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Recognition and Site-Selective Transformation of Monosaccharides by Using Copper(II) Catalysis

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Abstract: We demonstrate copper(II)-catalyzed acylation and tosylation of monosaccharides. Various carbohydrate derivatives, including glucopyranosides and ribofuranosides, are obtained in high yields and regioselectivities. Using this versatile strategy, the site of acylation can be switched by choice of ligand. Preliminary mechanistic studies support nucleophilic addition of a copper–sugar complex to the acyl chloride to be turnover limiting.

Introduction

As an abundant natural resource, monosaccharides appear to be an ideal feedstock for constructing medicines,[1] fuels,[2] and polymers.[3] These sugars are generally difficult to derivatize, however, owing to their many reactive hydroxyl sites. Organotin-based methods can be used to achieve selective transformation of various sugars[4] en route to valuable oligosaccharides, including anti-cancer vaccines.[5,6] To replace these toxic stoichiometric reagents, catalytic strategies have emerged, featuring Lewis acid catalysis (e.g., the use of organotin chloride by Matsumura et al. and borinic acids by Taylor et al.)[7,8] and organocatalysis (e.g., the use of chiral 4-dimethylaminopyridine (DMAP) by Kawabata et al., peptides by Miller et al., scaffolding imidazoles by Tan et al., and phosphoric acids by Nagorny et al.).[9–12] Designing catalytic methods for site-selective transformations with carbohydrates represents a valuable goal that promises to streamline access to oligosaccharides. Herein, we report that chiral copper complexes are versatile catalysts for the regioselective functionalization of monosaccharides. Our findings complement and corroborate an independent report by Allen and Miller.[13] In comparison to current methods, our strategy allows easy tailoring of the catalyst to transform a wide range of sugars, and control site selectivity by ligand choice.

Our study draws inspiration from lectins, which are proteins that recognize sugars with high specificity through diol coordination to a metal center (e.g., Ca, Mn, and Cu).[14–16] By analogy to these natural metalloproteins, we reasoned that synthetic metal complexes bearing a chiral ligand, would similarly bind and possibly activate sugars for selective functionalization (Figure 1).[17] We chose to investigate copper on the basis of reports in which stoichiometric salts, for example, $Cu(acac)_2$ (acac = acetylacetonate) and $Cu(TFA)_2$ (TFA = trifluoroacetate), were used to promote acylation of sugars.[18,19] As summarized in Figure 2, we imagined that the appropriate ligands (**L**^{n}) on copper would allow selective activation of hydroxyl groups in a wide range of sugars, including both pyranosides and furanosides.[20] Besides enhancing regiocontrol, the ligand should promote catalysis. Indeed, Onomura et al. has reported chiral copper(II) catalysts for desymmetrization of *meso*-1,2-vicinal diols.[21] Although widely applied in enantioselective catalysis,

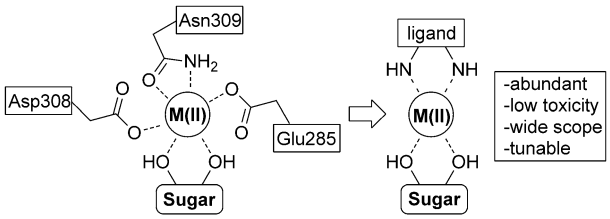

Figure 1. Binding-site structure of LangA lectin and proposed metal-complex binding.

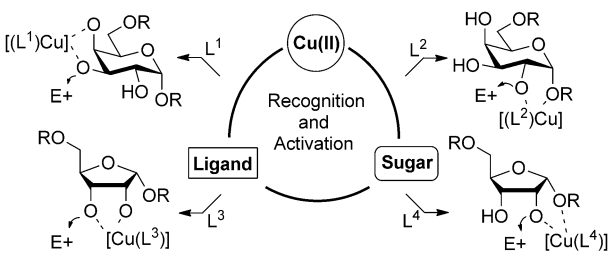

Figure 2. Proposed ligand-controlled site-selective binding with copper(II) complexes.

