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Chiral Copper(II) Complex-Catalyzed Reactions of Partially Protected Carbohydrates

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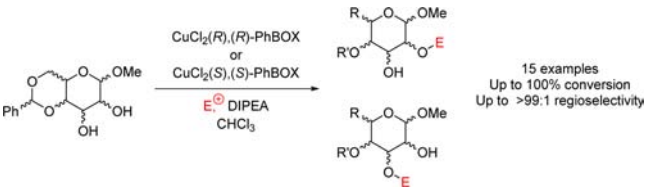
ABSTRACT



Catalyst-controlled regioselective functionalization of partially protected saccharide molecules is a highly important yet under-developed area of carbohydrate chemistry. Such reactions allow for the reduction of protecting group manipulation steps required in syntheses involving sugars. Herein, an approach to these processes using enantiopure copper−bis(oxazoline) catalysts to control couplings of electrophiles to various partially protected sugars is reported. In a number of cases, divergent regioselectivity was observed as a function of the enantiomer of catalyst that is used.

Sugars are highly important moieties in the development of therapeutic agents due to their essential role in biological processes. The presence of multiple reactive sites on saccharide molecules means the synthesis of sugar derivatives often relies on extensive protecting group manipulations or the use of enzymes.[1] Much effort has been directed toward regioselective reactions of partially or fully unprotected carbohydrates, as this is crucial for streamlining the functionalization of such molecules.[2] To this end, the diol-binding affinities of various transition metals[3−5] (usually in a stoichiometric amount) and of boron[6] have been exploited as a method for selective hydroxyl activation. Organocatalysts have also been applied to this challenge.[7,8] The more recent use of borinic ester catalysts has provided an alternative to the use of stoichiometric activating reagents, while maintaining the same high selectivity.[9] While all these methods generally offer high selectivity, access to regioisomers not inherently produced by a particular sugar-catalyst combination remains difficult.[10] Often, a specific stereochemical relationship between hydroxyl groups is strictly required to allow catalyst binding and subsequent site-specific reaction.[11] The development of reactions which would allow access to all possible regioisomers under catalyst control would expand the range of this important approach to saccharide functionalization. Tin reagents have received attention in this area, as a switch

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(2) Lee, D.; Taylor, M. S. *Synthesis* **2012**, *44*, 3421.
(3) (a) Evtushenko, E. V. *Carbohydr. Res.* **2012**, *359*, 111. (b) Osborn, H. M. I.; Brome, V. A.; Harwood, L. M.; Suthers, W. G. *Carbohydr. Res.* **2001**, *332*, 157.
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(6) (a) Kaji, E.; Nishino, T.; Ishige, K.; Ohya, Y.; Shirai, Y. *Tetrahedron Lett.* **2010**, *51*, 1570. (b) Oshima, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2315. (c) James, T. D.; Samankumara Sandanayake, K. R. A.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1910.
(7) (a) Ueda, Y.; Muramatsu, W.; Mishiro, K.; Kawabata, T. *J. Org. Chem.* **2009**, *74*, 8802. (b) Sánchez-Roselló, M.; Puchlopek, A. L. A.; Morgan, A. J.; Miller, S. J. *J. Org. Chem.* **2008**, *73*, 1774. (c) Griswold, K. S.; Miller, S. J. *Tetrahedron* **2003**, *59*, 8869. (d) Hu, G.; Vasella, A. *Helv. Chim. Acta* **2003**, *86*, 4369. (e) Mensah, E.; Camasso, N.; Kaplan, W.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013**10.1002/anie.201304298.
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(11) Nashed, M. A.; Anderson, L. *Tetrahedron Lett.* **1976**, *39*, 3503.
(12) (a) Muramatsu, W.; Takemoto, Y. *J. Org. Chem.* **2013**, *78*, 2336. (b) Demizu, Y.; Kubo, Y.; Miyoshi, H.; Maki, T.; Matsumura, Y.; Moriyama, N.; Onomura, O. *Org. Lett.* **2008**, *10*, 5075. (c) Kaji, E.; Shibayama, K.; In, K. *Tetrahedron Lett.* **2003**, *44*, 4881. (d) Boons, G.-J.; Castle, G. H.; Clase, J. A.; Grice, P.; Ley, S. V.; Pinel, C. *Synlett* **1993**, 913. (e) Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 24.

