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Catalyst recognition of *cis*-1,2-diols enables site-selective functionalization of complex molecules

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Abstract

Carbohydrates and natural products serve essential roles in nature, and also provide core scaffolds for pharmaceutical agents and vaccines. However, the inherent complexity of these molecules imposes significant synthetic hurdles for their selective functionalization and derivatization. Nature has in part addressed these issues by employing enzymes that are able to orient and activate substrates within a chiral pocket, which dramatically increases both the rate and selectivity of organic transformations. In this article we show that similar proximity effects can be utilized in the context of synthetic catalysts to achieve general and predictable site-selective functionalization of complex molecules. Unlike enzymes, our catalysts apply a single reversible covalent bond to recognize and bind to specific functional group displays within substrates. By combining this unique binding selectivity and asymmetric catalysis, we are able to modify the less reactive axial positions within monosaccharides and natural products.

Developing site-selective catalysts[1] for the functionalization of naturally occurring compounds offers an efficient means of accessing novel therapeutics[2] as well as expediting the synthesis of complex molecular probes. These molecules are often polyhydroxylated, creating a significant synthetic challenge where the catalyst is required to differentiate between multiple similar functional groups. The most prominent examples of these molecules are carbohydrates, which mediate a diverse array of biological processes, including the control of cell-to-cell communication via cell surface oligosaccharides[3] and the facilitation of protein folding in the endoplasmic reticulum[4]. Reflecting their diverse function, saccharides are incorporated in proteins, lipids, DNA, as well as clinically relevant natural products[5,6] such as digoxin. Although significant progress has been made in oligosaccharide synthesis,[7–10] the polyhydroxylated nature of these biomolecules requires elaborate protecting group strategies to ensure appropriate spatial and temporal control

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Author Contributions K.L.T. and X.S. were involved in the design and discovery of the catalysts; X.S. is responsible for the data obtained with methyl-α-D-mannose, arabinose, galactose, and digoxin; H.L. is responsible for the data obtained with methyl α-L-rhamnose and mupirocin; S.L. is responsible for the data obtained with uridine; K.L.T. conceived and directed the investigation and wrote the manuscript.

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during molecular assembly. Beyond carbohydrates, numerous natural products contain multiple hydroxyl groups (Fig. 1a), and therefore suffer from similar challenges in their selective derivatization. A suite of catalysts that have the ability to *selectively and predictably* target specific functional group displays (*i.e.* site selectivity) would prove to be a powerful approach for manipulating complex molecules without implementing complex protecting group sequences.

Early work by Breslow[11–13] demonstrated that steroids can be selectively oxidized using directing groups, and more recent studies using directing groups, reagents and catalysts have demonstrated the selective functionalization of a range of natural products[14–23]. Over the past decade particular attention has been devoted to using synthetic catalysts to control selectivity in the modification and functionalization of carbohydrates[24]. The Kawabata[25,26] and Miller[27] groups have demonstrated the catalyst-controlled acylation of the C4 equatorial hydroxyl group of monosaccharides. More recently Taylor and co-workers have demonstrated that borinic ester catalysts effectively transfer a range of electrophiles to the equatorial position of a *cis*-1,2-diol within monosaccharides[28–31]. Even with these successes, a major challenge in the area of site-selective catalysis is the design and application of catalysts that can overturn the inherent kinetic preference of the substrate. For most monosaccharides, an axial hydroxyl group tends to be kinetically inert, so selective modification of these groups has proven more elusive using catalyst-controlled methodologies[32].

Examining past triumphs for site-selective reactions, whether enzymatic or synthetic, reveals that proximity effects[33] are a powerful and reliable means of accessing less reactive sites in a molecule. For example, Howell and co-workers have elucidated the structure of α-1,2-mannosyltransferase Kre2p/Mnt1p, which catalyzes the mannosylation of the C2-hydroxyl of mannose; in the active site multiple hydrogen bonding and van der Waals interactions are used to orient mannose allowing for selective functionalization of the axial hydroxyl (Fig. 1b)[34]. In most cases enzymes require multiple non-covalent interactions to achieve substrate recognition, enabling highly selective reactions, but this high specificity often comes at the expense of broad substrate scope. A complementary approach is to design catalysts that recognize a specific functional group motif rather than the entire molecule. Such a catalyst would allow for site selectivity within a complex molecule, but would be broadly and predictably applicable to substrates that contain the targeted functional group display. In this article we report the application of catalysts that have the ability to recognize a selected functional group motif within polyol frameworks (Fig. 1). In a critical advance this chiral catalyst is able to overturn the substrates' inherent reactivity bias, allowing for the functionalization of the axial positions within six membered rings. Similar to enzymes the control of site selectivity arises from proximity effects within a substrate-binding pocket (Fig. 1b and 1c). In contrast to an enzyme, the catalyst is not constrained to a single substrate but rather is applicable to a broad spectrum of biologically relevant molecules. Moreover, the high selectivity is achieved with a catalyst that is orders of magnitude smaller (molecular weight 307 g/mol) than a typical enzyme.

