Organocatalysis

DOI: 10.1002/ange.201304298

Chiral Phosphoric Acid Directed Regioselective Acetalization of Carbohydrate-Derived 1,2-Diols**

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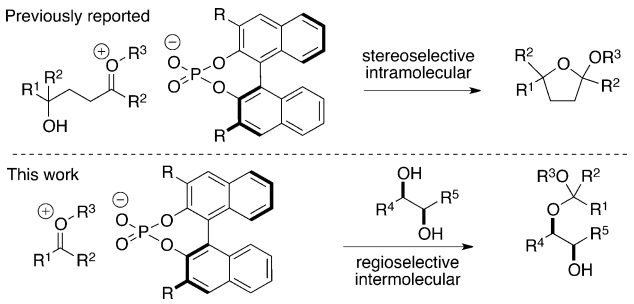
A number of important classes of natural products such as oligosaccharides or polyketides are polyols, and synthetic approaches to the regioselective functionalization of such compounds almost invariably involve multiple protecting group manipulations.[1]

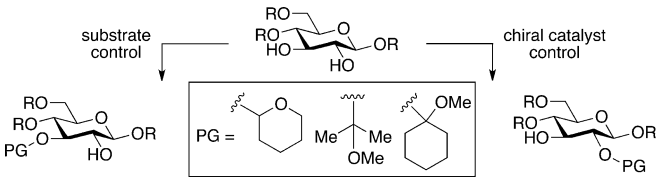
In contrast, nature utilizes a more direct approach and relies on enzymes to achieve selective functionalization of less reactive sites within a complex molecule. Recent findings suggest that small-molecule-based chiral catalysts could act similarly to enzymes and enhance or alter the inherent selectivity profiles exhibited by the substrates.[2] While there is a wide range of electrophiles that could be activated through Lewis base catalysis, no catalysts allowing regioselective trapping of oxocarbenium ions (or their equivalent) have been reported to date.

Recent reports indicate that chiral phosphoric acids (CPAs) could control the course of an intramolecular enantioselective nucleophilic addition to oxocarbenium ions.[3,4] Although the precise nature of the catalytic mechanism and intermediates in such transformations has yet to be clarified,[4i] the existence of an oxocarbenium/chiral phosphate ion pair has been invoked (Scheme 1). The chirality of



Scheme 1. CPA-catalyzed acetalizations.

the phosphate counterion could, in theory, control not only stereoselectivity, but also the regioselectivity of a polyol addition to an oxocarbenium ion. Considering that the majority of the known enantioselective protocols are based on the intramolecular trapping of the in situ generated oxocarbenium with a tethered oxygen-based nucleophile, accomplishing a CPA-controlled regioselective intermolecular acetalization reaction represents a significant challenge. Herein we summarize our studies that demonstrate that CPAs could significantly enhance or alter the inherent regioselectivity profiles exhibited by various monosaccharide-derived 1,2-diols in CPA-catalyzed reactions with enol ethers (Scheme 2).



Scheme 2. Regioselective protection of carbohydrate-derived diols. PG = protecting group.

This study represents the first example of a chiral-catalyst-controlled (rather than a substrate- or a reagent-controlled) regioselective acetalization. Such transformations could be employed to selectively functionalize/protect adjacent equatorial hydroxy groups of monosaccharides[5] in a manner that is complementary to known substrate-controlled transformations relying on organotin reagents[1a,6] and organoboron catalysts developed by the Taylor group.[7] The development of new protocols for the catalyst-controlled regioselective protection of saccharides could significantly reduce the number of steps required for protecting group manipulations and hence improve the accessibility of complex carbohydrates.[8,9]

Our studies commenced with the evaluation of various Brønsted acid catalysts in the reaction of the galactose derivative **1a** with dihydropyran (Table 1). Typically, substrate-controlled functionalization of β-galactosides such as **1a** takes place either at the C3 hydroxy group[10] or nonselectively.[11] Consistent with these observations, **1a** demonstrated little to no preference for THP-protection at C3 when achiral acids such as diphenylphosphoric acid (entry 1) or PPTS (entry 2) were employed as the catalysts. The following evaluation of both enantiomers of various binol-derived chiral phosphoric acids **2a–c** as the catalysts (entries 3–8) did not result in a substantial switch in regiocontrol, and approximately equimolar mixtures of **3a** and **3b** were observed in each case. Remarkably, a significantly different outcome was observed when the chiral phosphoric acid **2d** was employed as the catalyst (entries 9–11). While the reaction catalyzed by (*S*)-**2d** and (±)-**2d** were only weakly

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[**] We are grateful to the University of Michigan for financial support.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304298.