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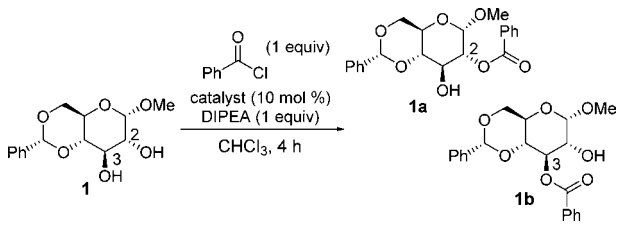
in regioselectivity can be achieved by changing the size of the alkyl groups on the organotin catalyst. However, this methodology leads to generation of potentially toxic alkyltin(IV) byproduct.[12] Recently, Tan et al. have shown that pairs of enantiopure molecules can successfully control regioselectivity in reactions of carbohydrates by employing "covalent scaffolding" catalysts.[8] The application of enantiopure catalysts to control problems in stereo- and regioselectivity of all types remains an important approach.[13a−c] Implicit in the effort is the identification of catalysts which can overcome the different intrinsic reactivities of various sites.[13d]

As part of our ongoing effort to develop regioselective functionalizations of carbohydrate substrates,[14] we chose to investigate the use of chiral copper−(bis)oxazoline complexes.[15] We were inspired by the work of Onomura et al., who reported the capacity of such complexes to influence selectivity in reactions of a variety of polyol substrates with a range of electrophiles.[16] Initial results proved promising (Table 1, entries 1 and 2), with catalyst-dependent regioselectivity observed with 10 mol % catalyst loading. Further optimization of the reaction conditions led to an increase in selectivity in the matched case (Table 1, entry 6) when the temperature was decreased to −40 °C, whereas optimal selectivity was achieved in the mismatched case at 0 °C. Change of (bis)oxazoline ligand (Table 1, entries 8−11), solvent (Table 1, entries 12 and 13), or base (Table 1, entries 14 and 15) led to loss of reactivity.

Table 1. Optimization of Reaction Conditions



entry	catalyst	temp (°C)	conv[e] (%)	ratio[e] **1a:1b**
1	$CuCl_2$-(*R*)-PhBOX	0	99	6.0:1
2	$CuCl_2$-(*S*)-PhBOX	0	100	1:5.7
3	$CuCl_2$	0	93	3.7:1
4	$CuCl_2$-(*R*)-PhBOX	−10	91	7.0:1
5	$CuCl_2$-(*S*)-PhBOX	−10	93	1:5.3
6	$CuCl_2$-(*R*)-PhBOX	−40	92	15.0:1
7	$CuCl_2$-(*S*)-PhBOX	−40	98	1:1.2
8	$CuCl_2$-(*R*)-BnBOX	−40	84	11.0:1
9	$CuCl_2$-(*S*)-^{t}BuBOX	−40	92	2.6:1
10	$CuCl_2$-(*R*)-Ph-PyBOX	−40	88	4.2:1
11	$CuCl_2$-(*S*)-Ph-PyBOX	−40	85	4.6:1
12[a]	$CuCl_2$-(*R*)-PhBOX	−10	31	5.3:1
13[b]	$CuCl_2$-(*R*)-PhBOX	−10	53	3.8:1
14[c]	$CuCl_2$-(*R*)-PhBOX	−10	34	1.5:1
15[d]	$CuCl_2$-(*R*)-PhBOX	−10	0	

Conditions: sugar (0.1 mmol, 1 equiv), benzoyl chloride (0.1 mmol, 1 equiv), DIPEA (0.1 mmol, 1 equiv), catalyst (10 mol %), $CHCl_3$ (0.4 mL). [a] THF as solvent. [b] PhMe as solvent. [c] 2,6-Lutidine as base. [d] K_2CO_3 as base. [e] Determined by ^{1}H NMR spectroscopy.

With optimized conditions in hand we turned our attention to a screen of sugar substrates (Table 2). The 4,6-benzylidene acetal motif was chosen as a convenient protecting group to block two of the hydroxyl groups of the hexopyranosides. Pleasingly, in each case, some degree of regioselectivity is imparted by at least one of the enantiomers of catalyst (compared with achiral $CuCl_2$ as catalyst). When the stereochemistry at the anomeric position is α, both enantiomers of catalyst affect the regioselectivity of the reaction, leading to an amplification of the selectivity observed with $CuCl_2$ as catalyst (Table 2, entries 1, 10, and 17) or an overturn of this selectivity to favor the other regioisomer (Table 2, entries 2, 9, and 18). However, when the stereochemistry at the anomeric position is *β*, only the (*S*)-enantiomer of catayst is found to significantly affect the regioselectivity (Table 2, entries 6 and 14), with the (*R*)-enantiomer of catalyst giving approximately the same results as found with $CuCl_2$ (Table 2, entries 5 and 13). These observations perhaps suggest that binding of the Cu−BOX catalyst to the diol is sensitive to the stereochemistry at the anomeric position.