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Results and Discussion

As a first step towards developing this concept, our aim was to design a catalyst that selectively functionalized *cis*-1,2-diols, a prevalent motif in biologically relevant molecules (Fig. 1a). We previously reported that scaffold **1**[35,36] is an effective catalyst for the desymmetrization of *cis*-1,2-diols[37] via silylation[38–43]. The catalyst binds to the substrate through a single reversible-formed covalent bond [44–47], minimizing the number of interactions needed for effective substrate localization, while enabling the desired proximity effects (Fig. 1c). The catalyst contains a catalytically active imidazole ring that is connected to the substrate-binding site via a chiral organic scaffold. We reasoned that although the catalyst can bind to multiple sites within the substrate it would only functionalize the site with the proper geometric and proximity constraints.

We investigated the effectiveness of the scaffolding catalyst in the context of a methyl-α-D-mannose derivative. Using *N*-methylimidazole as a control catalyst demonstrated that the C3 hydroxyl is ~4x more reactive than the C4 hydroxyl and ~15x more reactive than the C2 hydroxyl in silyl transfer (Table 1, entry 1). Silyl transfer with catalyst (+)-**1** reverses the selectivity so that the major product is the protected C2 axial hydroxyl (C2-OH: C3-OH= 90:10, Table 1, entry 2), allowing for isolation of practical quantities of **4a** (76% yield). Notably, at high conversion (95%), a minimal amount of bis-silylation (9%) was observed in the reaction, even though the more reactive C3 hydroxyl remains available in the product. The suppression of a second silylation event is attributed to the absence of a *cis*-1,2-diol in **4a**, such that the scaffolding catalyst cannot effectively activate the substrate for an additional electrophile transfer reaction. Switching to catalyst (−)-**2**, a pseudo-enantiomer of (+)-**1**, results in a highly site selective reaction for silylation of the C3-hydroxyl (98% yield, Table 1, entry 3). The excellent site selectivity is ascribed to the C3-hydroxyl being both the inherently most reactive site as well as the stereochemically-preferred site for catalyst (−)-**2** (*i.e.* the matched case between substrate and catalyst). Both the functionalization of the C3 and C2 hydroxyls were also carried out on a more synthetically useful scale (4 mmol/1.2 g) affording comparable selectivities and yields for the desired products (Table 1, entries 2 and 3). To probe the mechanism of catalysis, we performed two reactions with control catalysts (+)-**1b** and (−)-**2b,** whose substrate-binding sites have been excised. Both catalysts prefer functionalization at the C3-hydroxyl; moreover, a dramatic loss of activity is observed for both catalysts (<10% yield, Table 1, entries 4 and 5). The inability to achieve axial functionalization as well as the decreased catalyst performance are consistent with the hypothesis that reversible covalent bonding is necessary for the observed catalysis.

The scaffold-catalyzed transfer of a triethylsilyl group enables the selective protection of either the C2 or C3 hydroxyl groups within the mannose derivative through proper choice of catalyst. To further expand the utility of this method we investigated the transfer of both acetyl and mesyl groups. Acyl transfer offers both an orthogonal protecting group as well as a means of functionalizing monosaccharides, whereas a sulfonylating reagent can serve to activate the hydroxyl providing an avenue for further chemical manipulation. Catalyst (+)-**1** and (−)-**2** were effective in performing both acyl and sulfonyl transfer to the C2 and C3 hydroxyls, respectively. For catalyst (−)-**2**, the acyl- and sulfonylated products were formed exclusively at the C3 hydroxyl consistent with a matched relationship between the substrate

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and catalyst (Table 1, entries 8 and 11). Switching to catalyst (+)-**1** the site selectivity in acylation is altered to favor the axial position (C2-OH:C3-OH:C4-OH = 84:15:1, Table 1, entry 7). Similarly mesylation occurs at the C2 hydroxyl with 91:8:1 selectivity (C2-OH:C3-OH:C4-OH, Table 1, entry 10) and in an isolated yield of 80% of **4c**.