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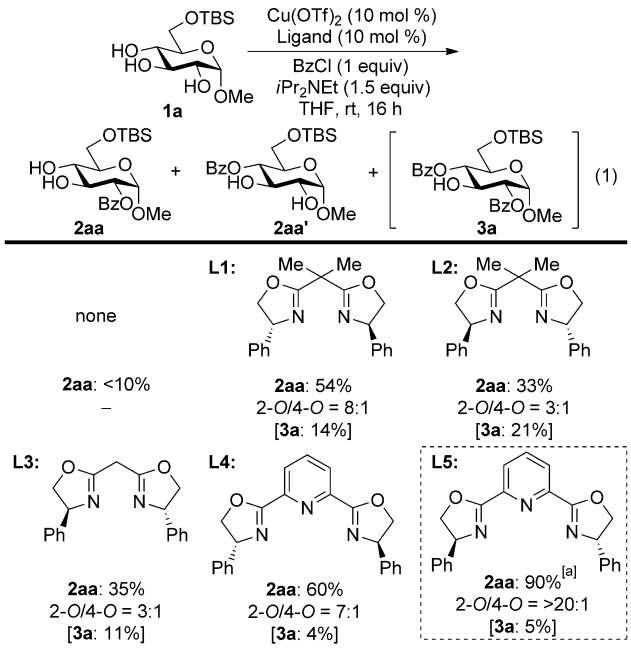
the use of chiral copper complexes for site-selective transformations warrants study.[22]

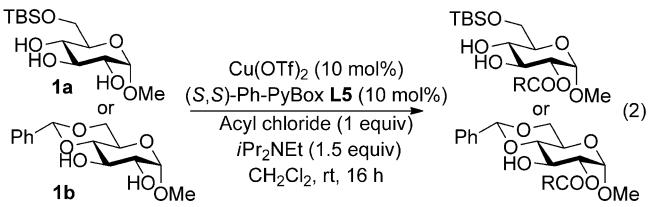
Results and Discussion

To test our hypothesis, we studied the benzoylation of α-glucopyranoside **1a** (Scheme 1). The silyl group protects the primary alcohol, leaving three secondary hydroxyl groups for possible functionalization. A control experiment in the absence of copper salts displayed no reactivity. In the absence of ligand, no catalyst turnover is observed; using 10 mol% copper(II) triflate yields less than 10% benzoylation after 16 h. Nitrogen-based ligands that are known to coordinate well to copper(II) species (e.g., bipyridine, terpyridine, and 1,10-phenanthroline) do not promote catalysis. The privileged chiral bisoxazoline (Box, **L1**–**L3**)[23] and pyridinebisoxazoline (PyBox, **L4** and **L5**) structures, however, enable catalyst turnover (33 to 90% yields).[24,25] In all cases, the 2-*O*-acylated isomer, **2aa**, is formed as the major product with regiocontrol (3:1 to >20:1, Scheme 1). The minor products include 4-*O*-acylated **2aa′** and dibenzoylated **3a**.[26] The absolute configuration of the ligand impacts selectivity. For example, (*R,R*)-Ph-PyBox **L4** results in benzoylation with 7:1 selectivity in favor of 2-*O*-benzoylated **2aa**, whereas its enantiomer (**L5**) gives >20:1 selectivity.



Scheme 1. Selective acylation of α-glucopyranosides. Yields for **2aa** and **3a** were determined by ^{1}H NMR spectroscopy (see the Supporting Information). The selectivity between **2aa** and **2aa′** was determined by ^{1}H NMR spectroscopy. The 3-*O*-acylated product was not observed by ^{1}H NMR spectroscopy. (Bz = benzoyl, TBS = *tert*-butyldimethylsilyl) [a] CH_2Cl_2 was used instead of THF; in THF, 87% yield and 16:1 selectivity was obtained.

Table 1. Selective acylation of α-glucopyranosides.[a,b]



Entry	Substrate	Acyl chloride	Product	Yield [%]	2-*O*/4-*O*
1	**1a**	BzCl	**2aa**	84	>20:1
2	**1a**	2-NO_2-C_6H_4COCl	**2ab**	80	>20:1
3	**1a**	*i*PrCOCl	**2ac**	82	9:1
4	**1a**	Piv-Cl	**2ad**	74	>20:1
5	**1a**	Cbz-Cl	**2ae**	83	15:1
6	**1a**	Fmoc-Cl	**2af**	71	7:1
7	**1b**	BzCl	**2b**	83	>20:1

[a] Isolated yields. [b] Selectivity ratios determined by ^{1}H NMR spectroscopy. Piv = pivaloyl.

