable degree of regioselectivity (entries 2–4). Under the present reaction conditions, the equatorial hydroxy group in C-3 position was more reactive than the adjacent axial hydroxy groups. However, these reaction conditions cannot be applied for the protection of sugars possessing an acyl protecting group. In fact, 4-chlorophenylation of 2,6-di-*O*-benzoyl-(4-methoxyphenyl)-β-D-galactopyranoside gave a complex mixture containing de-benzoylated compounds (data not shown). The reaction conditions were not appli-

Table 2 4-Chlorophenylation, Methoxylation, and Deprotection for Several Sugars

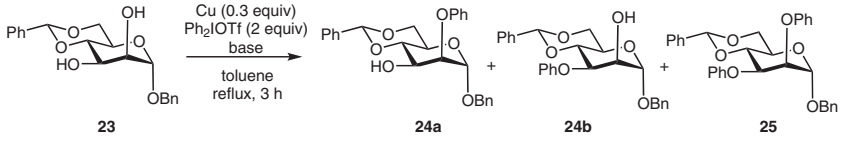


sugar **8–12** **13–17** **18–22** **8–12**

Entry	Sugar	4-Chlorophenylation, isolated yield (%)	Methoxylation, isolated yield (%)	Removal of MP, isolated yield (%)
1	 **8**	**13** (90)	**18** (86)	**8** (93)
2	 **9**	**14** (quant.)	**19** (90)	**9** (quant.)
3	 **10**	**15** (91)	**20** (93)	**10** (93)[a]
4	 **11**	**16** (74)	**21** (76)[b]	**11** (85)[a]
5	 **12**	**17** (85)	**22** (72)[b]	**12** (76)

[a] Reaction was performed at 0 °C, 5 min.
[b] Cs_2CO_3 was used instead of *t*BuONa.

Table 3 Regioselective Phenylation of a Mannose Derivative



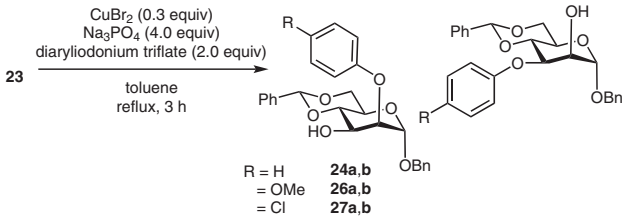
Entry	Reagent	Base (equiv)	Isolated yield of **24** (%)	**24a**/**24b**[a]	Yield of **25** (%)
1	–	Na_3PO_4 (4)	24	1:1.5	trace
2	$Cu(OTf)_2$	Na_3PO_4 (4)	17	1:1.4	trace
3	CuI	Na_3PO_4 (4)	21	1:1.8	trace
4	$CuCl_2$	Na_3PO_4 (4)	8	1:1.9	trace
5	CuCl	Na_3PO_4 (4)	20	1:1.5	trace
6	CuBr	Na_3PO_4 (4)	32	1:1.7	trace
7	$CuBr_2$	Na_3PO_4 (4)	68	1:7.9	0
8	$CuBr_2$	NaF (4)	0	–	0
9	$CuBr_2$	Cs_2CO_3 (4)	36	1:2.2	32
10	$CuBr_2$	*t*BuOK (4)	20	1:1.0	15
11	$CuBr_2$	K_2CO_3 (4)	60	1:4.2	trace
12	$CuBr_2$	DIEA (4)	48	1:2.2	0
13[b]	–	*t*BuOK (4)	24	1:1.6	0

[a] Ratios determined by ^{1}H NMR spectroscopy.
[b] Reaction was performed at rt.

cable to the protection of mono-ols. The reaction of 6-OH free galactopyranose derivative **2** with $CuBr_2$-diaryliodonium triflate system gave **4** in low yield (5%).