The critical test of the functional group recognition strategy was the application to other compounds that contain a *cis*-1,2-diol. Rhamnose is a monosaccharide that is prevalent as a glycone in natural products. Control reactions with *N*-methylimidazole with the three electrophiles reveal that all three hydroxyls of methyl-α-L-rhamnose are accessible with the C3 hydroxyl being the most reactive position (Table 2, entries 1, 4, and 7). Application of the scaffolding catalyst collection to methyl-α-L-rhamnose allowed for modification of both hydroxyls of *cis*-1,2-diol with all three electrophiles (Table 2, entries 1–9). As expected, catalyst (−)-**2** provided 5:1 to 11:1 selectivity depending on the electrophile for the C2 axial hydroxyl, demonstrating that inherent substrate bias can be overturned *via* catalyst control (Table 2, entries 2, 5, and 8). Catalyst (+)-**1** favors functionalization of the C3 hydroxyl in excellent yields (>97%) for the three electrophiles (Table 2, entries 3, 6, and 9); in these cases the other constitutional isomers were observed in trace quantities in the crude reaction mixture. Similarly, catalyst (+)-**1** and (−)-**1** were applied to the functionalization of methyl-β-L-arabinose allowing for the toggling of the functionalization between both the C3 and C4 hydroxyls of the *cis*-1,2-diol, while minimizing reaction at the C2 hydroxyl (Table 2, entries 10–18).

The substrate scope was further expanded to the derivatization of galactose, in which the C2 equatorial hydroxyl is generally the most reactive site. Catalyst (+)-**1** provides access to functionalization of the C3 hydroxyl with all three electrophiles (Table 3, entries 2, 4, and 6); however, attempts to functionalize the axial C4 hydroxyl were unsuccessful. In the control reaction with the galactose derivative no axially silylated product is observed, suggesting that this position is inherently at least 100-fold less reactive than the other hydroxyls. Although scaffolding catalyst (−)-**2** is unable to overturn this large substrate bias, simply employing 1,6-anhydro-β-D-galactose, in which the substrate is constrained into the $^{1}C_{4}$ chair, enables the functionalization of the C4- hydroxyl (Table 3, entries 8, 10, and 12). In the case of 1,6-anhydro-β-D-galactose use of catalyst (+)-**2** affords mesylation of the axial C3-OH as the major product (see Supp. Info. for details). Because 1,6-anhydro-β-D-galactose is unable to undergo a chair flip, the result implies that the scaffolding catalyst can bind to an equatorial position and then functionalize the axial hydroxyl (see Supp. Info Supplementary Fig. S1a). The result does not preclude the possibility that sugars able to undergo chair flipping (*e.g.* methyl-α-D-mannose) are reacting through a minor conformer in which the scaffolding catalyst binds to the axial position and functionalizes the equatorial position followed by interconversion back to the most stable conformer (see Supp. Info Supplementary Fig. S1b).

To further test the capabilities of the scaffolding catalysts, we investigated the functionalization of other biologically and therapeutically important compounds that contain *cis*-1,2-diols. We tested the site-selective functionalization of the monosaccharide Helicid, which contains a *cis, cis*-1, 2, 3-triol. In this case using (−)-**2** and (+)-**2** affords silylation of the C2 and C4 hydroxyls, respectively (Fig. 2). These results suggest that the scaffolding

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catalysts can be potentially applied to the derivatization of other *cis*, *cis*-1, 2, 3-triols such as *myo*-inositol. Suitably protected ribonucleoside monomers are required for the automated synthesis of RNA. It is common to use monomers with the 2′-hydroxyl protected with a *tert*-butyldimethylsilyl group (TBDMS) and the 5′-hydroxyl with a dimethoxytrityl group (DMTr), while leaving the C3-hydroxyl available for coupling. Direct silyation of DMTr protected ribonucleosides leads to a mixture of silylated products at the C3′ and C2′ hydroxyls; therefore, multistep protecting group sequences are often used to obtain the desired monomers[48]. Using scaffold catalyst (−)-**2,** a TBS group is efficiently transferred to the C2′-OH of uridine with minimal amounts of C3′-OH protection (93% yield, C2′-OH:C3′-OH= >98:<2, Fig. 3a). Digoxin, a natural product produced by *Digitalis lanta*, is a cardiac glycoside that is used in the treatment of congestive heart failure[49]. Starting from commercially available digoxin, which contains 6 free hydroxyls, we attempted to synthesize both α- and β-acetyl digoxin (also therapeutics for congestive heart failure) without the use of protecting groups. Applying catalyst (+)-**2** results in the formation of β-acetyl digoxin in 90% yield as a single isomer (Fig. 3b). Switching to catalyst (−)-**1** allows for the functionalization of the less reactive axial hydroxyl, yielding α-acetyl digoxin in 56% yield (α:β= 91:9, Fig. 3b). We further applied our scaffolding catalysts to the activation of the C6-OH and C7-OH of mupirocin methyl ester[50], an antibiotic that targets *t*RNA synthetase[51]. Using scaffolding catalyst (−)-**2** and (+)-**1** provides access to both mesylated hydroxyls of the *cis*-1,2-diol (Fig. 3c). In particular the axial C7-hydroxyl is mesylated with a site-selectivity of 18:82 (**28:29**) with an isomerically pure isolated yield of 57%.