With the copper–**L5** catalyst in hand, we found that α-glucopyranosides undergo acylation with a wide range of electrophiles (Table 1). Both aromatic and aliphatic acid chlorides are effective electrophiles (71–84% yields, entries 1–4). Commonly used protecting groups, such as carbobenzyloxy (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc) groups[27] can be incorporated (83% and 71% yields, entries 5–6, respectively). Glucose derivative **1b**, containing a 4,6-*O*-benzylidene acetal, undergoes acylation to provide 2-*O*-benzoylated **2b** in 83% yield and >20:1 regioselectivity. Asymmetric copper catalysis provides an organotin-free alternative for the regioselective transformation of α-glucopyranosides.[28,29]

To help explain the high regioselectivity observed, we performed a competition experiment between α-glucopyranoside **1a** and the corresponding β-anomer (Figure 3). The α-anomer of glucose **1a** undergoes benzoylation exclusively to give **2aa** in 87% yield. In agreement with the organotin study carried out by Muramatsu and Takemoto,[30] we reason that metal binding to the *cis*-dioxy motif (1-*O* and 2-*O*) of α-glucopyranoside occurs to activate the 2-*O*-hydroxyl group toward acylation.

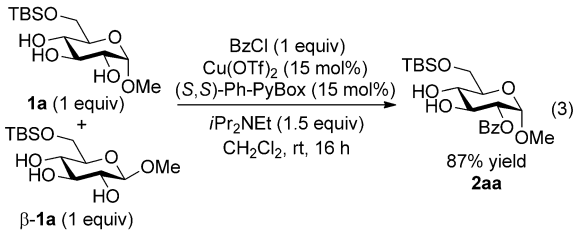
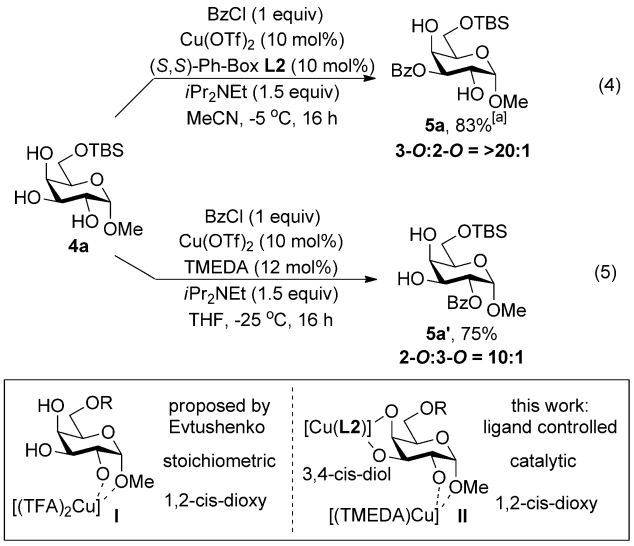
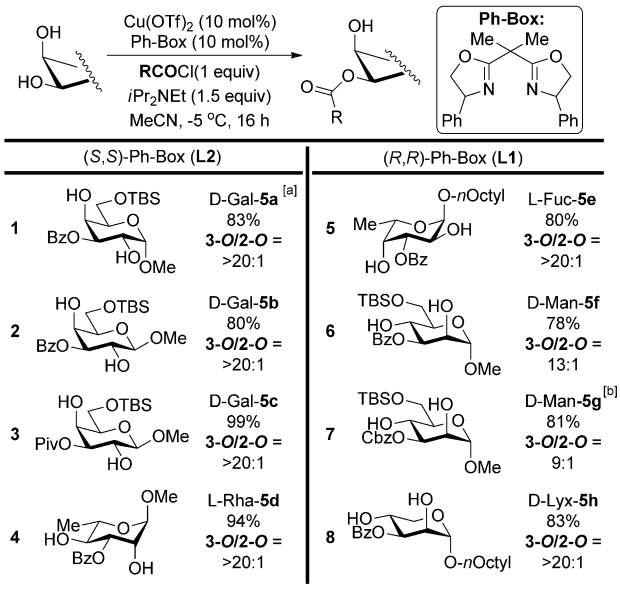


Figure 3. Competition study of α- and β-glucopyranoside with copper catalysis.

Next, we studied the acylation of α-galactopyranoside **4a**, which unlike α-glucopyranosides, contains two sets of *cis*-dioxy motifs (Scheme 2). Evtushenko proposed a 1,2-*cis*-dioxy copper intermediate, **I**, to explain the selective acylation of the 2-*O*-position of α-galactopyranosides when using stoichiomet-



Scheme 2. Ligand-controlled switch in regioselectivity by using copper catalysis. [a] 68% yield (>20:1 regioselectivity) when THF was used as the solvent.