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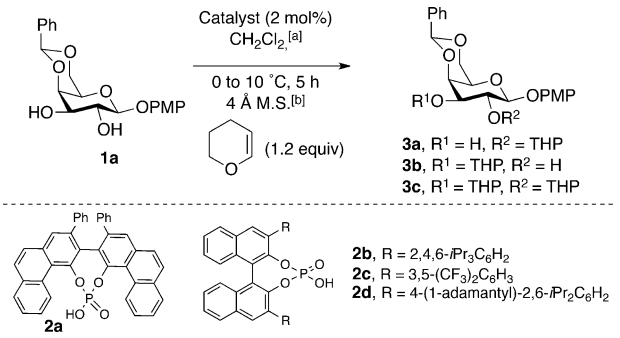
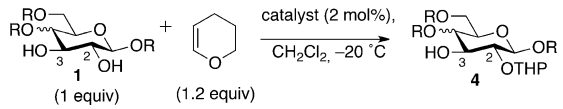
Table 1: Optimization of the reaction conditions for the regioselective tetrahydropyranylation of the D-galactose derivative **1a**.



Entry	Catalyst	Conv. [%][b]	**3a** (d.r.)	**3b** (d.r.)	**3a**/**3b**[c]
1	$(PhO)_2PO_2H$	57	>95:5	3.1:1	1:1.1
2	PPTS	95	4.2:1	2.9:1	1:1
3	(*S*)-**2a**	73	1.3:1	5.2:1	1:2.7
4	(*R*)-**2a**	42	1.9:1	1.1:1	1:1
5	(*S*)-**2b**	59	2.1:1	1.3:1	1.3:1
6	(*R*)-**2b**	78	1.7:1	3.2:1	2.4:1
7	(*S*)-**2c**	62	>95:5	1.4:1	1.1:1
8	(*R*)-**2c**	90	5.5:1	2:1	1:2.6
9	(*S*)-**2d**	78	1:1	1:1	1.7:1
10	(*R*)-**2d**	89	1.6:1	1.3:1	8:1
11	(±)-**2d**	90	1.3:1	1.4:1	3.5:1

[a] **1a** was found to be insoluble in the majority of other organic solvents. [b] Performed on 0.05 mmol scale (0.04 M solution) for 5 h. [c] Determined by ^{1}H NMR analysis of the crude reaction mixtures and comparison of the spectra to those of the independently prepared **3a** and **3b**. M.S. = molecular sieves, PMP = *para*-methoxyphenyl, PPTS = pyridinium *para*-toluenesulfonate, THP = tetrahydropyran.

Table 2: The scope of regioselective tetrahydropyranylation.[a]



Entry	Product	Catalyst	Yield [%][b] (conv.)	C2/C3[c]
1	**3a**	(*R*)-**2d**	78 (81)	8:1
		(*S*)-**2d**	n.d. (59)	1.7:1
		$(PhO)_2PO_2H$	48 (57)	1:1.8
2[d]	**4a**	(*R*)-**2d**	74 (85)	8.4:1
		(*S*)-**2d**	n.d. (62)	2.9:1
		$(PhO)_2PO_2H$	69 (70)	1.3:1
3[e]	**4b**	(*R*)-**2d**	54 (58)	6:1
		(*S*)-**2d**	n.d. (31)	1:2.6
		$(PhO)_2PO_2H$	31 (n.d.)	1:1
4	**4c**	(*R*)-**2d**	86 (87)	11:1
		(*S*)-**2d**	n.d. (15)	1:2
		$(PhO)_2PO_2H$	43 (48)	1:2.2
5	**4d**	(*R*)-**2d**	82 (91)	6:1
		(*S*)-**2d**	n.d. (11)	1:1
		$(PhO)_2PO_2H$	41 (46)	1.6:1
6	**4e**	(*R*)-**2d**	77 (96)	10:1
		(*S*)-**2d**	n.d. (18)	1.6:1
		$(PhO)_2PO_2H$	37 (55)	1:1.4

[a] Reactions were performed on 0.05 mmol scale (0.04 M solution, 5 h). [b] Yield of isolated product; conversion values are given in parentheses. [c] Determined by ^{1}H NMR analysis of the crude reaction mixtures and comparison of the spectra to those of the independently prepared regioisomeric THP ethers. [d] Performed on 1.1 mmol scale. [e] Warmed from 0 to 10 °C during the course of the reaction.

selective for the formation of **3a** (**3a**/**3b** = 1.7:1 and 3.5:1, respectively), the reaction catalyzed by the *R* enantiomer of this catalyst was found to be substantially more selective (**3a**/**3b**=8:1). In all of these cases (entries 3–11) only minor quantities (ca. 3–5 %) of the bis(protected) product **3c** were formed.