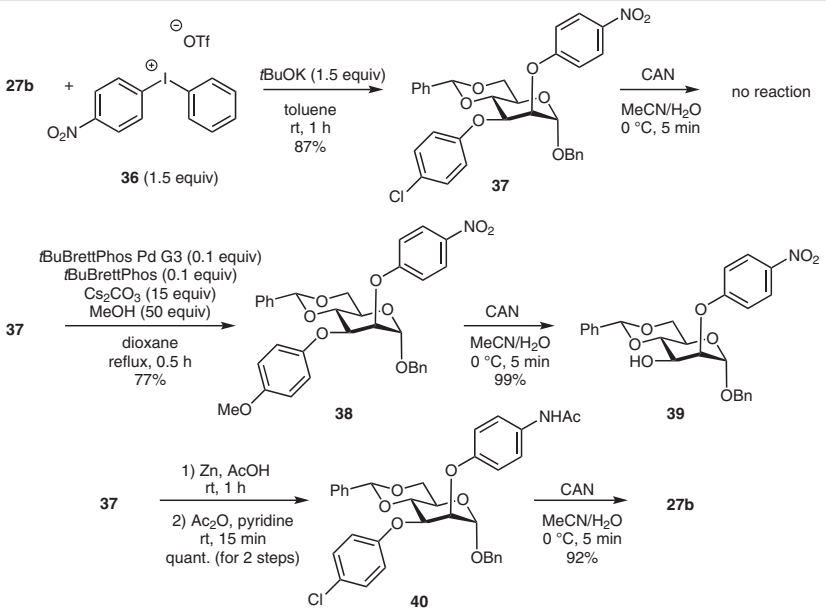
Finally, the selective removal of the 4-ClPhe ether and 4-nitrophenyl (4-NP) ether was investigated (Scheme 2). The 4-NP ether was easily introduced into mannopyranoside **27b** by using 4-nitrophenylphenyliodonium triflate (**36**) to obtain compound **37** in good yield. We then investigated the selective removal of the 4-ClPhe or 4-NP groups from **37**. The methoxylation of **37** was not achieved by using *t*BuOK as a base because a by-product was obtained. Therefore, methoxylation was carried out with Cs_2CO_3 as a base to give MP ether **38** in good yield. Subsequently, the MP ether in **38** was removed selectively by using CAN in the presence of the incorporated 4-NP ether. Compound **38** was converted to an acetamidophenyl ether **40** by reduction of the nitro moiety with zinc followed by acetylation.[12] The 4-acetamidophenyl ether was selectively removed with use of CAN in the presence of the incorporated 4-ClPhe ether. Thus, 4-ClPhe ether and 4-NP ether can be orthogonally used for their selective removal as aryl ether protecting groups.

Table 4 4-Methoxylphenylation and 4-Chlorophenylation of Mannopyranoside **23**



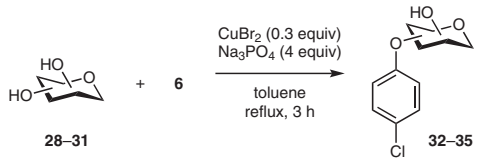
Entry	Diaryliodonium triflate	Products (isolated yield, %)[a]	Ratio
1	**1**	**26a**,**b** (10)	**26a**/**26b** 1:1.4
2	**5**	**27a**,**b** (10) **24a**,**b** (17)	**27a**/**27b** 1:2.0 **24a**/**24b** 1:1.7
3	**7**	**27a**,**b** (24) **26a**,**b** (33)	**27a**/**27b** 1:1.7 **26a**/**26b** 1:3.0
4	**6**	**27a**,**b** (75)	**27a**/**27b** 1:5.0

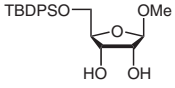
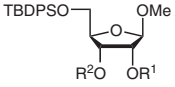
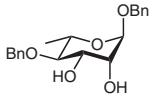
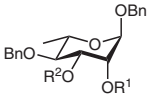
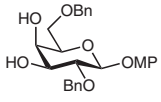
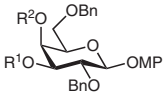
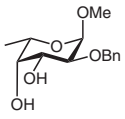
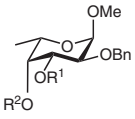
[a] Ratios determined by ^{1}H NMR spectroscopy.



Scheme 2 Orthogonal removal of two aryl protecting groups, 4-chlorophenyl ether and 4-nitrophenyl ether

Table 5 4-Chlorophenylation of Several Sugar Derivatives



Entry	Sugar	Products	Isolated yield (%)	Ratio
1	 **28**	 R^1 = 4-ClPhe, R^2 = H **32a** R^1 = H, R^2 = 4-ClPhe **32b**	65	**32a**/**32b** 1:1.2
2	 **29**	 R^1 = 4-ClPhe, R^2 = H **33a** R^1 = H, R^2 = 4-ClPhe **33b**	86	**33a**/**33b** 1:1.7
3	 **30**	 R^1 = 4-ClPhe, R^2 = H **34a** R^1 = H, R^2 = 4-ClPhe **34b**	86	**34a**/**34b** 2.4:1
4	 **31**	 R^1 = 4-ClPhe, R^2 = H **35a** R^1 = H, R^2 = 4-ClPhe **35b**	80	**35a**/**35b** 3.3:1

In summary, we have shown that the protecting group 4-chlorophenyl ether, which has not been used for the protection hydroxy groups so far, can be easily introduced into sugar hydroxyl groups by using diaryliodonium triflate.[13] This protecting group can then be removed by conversion into an MP ether by initial methoxylation with use of a Pd catalyst followed by oxidation with CAN.[14] We have also shown that 4-chlorophenyl ether can be regioselectively introduced to some vicinal *cis*-diols in pyranose sugars by using a copper catalyst and diaryliodonium triflate.[15] The 4-chlorophenyl ether and 4-nitrophenyl ether are orthogonally removable protecting groups. Currently, we are developing applications to carbohydrate synthesis of the chemistry described herein using aryl ether protecting groups.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591984.