The most notable result was observed with methyl 4,6-benzylidene-α-mannopyranoside (**5**) as the sugar substrate (Table 2, entries 17−20). Almost complete selectivity for benzoylation at the 3-position was found when $CuCl_2$-(*R*)-PhBOX was used as catalyst, demonstrating a large amplification of the selectivity observed when achiral $CuCl_2$ was used. Pleasingly, $CuCl_2$-(*S*)-PhBOX was shown to overturn this selectivity and favor benzoylation at the 2-position in a ratio of 11.5:1 (Table 2, entry 18).

The reaction conditions were found to be applicable to a range of electrophiles (Table 3). Several acyl chlorides gave high conversions into the functionalized sugars, albeit with diminished regioselectivities. Acetyl chloride produced the best results of the electrophiles tested (Table 3, entries 1 and 2), with high conversion and good regioselectivity observed with both enantiomers of catalyst. Methyl adipoyl chloride (Table 3, entries 7 and 8) and 5-pentenoyl chloride (Table 3, entries 9 and 10) both gave full conversion with respect to the sugar, but with lower regioselectivity than observed with benzoyl chloride. Although a catalyst dependency was still clear, substituted benzoyl chlorides did not provide the same high conversions or regioselectivities observed with the unsubstituted benzoyl

(13) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1. (b) Kumar, R. R.; Kagan, H. B. *Adv. Synth. Catal.* **2010**, *352*, 231. (c) Lewis, C. A.; Merkel, J.; Miller, S. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6007. (d) Lewis, C. A.; Miller, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5616.

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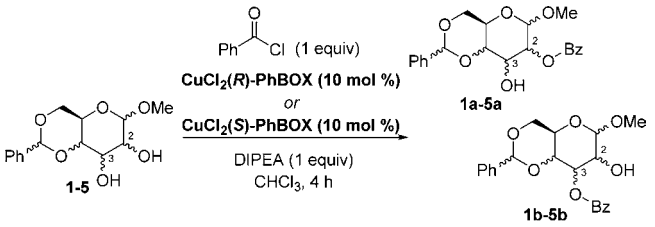
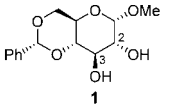
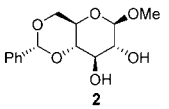
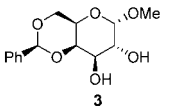
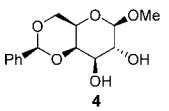
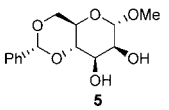
(15) (a) Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325. (b) Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651. (c) Mazet, C.; Roseblade, S.; Köhler, V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879. (d) Lee, J. Y.; You, Y. S.; Kang, S. H. *J. Am. Chem. Soc.* **2011**, *133*, 1772.

(16) (a) Maki, T.; Ushijima, N.; Matsumura, Y.; Onomura, O. *Tetrahedron Lett.* **2009**, *50*, 1466. (b) Demizu, Y.; Matsumoto, K.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2007**, *48*, 7605. (c) Matsumura, Y.; Maki, T.; Tsurumaki, K.; Onomura, O. *Tetrahedron Lett.* **2004**, *45*, 9131. (d) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052.

Table 2. Screen of Sugars Bearing Vicinal Hydroxyl Groups*



entry	sugar	cat.	temp (°C)	conv (%)[a]	ratio[b] a:b
1		(*R*)	-40	92 (85, **1a**)	15.0:1
2		(*S*)	0	94 (69, **1b**)	1:5.7
3		$CuCl_2$	0	82	3.7:1
4		-	0	19	14.0:1
5		(*R*)	-40	100 (30, **2a**)	1:1.4
6		(*S*)	0	100 (71, **2b**)	1:4.0
7		$CuCl_2$	0	100	1:1.6
8		-	0	0	-
9		(*R*)	0	100	1:1.4
10		(*S*)	0	100	2.5:1
11		$CuCl_2$	0	74	1.9:1
12		-	0	10	1:1
13		(*R*)	-40	100 (81, **4b**)	1:11.5
14		(*S*)	0	100	1.4:1
15		$CuCl_2$	0	92	1:12.0
16		-	0	28	0:1
17		(*R*)	-40	100 (87, **5b**)	1:>99
18		(*S*)	0	90 (79, **5a**)	11.5:1
19		$CuCl_2$	0	100	1:4.2
20		-	0	52	3.2:1