Conclusion

In this article we have demonstrated that chiral catalysts that use reversible covalent bonding to the substrate are able to selectively functionalize multiple sites within complex molecules, including sites that are naturally kinetically less reactive. Similar to enzymes, this is achieved by properly leveraging proximity effects within a chiral binding pocket. In the future, we envision –through the proper choice of the scaffold– the catalytic residue can be reoriented to activate other sites within polyfunctional molecules. Moreover, the catalysts can be reappropriated to perform transformations beyond electrophile transfer simply through the judicious choice of the catalytic residue. A library of these catalysts, in which each catalyst targets a specific functional group array, would allow for the general reengineering of complex molecular architectures devoid of using sophisticated protecting group strategies.

Methods

In a dry box, a solution of **3** (62 mg, 0.20 mmol), catalyst (+)-**1** (11 mg, 0.040 mmol, 20 mol %), and *N*,*N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous *tert*-amyl alcohol (1.0 mL, distilled over CaH_2 before use) was prepared in a glass reaction vial (4 mL, oven dried). The solution was brought out of the dry box, and *N*,*N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq, distilled over CaH_2 before use) was added to the stirring reaction at room temperature. The reaction was stirred at 4 °C for 10 minutes, followed by dropwise addition of chlorotriethylsilane (40 μL, 0.24 mmol, 1.2 eq, distilled over CaH_2 before use). The reaction was stirred at 4 °C for 2 hours. MeOH (50 μL,

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reagent grade) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL, reagent grade). The solvent was removed under reduced pressure. Column chromatography (Hexane/EtOAc = 20/1 to 1/1) afforded the bis-functionalized products (10 mg, 9%), the substrate **3** (3 mg, 5%), and a mixture of mono-functionalized products (71 mg, 84%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 = 90:10:-). A second column chromatography (Hexane/EtOAc = 20:1 to 5:1) was performed to isolate the pure product **4a** (64 mg, 76%).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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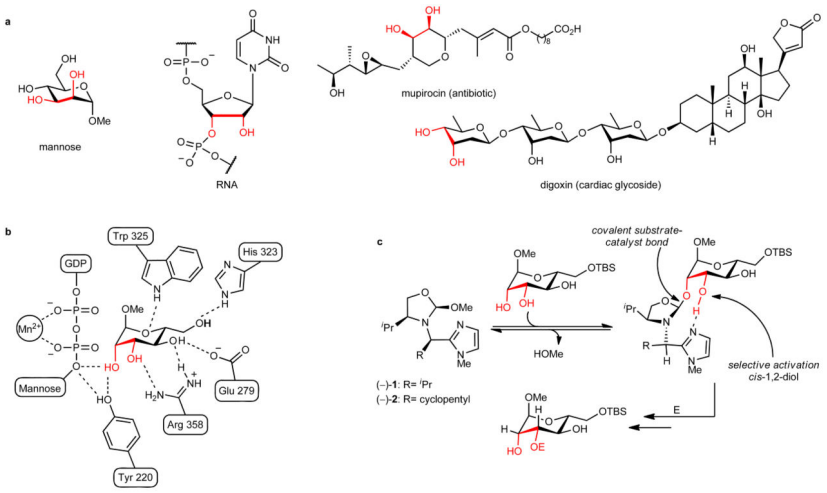

Figure 1. The role of selectively modified polyols in naturally occurring compounds and approaches to their site-selective functionalization

a. Representative biologically relevant molecules that contain a *cis*-1,2-diol structural motif. **b.** Representation of the active site interactions between Kre2p/Mnt1p α-1,2-mannosyltransferase and mannose. **c.** Proposed mode of substrate activation for scaffolding catalyst and methyl-α-D-mannose.