References and Notes

(1) Lawandi, J.; Rocheleau, S.; Moitessier, N. *Tetrahedron* **2016**, *72*, 6283.
(2) (a) Matsuzaki, Y.; Ito, Y.; Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1993**, *34*, 1061. (b) Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1989**, *192*, 131.
(3) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885. (b) Mitra, A.; Mukhopadhyay, B. *RSC Adv.* **2016**, *6*, 85135. (c) Santra, A.; Misra, A. K. *Tetrahedron: Asymmetry* **2010**, *21*, 2612. (d) Budhadev, D.; Mukhopadhyay, B. *Tetrahedron* **2015**, *71*, 6155.
(4) Tolnai, G. L.; Nilsson, U. J.; Olofsson, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 11226.
(5) Kuriyama, M.; Hamaguchi, N.; Onomura, O. *Chem. Eur. J.* **2012**, *18*, 1591.
(6) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, 592.
(7) Cheung, C. W.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 3998.
(8) Viuff, A. H.; Heuckendorff, M.; Jensen, H. H. *Org. Lett.* **2016**, *18*, 5773.
(9) Marshall, J. A.; Partridge, J. J. *J. Am. Chem. Soc.* **1968**, *90*, 1090.
(10) Dimakos, V.; Graham, E.; Garrett, G. E.; Taylor, M. S. *J. Am. Chem. Soc.* **2017**, *139*, 15515.
(11) Shang, W.; Mou, Z-D.; Tang, H.; Zhang, X.; Liu, J.; Fu, Z.; Niu, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 314.
(12) Fukase, K.; Yasukochi, T.; Nakai, Y.; Kusumoto, S. *Tetrahedron Lett.* **1996**, *37*, 3343.
(13) **General Procedure for 4-Chlorophenylation of Mono-ols**
Sugar mono-ol (100 mg, 0.384 mmol, 1.0 equiv) was stirred in toluene (3.8 mL, 0.1 M). To the solution were added 4-chlorophenyl(4-methoxyphenyl)iodonium trifluoromethanesulfonate (**7**, 760 mg, 1.54 mmol, 4.0 equiv) and *t*BuOK (172 mg, 1.54 mmol, 4.0 equiv), and the mixture was stirred for overnight at rt. Upon completion, the mixture was concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel (Toluene/AcOEt = 5/1) to afford the corresponding 4-ChPhe protected sugar.
(14) **1,2:3,4-Di-*O*-isopropylidene-6-*O*-(4-chlorophenyl)-α-D-galactopyranose (4)**
117.5 mg (83%), as a colorless oil.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.22–7.20 (m, 2 H, Cl-Ph-OR-2H, Cl-Ph-OR-6H), 6.88–6.86 (m, 2 H, Cl-Ph-OR-3H, Cl-Ph-OR-5H), 5.56 (d, *J* = 5.03 Hz, 1 H, H-1), 4.65 (dd, *J* = 8.01, 2.52 Hz, 1 H, H-3), 4.35–4.33 (m, 2 H, H-2, H-4), 4.16–4.08 (m, 3 H, H-5, H-6, H-6'), 1.52 (s, 3 H, isopropyl), 1.47 (s, 3 H, isopropyl), 1.36 (s, 3 H, isopropyl), 1.34 (s, 3 H, isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.2, 129.2, 125.8, 116.1, 109.5, 108.7, 96.3, 70.9, 70.6, 70.5, 67.0, 66.2, 26.0, 26.0, 24.9, 24.4; HRMS: *m*/*z* calcd for $C_{18}H_{23}ClNaO_6$ [M + Na]$^+$: 393.1075; found : 393.1061.
(15) **General Procedure for Methoxylation of 4-Chlorophenyl Protecting Groups**
A mixture of 4-ChPhe-protected sugar (12 mg, 0.0324 mmol, 1.0 equiv), *t*BuBrettPhos Pd G3 (2.8 mg, 0.00324 mmol, 0.1 equiv), *t*BuBrettPhos (1.6 mg, 0.00324 mmol, 0.1 equiv), *t*BuONa (12.5 mg, 0.139 mmol, 4.0 equiv) and MeOH (0.066 mL, 50 equiv) was stirred in dioxane (0.324 mL, 0.1 M) under Ar and heated to reflux for 0.5 h. After diluting with AcOEt, the organic phase was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel (n-Hexane/AcOEt = 1/1) to afford the corresponding MP-protected sugar.
1,2:3,4-di-*O*-isopropylidene-6-*O*-(4-methoxyphenyl)-α-D-galactopyranose (3)
10.0 mg (84%), as a colorless oil.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.90–6.86 (m, 2 H, MeO-Ph-OR-2H, MeO-Ph-OR-6H), 6.83–6.79 (m, 2 H, MeO-Ph-OR-3H, MeO-Ph-OR-5H), 5.57 (d, *J* = 5.03 Hz, 1 H, H-1), 4.64 (dd, *J* = 7.78, 2.29 Hz, H-3), 4.36–4.33 (m, 2 H, H-2, H-4), 4.16–4.07 (m, 3 H, H-5, H-6), 3.76 (s, 3 H, MeO), 1.51 (s, 3 H, isopropyl), 1.47 (s, 3 H, isopropyl), 1.36 (s, 3 H, isopropyl), 1.34 (s, 3 H, isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.9, 152.7, 115.9, 114.5, 109.4, 108.7, 96.3, 71.0, 70.6, 67.3, 66.1, 55.7, 26.0, 26.0, 24.9, 24.4; HRMS: *m*/*z* calcd for $C_{19}H_{26}NaO_7$ [M + Na]$^+$: 389.1571; found: 389.1565.
(16) **General Procedure for Regioselective 4-Chlorophenylation of *cis*-Diols**
Under Ar, a test tube was charged with $CuBr_2$ (3.7 mg, 0.0167 mmol, 0.3 equiv) and Na_3PO_4 (37 mg, 0.223 mmol, 4.0 equiv), and then toluene (0.1 M) was added. The mixture was stirred for 10 min at rt. Sugar *cis*-diol (20.0 mg, 0.0558 mmol, 1.0 equiv) and bis(4-chlorophenyl)iodonium trifluoromethanesulfonate (41.8 mg, 0.0837 mmol, 1.5 equiv) were added and the reaction mixture was heated to reflux for 1 h. Then bis(4-chlorophenyl)iodonium trifluoromethanesulfonate (16.3 mg, 0.0227 mmol, 0.5 equiv) was added and the reaction mixture was heated to reflux for 2 h. The mixture was cooled to rt and water and sat. aqueous NH_4Cl were added. After diluting with AcOEt, the organic phase was washed with H_2O and brine, dried