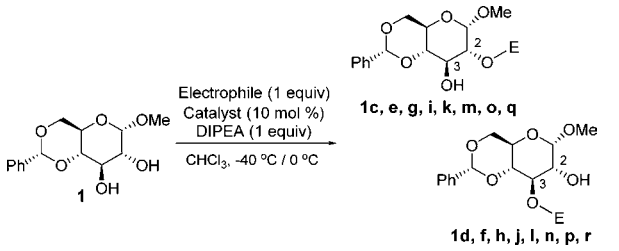
* Conditions: sugar (0.1 mmol, 1 equiv), benzoyl chloride (0.1 mmol, 1 equiv), DIPEA (0.1 mmol, 1 equiv), catalyst (10 mol %), $CHCl_3$ (0.4 mL). Results average of two identical runs. [a] Isolated yield in parentheses with regioisomer isolated in bold. [b] Determined by ^1H NMR spectroscopy.

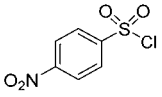
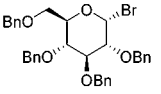
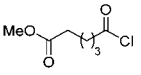
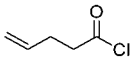
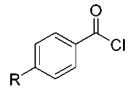
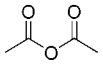
chloride (Table 3, entries 11−16). This discrepancy is conceivably due to a lack of solubility of some benzoyl chlorides in the reaction solvent.

While acetic anhydride successfully acylated **1**, the ratio of 2- to 3-position functionalization was approximately the same with both enantiomers of catalyst (Table 3, entries 17 and 18). This lack of regioselectivity (and indeed the diminished regioselectivity observed in other cases) could possibly be attributed to the electrophile forming a complex with the copper and displacing the chiral ligands, which would still lead to a reaction but with no element of regiocontrol. Alkyl halides were not successful in this reaction, even in the presence of 1 equiv of promotor Ag_2O. Only modest selectivity was observed when attempting to glycosylate the glucose diol with 2,3,4,6-*tetra*-*O*-benzylglycopyranosyl bromide (Table 3, entries 5 and 6).

In an effort to further streamline the synthesis of monosubstituted sugar derivatives, a one-pot, two-step benzoylation−acetal deprotection procedure was attempted (Figure 1).

Table 3. Screen of Electrophiles*



entry	electrophile	cat.	*t* (h)	conv (%)[a]	ratio[b]
					1c:1d
1		(*R*)	18	91 (74, **1c**)	7.0:1
2		(*S*)	18	79 (41, **1d**)	1:4.5
					1e:1f
3		(*R*)	18	44	2.9:1
4		(*S*)	18	40	1:2.5
					1g:1h
5[c]		(*R*)	4	82 (51, **1g**)	3.6:1
6[c]		(*S*)	4	84 (41, **1h**)	1.6:1
					1i:1j
7		(*R*)	20	100 (69, **1i**)	3.3:1
8		(*S*)	20	100 (61, **1j**)	1:2.1
					1k:1l
9		(*R*)	20	100 (50, **1k**)	1.3:1
10		(*S*)	20	100 (57, **1l**)	1:1.6
					1m:1n
11		(*R*)	22	22	2.0:1
12	R = NO_2	(*S*)	22	28	1.3:1
					1o:1p
13	R = Br	(*R*)	18	46	5.9:1
14		(*S*)	18	48	1.1:1
					1q:1r
15	R = OMe	(*R*)	18	49	7.2:1
16		(*S*)	18	46	1:1.5
					1c:1d
17		(*R*)	24	69	1.8:1
18		(*S*)	24	75	1.6:1

* Conditions: sugar (0.1 mmol, 1 equiv), electrophile (0.1 mmol, 1 equiv), DIPEA (0.1 mmol, 1 equiv), catalyst (10 mol %), $CHCl_3$ (0.4 mL). Results average of two identical runs. [a] Isolated yield in parentheses with regioisomer isolated in bold. [b] Determined by ^1H NMR spectroscopy. [c] Ag_2O (1 equiv) added to the reacion mixture.