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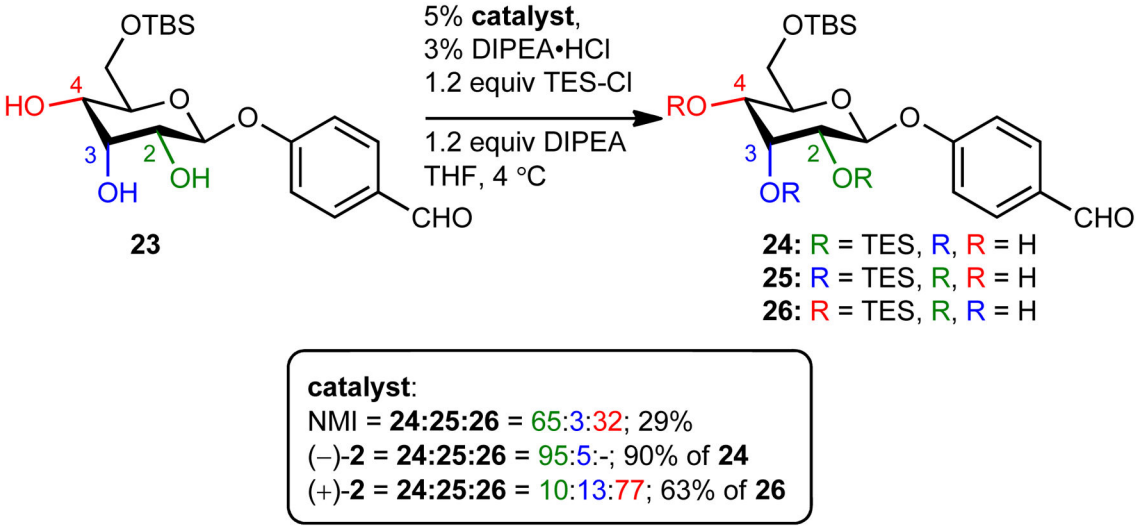

Figure 2. The site-selective modification of both the C2 and C4 hydroxyls of Helicid

Achiral catalyst *N*-methylimidazole leads to an approximately 2:1 mixture of both C2 and C4 protected products. In contrast, use of catalyst (−)-**2** gives almost entirely C2 protected product with no detectable C4 protection. Switching to catalyst (+)-**2** leads to selective protection of the C4 hydroxyl with an approximately 8:1:1 ratio of products.

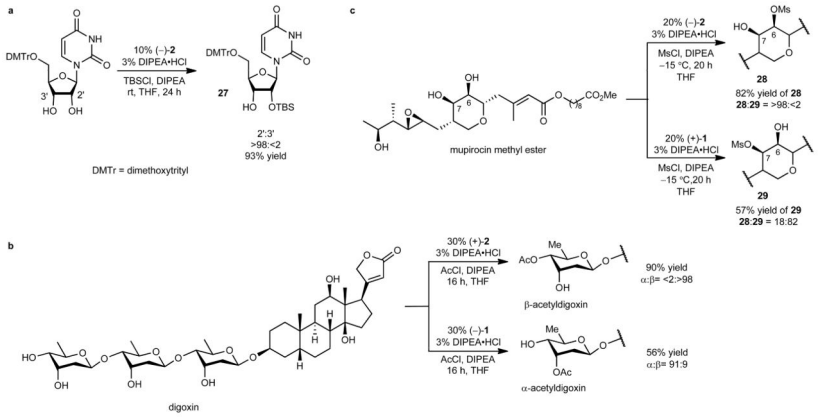

Figure 3. Expansion of scaffolding catalyzed electrophile transfer beyond monosaccharides

a. Silyl protection of the C2′-OH of uridine, an efficient synthesis of an appropriately protected uridine for automated RNA synthesis. **b.** Site-selective acylation of digoxin, towards a synthesis of α- and β-acetyl digoxin devoid of protecting groups. **c**. Site-selective mesylation of mupirocin methyl ester, a means of derivatizing antibiotics.