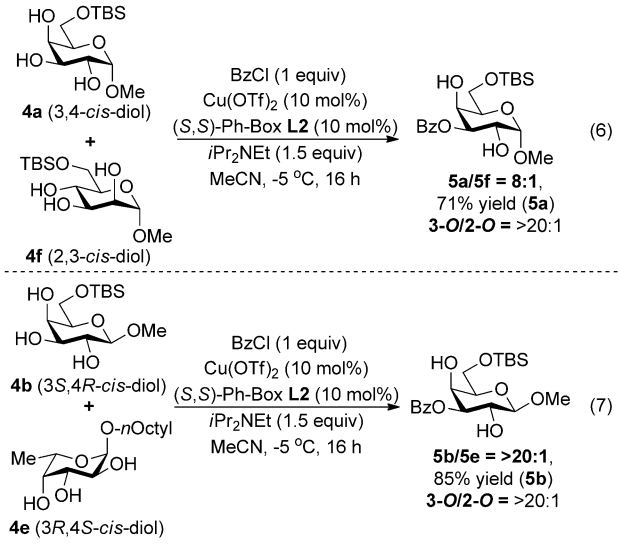


Scheme 3. Copper(II)-catalyzed acylation of carbohydrate derivatives containing *cis*-diol motif. Isolated yields are shown. Ratios determined by ^{1}H NMR spectroscopy. [a] 3-*O*/2-*O* = 1:1.5 when (*R*,*R*)-Ph-Box was used as ligand [b] (*R*,*R*)-Ph-PyBox used as ligand.

ric $Cu(TFA)_2$.[19] In contrast, we found a marked ligand effect. Treatment with (*R*,*R*)-Ph-Box **L1** affords a mixture of 3- and 2-*O*-benzoylated products (1:1.5), whereas the enantiomeric ligand (*S*,*S*)-Ph-Box **L2** enables preferential access to the 3-*O*-benzoylated **5a** with >20:1 regioselectivity (Scheme 2, [Eq. (4)]).[31] Moreover, by applying achiral *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as the ligand, we can switch the regioselectivity to favor 2-*O*-acylated **5a**′ with 10:1 regioselectivity (Scheme 2, [Eq. (5)]).[32] The ligand choice (amino-based TMEDA versus imino-based Ph-Box) influences the catalyst preference for "1,2-dioxygen" (XL-type binding) versus "3,4-diol" (XX-type binding).

Through the choice of ligand, the copper catalyst can be tuned for a specific sugar substrate (Scheme 3). For example, the copper-(*S*,*S*)-**L2** catalyst enables wide scope, including benzoylation and pivaloylation of both α- and β-galactopyranosides to afford acylated **5a**–**5c** (entries 1–3, 80–99%, >20:1). Acylation of L-rhamnose gives 3-*O*-benzoylated **5d** (entry 4, 94%, >20:1), but L-fucose, containing a 3,4-*cis*-diol, requires (*R*,*R*)-Ph-Box **L1** to afford high regioselectivity (entry 5) for 3-*O*-Bz **5e**.[33] For substrates containing 2,3-*cis* diols (e.g., D-mannose and D-lyxose, entries 6–8), (*R*,*R*)-Ph-Box **L1** is the "matched" ligand and provides 3-*O*-acylated products **5f**–**5h** in regioselectivities from 9:1 to >20:1. In general, our results are consistent with site-selective functionalization occurring at the more reactive equatorial OH group adjacent to axial OH/OR groups.[34]

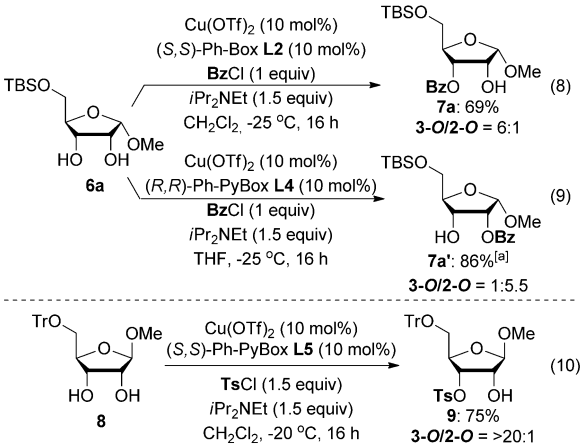
A mixture of two carbohydrates can be selectively acylated by enzyme catalysis.[35] Inspired by these enzymatic studies, we performed competition experiments to demonstrate the ability of simple copper complexes to recognize sugars (Scheme 4).[36] In the presence of (*S*,*S*)-Ph-Box **L2**, a mixture of α-galactopyranoside **4a** and α-mannopyranoside **4f**, both containing a *cis*-diol motif (3,4-*cis*-diol and 2,3-*cis*-diol), undergoes benzoylation