The regioselective tetrahydropyranylation of various D-galactose- and D-glucose-derived 2,3-diols catalyzed by (*R*)-**2d** was evaluated next (Table 2). More soluble than **1a**, a thioglycoside substrate (entry 2) underwent a regioselective reaction on a 1.1 mmol scale at −20 °C and resulted in the predominant formation of the C2-protected derivative **4a** (74 % yield, C2/C3 = 8.4:1). Both the reaction catalyzed by the enantiomeric catalyst (*S*)-**2d** as well as by $(PhO)_2PO_2H$ resulted in lower levels of regiocontrol. The (*R*)-**2d**-catalyzed reactions of pseudo-C2-symmetrical D-glucose-derived diols (entries 3–6) all resulted in the selective protection of the C2 position of the glucose. In contrast, functionalization of the C3 position has been observed for the substrate-controlled reactions of the β-D-glucose-derived 2,3-diols.[12] Because of the low solubility of the precursor to **4b**, its reaction with dihydropyran was significantly slower than those leading to **3a** and **4a**, even at 0 °C. While the reaction catalyzed by (*R*)-**2d** provided **4b** (entry 3, C2/C3 = 6:1), the reaction catalyzed by (*S*)-**2d** was sluggish and favored formation of the C3-protected isomer (C2/C3 = 1:2.6). A control experiment using $(PhO)_2PO_2H$ provided an equimolar mixture of the C2 and C3 products in low yield. The diol precursor to **4c** was significantly more soluble, and the reaction catalyzed by (*R*)-**2d** could be conducted at lower temperature (−20 °C) to provide **4c** in good yield and selectivity (86 % yield, C2/C3 = 11:1). In contrast, reactions with (*S*)-**2d** and $(PhO)_2PO_2H$ resulted in protection of the C3 position and were significantly slower. To investigate the influence of the C4,C6 protecting group on the reaction selectivity, cyclohexylidene- and isopropylidene-containing D-glucose derivatives were synthesized and evaluated (entries 5 and 6). The (*R*)-**2d**-catalyzed reactions of these substrates resulted in THP protection at C2 in good yields and good to excellent selectivities (**4d**: C2/C3 = 6:1; **4e**: C2/C3 = 10:1).

Other types of mixed-acetal protecting groups such as 2-methoxy-2-propyl (MOP) and 1-methoxy-1-cyclohexyl acetals have been used as alternatives to tetrahydropyrans.[13–15] Therefore, regioselective catalyst-controlled introduction of such protecting groups was investigated next (Table 3). As before, (*R*)-**2d** could significantly alter or enhance the inherent regioselectivity profiles exhibited by the substrates, and excellent to good levels of regiocontrol (up to 25:1) were observed in these transformations. In contrast, the reactions catalyzed by (*S*)-**2d** or diphenylphosphoric acid were significantly less selective, which indicates that the chirality of (*R*)-

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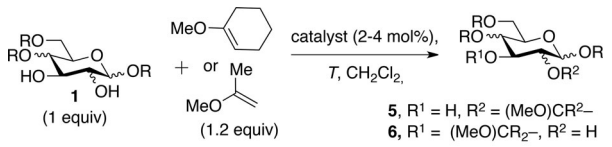
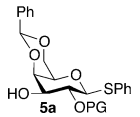
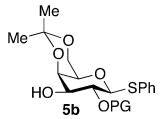
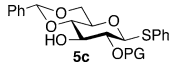
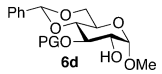
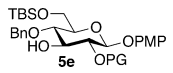
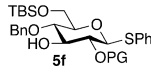
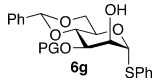
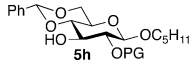
Table 3: The scope of regioselective protection with 2-methoxypropene and 1-methoxycyclohexene.[a]