over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel (Toluene/AcOEt = 10/1) to afford the corresponding 4-ChPhe protected sugar.

Benzyl 4,6-*O*-benzylidene-3-*O*-(4-chlorophenyl)-α-D-mannopyranoside (27b)

27a, **27b** (75%), as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.39–7.29 (m, 10 H, Ph), 7.23–7.19 (m, 2 H, ClPh), 7.03–6.99 (m, 2 H, Cl-Ph), 5.60 (s, 1 H, PhC<u>H</u>), 5.01 (d, *J* = 1.37 Hz, H-1), 4.74 (d, *J* = 11.9 Hz, 1 H, PhC<u>H</u>$_2$), 4.64 (dd, *J* = 9.61, 3.66 Hz, 1 H, H-3), 4.54 (dd, *J* = 11.9 Hz, 1 H, PhC<u>H</u>$_2$), 4.30 (dd, *J* = 10.1, 4.58 Hz, 1 H, H-6), 4.25 (dd, *J* = 9.61, 9.61 Hz, 1 H, H-4), 4.23–4.21 (m, 1 H, H-2), 3.99 (ddd, *J* = 10.1, 9.61, 4.58 Hz, 1 H, H-5), 3.90 (dd, *J* = 10.1, 10.1 Hz, 1 H, H-6'), 2.60 (d, *J* = 2.29 Hz, 0.9 H, O<u>H</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.6, 137.1, 136.6, 129.3, 128.9, 128.6, 128.2, 128.2, 127.2, 125.9, 118.6, 101.6, 99.2, 77.7, 76.6, 70.0, 69.6, 68.8, 63.9; HRMS: *m*/*z* calcd for $C_{26}H_{25}NaClO_6$ [M + Na]$^+$: 491.1232; found: 491.1216.