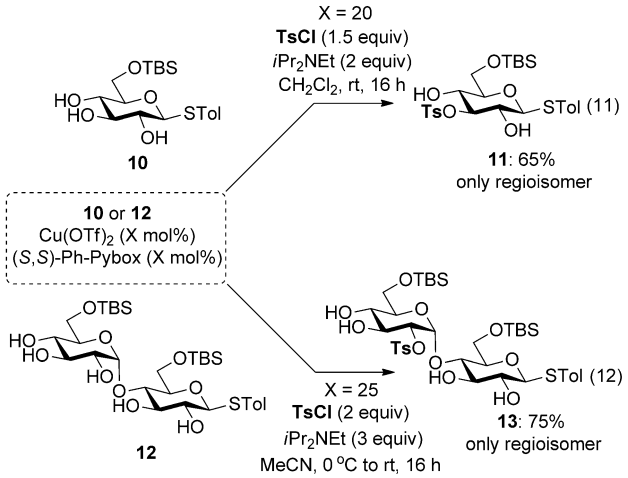
Scheme 4. Copper(II)-catalyzed carbohydrate differentiation and recognition.

selectively with **4a** to give benzoate **5a** in 71% yield (**5a**/**5f** = 8:1). Another competition experiment was performed with two pseudo-enantiomeric sugars (D-β-galactopyranoside **4b** and L-α-fucopyranoside **4e**). The benzoylation occurred exclusively in **4b** to give 3-*O*-benzoylated **5b** in 85% yield (>20:1 regioselectivity).

Our strategy extends to making ribofuranosides, which are of interest because of their potential as nucleoside therapeutics.[37] Acylation of α-ribofuranoside[38] **6a** with (*S*,*S*)-Ph-Box **L2** in CH_2Cl_2 solvent favors benzoylation at the 3-*O*-position, whereas (*R*,*R*)-Ph-PyBox **L4** in THF solvent favors benzoylation at the 2-*O*-position (Scheme 5, [Eq. (8) and (9)]).[39] As a comple-



Scheme 5. Ligand-controlled switch in regioselectivity by using copper catalysis. Isolated yields are shown. Selectivity ratios determined by ^{1}H NMR spectroscopy. [a] Isolated as a mixture of isomers. Tr = trityl.



Scheme 6. Selective tosylation of thioglycosides. Tol = *para*-tolyl.

ment to the silylation of ribofuranosides reported by Tan et al., we show control over the site of functionalization.[11b] Furthermore, the copper(II)-PyBox **L5** system promotes tosylation of β-ribofuranoside **8** to give isomer **9** in 75% yield and >20:1 regioselectivity (Scheme 5, [Eq. (10)]).

These copper(II) catalysts regioselectively tosylate thioglycosides that contain no *cis*-diol motifs (Scheme 6).[40] In the presence of an anomeric β-thioether, the 3-*O*-position of β-thioglucoside **10** transforms into **11** in 65% yield with high selectivity (Scheme 6, [Eq. (11)]). Remarkably, maltose derivative **12**, with five free hydroxyl groups, can be selectively tosylated by using the copper-**L5** catalyst. In this case, tosylation occurs at the 2-*O*-position adjacent to the α-glycosidic bond (Scheme 6, [Eq. (11)]).[41] These examples showcase the generality of our strategy for preparing complex carbohydrate derivatives that are not feasible with previous catalysts.

On the basis of literature reports,[7b,8a] and our preliminary kinetic studies with α-glucopyranoside **1a**,[42] we propose the mechanism shown in Figure 4. Copper(II) complex **III** binds reversibly to glucopyranoside **1a** through the 1,2-*cis*-dioxy motif to form complex **IV**. The copper–sugar adduct, **IV**, is deprotonated by diisopropylethylamine to form copper(II) alkoxide **V**. This species (**V**) is analogous to organotin complexes proposed previously, in which metal coordination occurs through an LX-type interaction to enhance the nucleophilicity at the 2-*O*-position. In the turnover-limiting step, benzoylation occurs to furnish product **2aa** and regenerate catalyst **III**. Our study shows no rate dependence on varying the glucose concentration, implying saturation kinetics in glucose substrate. A first-order dependence on the electrophile suggests that nucleophilic addition of alkoxide **V** to benzoyl chloride is turnover-limiting. Further mechanistic studies are ongoing.