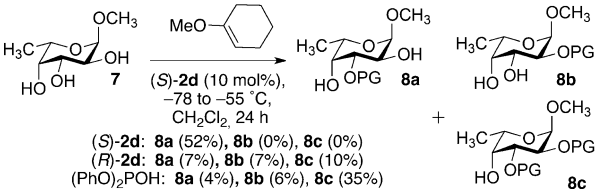
Entry	Product	PG	Catalyst	Yield [%][b] (conv.)	5/6[c]
1	 5a		(*R*)-**2d**	76 (83)	10:1
			(*S*)-**2d**	n.d. (30)	2.3:1
			$(PhO)_2PO_2H$	40 (45)	1:2.3
			(*R*)-**2d**	93 (95)	20:1
			(*S*)-**2d**	n.d. (95)	12:1
			$(PhO)_2PO_2H$	79 (88)	1:2.3
2	 5b		(*R*)-**2d**	51 (55)	>25:1
			(*S*)-**2d**	n.d. (10)	1:1
			$(PhO)_2PO_2H$	40 (57)	1:2.3
			(*R*)-**2d**	84 (95)	20:1
			(*S*)-**2d**	n.d. (95)	3.5:1
			$(PhO)_2PO_2H$	57 (90)	1:4.1
3	 5c		(*R*)-**2d**	95 (97)	>25:1[d]
			(*S*)-**2d**	n.d. (79)	1:1.7
			$(PhO)_2PO_2H$	62 (67)	1:1.3
			(*R*)-**2d**	72 (95)	>25:1
			(*S*)-**2d**	n.d. (69)	1:2.7
			$(PhO)_2PO_2H$	39 (79)	1:1.7
4	 6d		(*R*)-**2d**	79 (80)	1:8.8
			(*S*)-**2d**	n.d. (93)	1:2.4
			$(PhO)_2PO_2H$	70 (77)	2.2:1
			(*R*)-**2d**	69 (96)	1:6.3
			(*S*)-**2d**	n.d. (97)	1:1.7
			$(PhO)_2PO_2H$	53 (66)	2.4:1
5	 5e		(*R*)-**2d**	79 (88)	5:1
			(*S*)-**2d**	n.d. (83)	1:1.3
			$(PhO)_2PO_2H$	66 (72)	2:1
			(*R*)-**2d**	88 (>95)	7:1
			(*S*)-**2d**	n.d. (74)	2.7:1
			$(PhO)_2PO_2H$	68 (>95)	1:1.2
6	 5f		(*R*)-**2d**	78 (93)	7:1
			(*S*)-**2d**	n.d. (55)	2.5:1
			$(PhO)_2PO_2H$	64 (n.d.)	1:3.1
7	 6g		(*R*)-**2d**	60 (84)	1:12.6
			(*S*)-**2d**	n.d. (81)	1:7.2
			$(PhO)_2PO_2H$	18 (39)	1:2.6
8	 5h		(*R*)-**2d**	80 (82)	>25:1
			(*S*)-**2d**	n.d. (65)	1:1.7
			$(PhO)_2PO_2H$	45 (71)	1:1

[a] Reactions were performed on 0.05 mmol scale (0.04 M solution, 18–24 h) at −55 °C (1-methoxycyclohexene) or −78 °C (2-methoxypropene). [b] Yield of isolated product; conversion values are given in parentheses. [c] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [d] Performed on 2.78 mmol (1.0 g) scale. TBS = *tert*-butyldimethylsilyl.

2d is essential for attaining high levels of regiocontrol. The protection of the β-(D)-glucose-derived 2,3-diols (entries 3, 5, and 6) and the β-(D)-galactose-derived 2,3-diols (entries 1 and 2) resulted in the formation of the C2-protected products **5**. This method seems to be tolerant to changes in the C4 and C6 protecting groups, and the use of the conformationally locked substrates is not essential (entries 5 and 6). Importantly, the reaction of the precursor to **5c** (entry 3) and 1-methoxycyclohexene catalyzed by (*R*)-**2d** was executed on a gram scale without any erosion in yield or selectivity (0.05 mmol scale: 25:1, 65 % yield, 2.78 mmol scale: >25:1, 95 % yield). The protection of the methyl α-D-glucose-derived 2,3-diol (entry 4) resulted in the formation of the C3-protected products **6d**.