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Table 1

Functionalization of mannose derivative

entry[a]	electrophile	catalyst	C2:C3:C4[b]	yield (%)[c,d]
1		20 % NMI	5:78:17	77
2		20% (+)-**1**	90:10:-	84 (76/74[g])
3	TESCl[e]	5% (−)-**2**	-:100:-	(>98/>98[g])
4		20% (+)-**1b**	3:92:5	7
5		20% (−)-**2b**	2:92:6	9
6		20% NMI	9:84:7	39
7	AcCl[e]	20% (+)-**1**	84:15:1	74
8		5% (−)-**2**	1:99:-	(96)
9		20% NMI	22:56:22	68
10	MsCl[f]	20% (+)-**1**	91:8:1	(80)
11		5% (−)-**2**	-:100:-	(97)

[a] Detailed reaction conditions can be found in supplementary information.

[b] A dash (−) indicates the isomer was not observed by the mode of detection used.

[c] Isolated yield of the isomeric mixture.

[d] Yields in parentheses are of the isolated major isomer.

[e] Selectivity determined by ^{1}H NMR.

[f] Selectivity determined by GC.

[g] Reactions performed on 4 mmol scale (1.2 g) of substrate; selectivity matched small scale reaction

Note: DIPEA = *N*,*N*-Diisopropylethylamine, TESCl = triethylsilyl chloride, AcCl = acetyl chloride, MsCl = methane sulfonyl chloride, NMI = *N*-methylimidazole

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Table 2

Site-selective functionalization of methyl-α-L-rhamnose and methyl-β-L-arabinose

entry[a]	E	catalyst	C2:C3:C4[b]	yield (%)[c,d]	entry	catalyst	C2:C3:C4[b]	yield (%)[c,d]
1		20% NMI	7:79:14	78	10	20% NMI	27:14:59	39
2	TESCl	20% (−)-**2**	89:11:-	88	11	20% (−)-**1**	-:3:97	(92)
3[e]		5% (+)-**1**	-:100:-	(>98)	12	5% (+)-**1**	-:98:2	(97)
4		20% NMI	12:79:9	83	13	20% NMI	22:72:6	6
5	AcCl	20% (−)-**2**	84:14:2	73	14[f]	20% (−)-**1**	5:9:86	61
6		5% (+)-**1**	1:99:-	(98)	15	5% (+)-**1**	3:96:1	(83)
7[g]		20% NMI	24:57:19	72	16	20% NMI	68:23:9	27
8[g]	MsCl	20% (−)-**2**	92:8:-	(82)	17	20% (−)-**1**	3:10:87	93
9[g]		5% (+)-**1**	1:99:-	(>98)	18	5% (+)-**1**	1:92:7	(91)

[a] The monosaccharides were functionalized with catalysts as listed, 3 mol % DIPEA•HCl, 1.2 equiv electrophile, and 1.2 equiv DIPEA, 4 h. Reactions were performed in *tert*-Amyl-OH or THF at −15 °C or 4 °C. Detailed reaction conditions can be found in supplementary information.

[b] A dash (−) indicates the isomer was not observed by the mode of detection used. Selectivities were determined by ^{1}H NMR.

[c] Isolated yields of the isomeric mixture.

[d] Yields in parentheses are of the isolated major isomer.

[e] Reaction time 20 h.

[f] Reaction time 8h.

[g] Selectivity determined by GC.

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Table 3

Site-selective functionalization of galactose derivative and 1,6-anhydro-β-D-galactose

catalyst	E	catalyst	C2:C3:C4[b]	yield (%)[c,d]	entry	catalyst	C2:C3:C4[b]	yield (%)[c,d]
1	TESCl	20% NMI	86:14:-	77	7	20% NMI	91:-:9	51
2		20% (+)-**1**	6:94:-	95	8	5% (−)-**2**	1:-:99	(98)
3	AcCl	20% NMI	42:58:-	26	9	20% NMI	75:8:17	53
4		20% (+)-**1**	19:81:-	96	10	5% (−)-**2**	-:3:97	(93)
5	MsCl	20% NMI	76:24:-	62	11	20% NMI	75:6:19	50
6		20% (+)-**1**	-:100:-	(74)	12	5% (−)-**2**	-:1:99	(88)

[a] The monosaccharides were functionalized with catalysts as listed, 3 mol % DIPEA•HCl, 1.2 equiv electrophile, and 1.2 equiv DIPEA, 4 h. Reactions were performed in *tert*-Amyl-OH or THF at −15 °C or 4 °C. Detailed reaction conditions can be found in supplementary information.

[b] A dash (−) indicates the isomer was not observed by the mode of detection used. Selectivities were determined by ^{1}H NMR.

[c] Isolated yields of the isomeric mixture.

[d] Yields in parentheses are of the isolated major isomer.