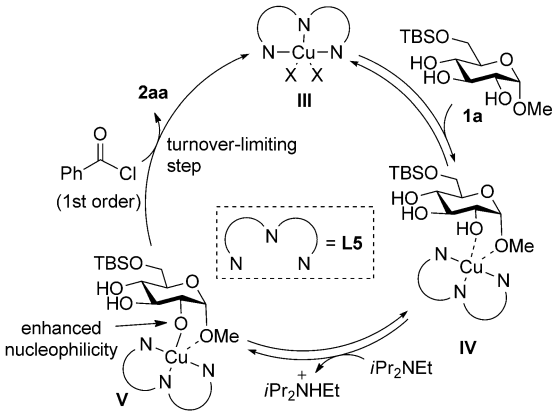


Figure 4. Proposed mechanism for copper(II)-catalyzed acylation of **1a**.

Conclusion

We have described a copper(II)-catalyzed strategy for activating a wide variety of carbohydrate derivatives, including thioglycosides and ribofuranosides. Furthermore, switching the regioselectivity is facilitated by the tunable copper complex. The versatility of this approach promises to streamline access to materials derived from sugar feedstocks.

Carbohydrate recognition is achieved by use of these unique ligand–metal–carbohydrate interactions in facilitating the differentiation of structurally similar carbohydrate derivatives. This protocol can be extended to develop chiral metal complexes capable of recognizing specific oligosaccharides. Expanding the scope of this protocol to other electrophiles and complex carbohydrates is underway.

Experimental Section

A vial was charged with copper(II) trifluoromethanesulfonate (3.6 mg, 0.01 mmol), (*S*,*S*)-Ph-PyBox **L5** (3.7 mg, 0.01 mmol), TBS-glucopyranoside **1a** (30.8 mg, 0.1 mmol), and dichloromethane (0.5 mL) in a N_2-filled glovebox. Diisopropylethylamine (26 μL, 0.15 mmol) was added and this mixture was stirred at ambient temperature for 5 min. Benzoyl chloride (12 μL, 0.1 mmol) was then added by using a microsyringe and the reaction mixture was maintained at room temperature for 16 h. The reaction mixture

was diluted with dichloromethane (2 mL) and quenched with H_2O. After allowing the mixture to undergo phase separation, the organic layer was removed and dried over anhydrous Na_2SO_4. The inorganic salts were removed by filtration through a small cotton plug, and the filtrate was concentrated in vacuo. The regioselectivity for the transformation was measured by performing ^{1}H NMR analysis of the unpurified reaction mixture. The crude material was purified by preparative thin-layer chromatography (eluting with hexanes/EtOAc = 2:1) to give the acylated product **2aa** 34.6 mg, 84% yield. $[\alpha]_D^{20} = +80\ cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 8.05$–8.12 (m, 2H), 7.66–7.56 (m, 1H), 7.57–7.42 (m, 2H), 5.15 (d, $J = 3.7$ Hz, 1H), 4.92 (d, $J = 3.7$ Hz, 1H), 4.19–4.10 (m, 1H), 3.94 (dd, $J = 10$, 4.4 Hz, 1H), 3.82–3.89 (m, 1H), 3.60–3.72 (m, 2H), 3.38 (s, 3H), 2.48 (broad s, 1H), 1.56 (broad s, 1H), 0.92 (s, 9H), 0.12 (s, 3H); 0.11 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) $\delta = 166.5$, 133.3, 129.9, 129.6, 128.4, 97.1, 73.8, 73.3, 71.7, 69.8, 64.4, 55.3, 25.9, 18.3, −5.5 ppm; IR (ATR, neat): $\tilde{\nu} = 3429$, 3414, 2955, 1714, 1276, 1049, 837, 711 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{20}H_{32}O_7Si + H^+$: 413.1990 [M+H^+]; found 413.1979.

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Keywords: carbohydrates · catalysis · molecular recognition · site-selective functionalization · transition metals

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