Considering that organotin-mediated protections of α-D-glucopyranosides are known to proceed at the C2 position, our method is complementary to the known organotin methods.[1a,10a] At the same time, the protection of the unsymmetrical α-D-mannose-derived diol (Table 3, entry 7) proceeded at the equatorial C3 rather than the axial C2 position to provide the derivative **6g**. This outcome is consistent with other methods which rely on substrate control.[1a,7] However, it is noteworthy that the use of (*R*)-**2d** resulted in significant enhancement of the selectivity (C2/C3=1:12.6) in comparison with the reaction catalyzed by achiral $(PhO)_2PO_2H$ (C2/C3 = 1:2.6). Finally, to demonstrate that this methodology could be used to functionalize simple alkylpyranosides, acetalization of a 1-pentanol-derived β-glucose derivative was investigated (entry 8). Consistent with the prior observations for the similar substrate (entry 3), the formation of **5h** was observed in good yields and excellent selectivities when (*R*)-**2d** was employed as a catalyst.

The CPA-controlled derivatization of the commercially available α-L-fucose derivative **7** was also investigated [Eq. (1)]. The control reaction catalyzed by the achiral $(PhO)_2PO_2H$ resulted in the formation of the bis(protected) derivative **8c** (35 % yield) and only minor amounts of **8a** and



(1)

8b (4 % and 6 % correspondingly) were observed after 24 hours. In contrast, the reaction catalyzed by (*S*)-**2d** resulted in the selective formation of **8a** (>20:1:1, 53 % conversion, 52 % yield). The corresponding reaction with (*R*)-**2d** was sluggish (10 % of **8c**, and 7 % of **8a** conversions and 7 % of **8b** were observed after 24 h). Although the functionalization of the C3 position of α-L-fucose could be accomplished using organoboron and organotin chemistry, the chirality of the CPA is clearly important for the selective formation of **8a**.

Our preliminary results suggest that the acetalization reactions take place under kinetic control. Thus, no isomerization of the product acetals was observed under the reaction conditions, and the observed selectivity for the formation of **5c** catalyzed by (*R*)-**2d** remained constant throughout the reaction progression at −55 °C (see the Supporting Information). To rationalize the observations, both a concerted mechanism[4j,16,17] or a more traditional stepwise mechanism proceeding through a carbocationic intermediate might be proposed. Thus, chiral phosphate is involved in the formation

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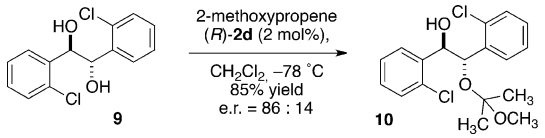
of a hydrogen bond with the diol, and the observed regioselectivities likely result from a more favored coordination of the catalyst to the substrate (see the Supporting Information). Achiral counterion-directing effects have been previously observed for the 4-(*N*,*N*-dimethylamino)pyridine-catalyzed acetylation of β-D-glucopyranosides,[18] and our observations summarized herein indicate that the chirality of the anion also plays an important role in differentiating the site of the reaction with the electrophile.

The carbohydrate-derived substrates tested in acetalization reactions (Tables 1–3) possess pseudo-C_2 symmetry axes and therefore similar chirality of the diol stereocenters. However, because of the presence of other stereocenters, the steric environment around each alcohol functionality is different, and thus the C_2-symmetric catalyst (*R*)-**2d** could stereodifferentiate between the hydroxy groups. Considering that the chiral catalyst could recognize rather subtle differences in the steric environment of substrates such as **5c** (Table 3), other types of stereoselective processes such as intermolecular desymmetrization of *meso* diols such as **9** could be envisioned (Scheme 3). In accordance with this proposal, the exposure of **9** to 2-methoxypropene catalyzed by (*R*)-**2d** (unoptimized) resulted in the formation of enantioenriched product **10** (e.r. = 86:14).



Scheme 3. Desymmetrization of *meso* diols.

In conclusion, this study represents the first example of chiral-catalyst-controlled regioselective acetalization of chiral polyols and enantioselective desymmetrization of *meso* diols.[19] We have discovered that chiral binol-derived phosphoric acids could direct regioselective additions of chiral polyols to oxocarbenium ions generated in situ by the protonation of various alkyl enol ethers. The described method significantly expands the scope of electrophiles which could be employed for regioselective chiral-catalyst-controlled chiral polyol functionalization.

Received: May 19, 2013
Revised: July 29, 2013
Published online: October 9, 2013

Keywords: carbohydrates · organocatalysis · protecting groups · regioselectivity · synthetic methods

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