After completion of the reaction of methyl 4,6-benzylidene-α-mannopyranoside with benzoyl chloride, the solvent was removed in vacuo and a hydrogenolysis of the cyclic benzylidene acetal then immediately performed

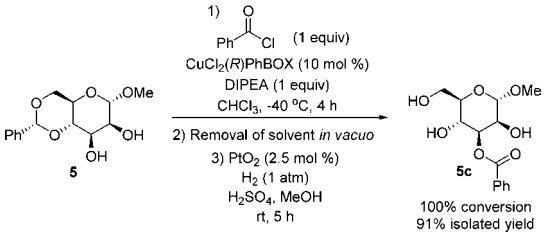


Figure 1. In situ 4,6-acetal deprotection.

using Adam's catalyst/H_2. After workup, methyl 3-benzoyl-α-mannopyranoside was isolated in 83% yield (along with an inseparable 8% methyl 6-benzoyl-α-mannopyranoside impurity).

Three competition reactions were then run in an effort to gain insight into how the relative stereochemistry of each hydroxyl on the sugar ring affects the binding of the catalyst (if it is indeed forming a complex with the diol *in situ*). First, a 1:1 mixture of methyl 4,6-benzylidene-α-glucopyranoside and methyl 4,6-benzylidene-α-galactopyranoside (stereochemistry different at the 4-position) was subjected to the standard reaction conditions with 1 equivalent of benzoyl chloride. No preference for either sugar was observed with either catalyst. Each substrate reached approximately 50% conversion with regioselectivity ratios very similar to those reported in Table 1. Second, a 1:1 mixture of methyl 4,6-benzylidene-α-galactopyranoside and methyl 4,6-benzylidene-β-galactopyranoside (stereochemistry different at the 1-position) was subjected to the same conditions. In this case, the (*R*)-enantiomer of catalyst appeared to show a preference for the β anomer, with this substrate reaching 48% conversion compared with the α anomer which only reached 2% conversion. Moreover, the β anomer reacted preferentially at the 3-position in a 1:20 ratio (2:3 position benzoylation). The same site selectivity was observed previously with this substrate (Table 1, entry 13). Conversely, the (*S*)-enantiomer catalyst only showed a slight bias toward the β anomer, with no strong regioselectivity displayed.

Lastly, a 1:1 mixture of methyl 4,6-benzylidene-α-glucopyranoside and methyl 4,6-benzylidene-α-mannopyranoside (stereochemistry different at the 2-position) was subjected to the reaction conditions. Strikingly, with both enantiomers of catalyst, complete selectivity for methyl 4,6-benzylidene-α-mannopyranoside was observed. This observation also demonstrates a significant difference from when the achiral catalyst $CuCl_2$ was used. The observed selectivity may be

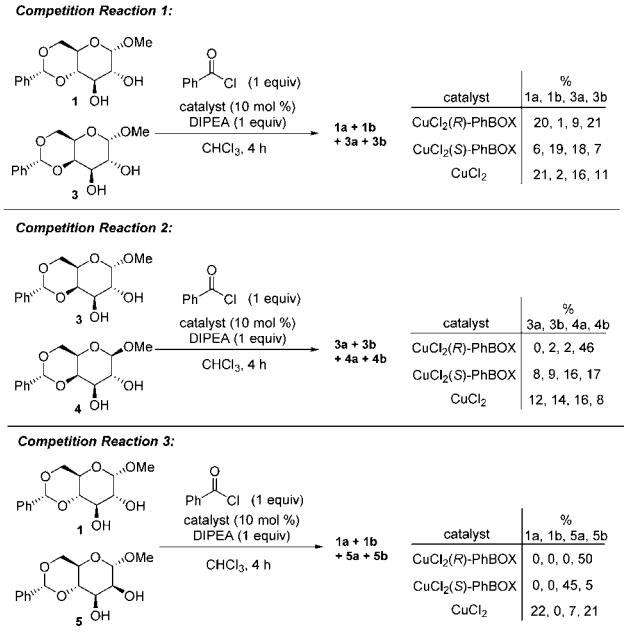


Figure 2. Competition reactions.

attributed to the different stereochemical relationship between the two sets of free hydroxyls on the sugar substrates; the glucose derivative bears a *trans* vicinal diol and the mannose derivative bears a *cis* vicinal diol (Figure 2).

In summary, we have shown that enantiopure copper complexes can influence the regioselectivity of reactions of partially protected sugars. These complexes can lead to a significant enhancement of the "inherent" reactivity of the sugar or, in some cases, an overturn of this selectivity to favor the other, less accessible regioisomer. The current reaction conditions were also shown to be compatible with several different electrophiles. One-pot, orthogonal deprotection of the benzylidene acetal was demonstrated. Efforts to improve the regioselectivity and scope of the reaction via modification of the catalyst continue in our laboratory.

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Supporting Information Available. Procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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